World Guide
for Drug Use and
Pharmacogenomics

ISBN: 978-84-940770-0-5
Legal deposit: C 2091-2012

Medical knowledge is constantly changing. As new information becomes available, changes in treatment, procedures, equipment and the use of drugs and novel biomarkers become necessary.

Drug and gene nomenclature has been respected according to international standards (National Center for Biotechonology Information; Human Cytochrome P450 (CYP) Allele Nomenclature Committee). Original authors are reflected in references on the website and attached CD.

EUROESPES PUBLISHING.

EuroEspes Building, 1F
Santa Marta de Babío, s/n
15165 Bergondo, Corunna, Spain
Phone +34 981 780 505
info@euroespespublishing.com
www.euroespespublishing.com

Printed in Corunna, Spain

www.wgpgx.com

www.europharmagenics.com
The Pharmacogenomics database

World Guide
for Drug Use and
Pharmacogenomics

Ramón Cacabelos
editor

Director, EuroEspes Biomedical Research Center,
Institute for Central Nervous System Disorders and Genomic Medicine, Bergondo, Corunna

Professor and Chairman, EuroEspes Chair of Biotechnology and Genomics
Camilo José Cela University, Madrid, Spain

President, World Association of Genomic Medicine

World Association of Genomic Medicine

EUROESPES PUBLISHING

Corunna, Spain

First Edition
2012

Editor

RamónCacabelos

Associate Editors

LolaCorzo

LucíaFernández-Novoa

Authors

RamónCacabelos

LucíaFernández-Novoa

JuanCarlosCarril

LolaCorzo

ValterLombardi

IvánTellado

IvánCarrera

AmandaBello

CarmenFraile

MasatoshiTakeda

Preface

The Path to Pharmacogenomics

These are times of change and reconceptualization in medical science, education, politics and economics. Healthcare expenditure is becoming a major political and economic problem in the developed world, especially in the USA and the EU. In some European countries, the cost of healthcare is causing a global bankruptcy in the public sector. Pharmaceutical expenditure represents about 10-20% of total healthcare costs. Spending on pharmaceuticals throughout the OECD countries has increased by over 35% since 2000. In 2003, spending on drugs represented around 18% of total health expenses in OECD countries (30% in the Slovak Republic, Korea and Hungary, and 10% in Denmark and Norway). However, a combination of slower growth in healthcare spending and in the expansion of economies has led to a stabilization of health expenditure as a proportion of the GDP in many OECD countries. During the first half of the past decade until 2006, health spending in OECD countries grew in real terms by over 3% on average, the lowest rate since 1997. Health expenditure grew rapidly in many countries between 2000 and 2003, with an annual average growth rate of 6.2%. Since 2003, the rise in health expenditure has slowed to an average of 3.6% per year. In 2006, pharmaceutical spending in OECD countries increased by 2%, compared with growth rates of 6-7% annually between 2000 and 2003, and 3-3.5% per year during 2004 and 2005. The health expenditure share of the GDP in OECD countries remained unchanged, this being between 6-9%. Public spending on prescription drugs in the USA increased by 30% in 2006, because of the introduction of the new Medicare drug program for the elderly and the disabled. Private spending was reduced by 4%. In 2010, the growth in spending on prescription drugs in the USA ($307.4 billion) slowed to 2.3%, the second lowest level in half a century (1.8% in 2008), and was 5.1% lower than the growth recorded in 2009. When adjusted by the GDP price deflator, real total spending increased from $261 billion in 2006 to $277 billion in 2010. Real spending per capita increased from $876 in 2006 to $898 in 2010, the highest in the world, followed by Canada, Belgium and France, and at a great distance by other countries such as Mexico, Poland, Denmark and New Zealand, with spending ranging from $180 to $300 per capita. OECD pharmaceutical spending was over $650 PPP in 2010. These international differences in drug expenditure, in part, also reflect similar differences in applied health technology, the furtherance of science and scientific production, together broadening the inequalities among countries and enhancing the economic disequilibrium aggravated by the global crisis in which the engines of the world economy (USA, EU, Japan) are now immersed. This circumstance will undoubtedly affect the implementation and/or maintenance of national healthcare programs, the cost of drugs, new investments in drug development and budgetary decisions in medical science.

For drugs entering human clinical trials for the first time between 1989 and 2002, the estimated cost per new drug ranged from $500 million to over $2,000 million, depending on the pharmaceutical category and the company involved in the development of the drug. This kind of investment is affordable by only a few companies. To increase capitalization and accessibility to bigger markets, middle- and small-size companies are forced to undergo merging procedures with the consequent loss of jobs and industrial shrinkage. The pharmaceutical industry has to rebuild its strategic plans to improve its portfolio, and has to face restrictions in healthcare costs, and in the price of medicines influenced by the expiration of patents and by the impact of generics on nominal accounts, together with the challenges posed by pharmaceutical biotechnology and the increasing influence of biopharma on the sector, and the conceptual revolution driven by Genomic Medicine.

The Challenges of Genomic Medicine and Pharmacogenomics

The heroic task of the pioneering leaders of the Human Genome, who were able to motivate politicians and investors to create international consortia in order to accelerate the mapping of genes integrated in the human genome, has crystallized into the conceptual revolution which substantiates the foundations of a modern, innovative genomic medicine. At present, genomic medicine is not fulfilling the naïve expectations created 20 years ago; however, the future of genomic medicine will be brilliant and indispensable for the progress of medical praxis in the short- and medium-terms. Health priorities have changed in Western countries. A clear shift from acute diseases (e.g. infections) to chronic diseases (e.g. degenerative disorders) has been observed over the past 50 years in developed countries. In developing countries, infectious diseases still remain as a dominant concern; however, the aging of the population is also modifying the medical epidemiology of developing economies. In countries with low and middle income, dementia makes the largest contribution to disability with a median population-attributable prevalence fraction of 25.1%, followed by stroke (11.4%), limb impairment (10.5%), arthritis (9.9%), depression (8.3%), eyesight problems (6.8%) and gastrointestinal impairments (6.5%).

The major causes of death in developed countries are cardiovascular disorders (25-30%), cancer (20-25%), and CNS disorders (10-15%). According to the NCBI PubMed Database, 2.5 million references on cancer have been published since 1818 (415,371 references on genetics of cancer), 1.6 million references on cardiovascular disorders have been published since 1927 (103,470 on genetics of cardiovascular disorders), and 1.01 million references have been published on CNS disorders since 1893 (110,426 references on genetics of CNS disorders). The growth of the elderly population is a common phenomenon in both developed and developing countries, bringing about future challenges in terms of health policy and disability rates. In the USA, death rates for the leading causes of death are heart disease (200.2 per 100,000), cancer (180.7 per 100,000), and stroke (43.6 per 100,000). Dementia is becoming a major problem of health, and concomitant pathologies are highly common among patients with dementia. Approximately 20% of patients with Alzheimer's disease are hypertensive, 25% are diabetic, 50% are hypercholesterolemic, and 23% are hypertriglyceridemic. Over 25% of the patients exhibit high GGT activity, 5-10% show anemic conditions, 30-50% show an abnormal cerebrovascular function characterized by poor brain perfusion, and over 60% have an abnormal electroencephalographic pattern. Significant differences are currently seen between females and males, indicating the effect of gender on the phenotypic expression of the disease. Elderly patients may take 6-12 different drugs per day, with the consequent risk for adverse drug reactions and side-effects associated with drug interactions.

CNS disorders represent a typical paradigm of healthcare inefficiency in most countries. The total annual cost of brain disorders in Europe is about €386 billion, with €135 billion of direct medical expenditures (€78 billion, inpatients; €45 billion, outpatients; €13 billion, pharmacological treatment), €179 billion of indirect costs (lost workdays, productivity loss, permanent disability), and €72 billion of direct non-medical costs. Mental disorders represent €240 billion (62% of the total cost, excluding dementia), followed by neurological diseases (€84 billion, 22%). Despite the personal impact of brain disorders on those who suffer a deterioration of their mental activities, these diseases pose several challenges to our society and the scientific community: (i) they represent an epidemiological problem and a socio-economic, psychological and family burden; (ii) most of them have an obscure/complex pathogenesis; (iii) their diagnosis is not easy and lacks specific biomarkers; and (iv) their treatment is difficult and not cost-effective.

The major challenges of genomic medicine are concentrated around 4 main areas: (i) pathogenesis, (ii) diagnosis, (iii) treatment and (iv) prevention. The pathogenic mechanisms underlying human diseases are largely unknown; our understanding of major complex disorders is deficient because the pathogenesis of these diseases is poorly defined in more than 80% of the cases. At present, we lack predictive markers of disease (many years before the onset of the disease); and medical diagnosis is based on clinical symptoms (phenotypes) devoid of accurate biomarkers (except for infectious diseases and a few other medical conditions). In many cases, diagnosis is late and inaccurate. In global terms, pharmacological treatment is effective in only 20-30% of the cases. It is expected that genomic medicine will help us to develop predictive markers for an early diagnosis, assuming that in over 70-80% of complex disorders the clinical phenotype is the result of a defective genomic background in conjunction with environmental factors and epigenetic phenomena. Without predictive biomarkers, prevention is a difficult task, if not impossible. There is an appealing golden rule in complex genomics of human disease: the greater the number of defective genes associated with a particular disease, the earlier the onset of the disease and the poorer the therapeutic outcome; and the lower the number of genes affected, the later the onset and the better the therapeutic response to conventional therapeutics. Since treatment and the search for health conditions is the final goal of any medical process, it is reasonable to predict that one of the first priorities of genomic medicine might be the implementation of programs for a personalized treatment. Major impact factors associated with drug efficacy and safety include: (i) the mechanisms of action of drugs, (ii) drug-specific adverse reactions, (iii) drug-drug interactions, (iv) nutritional factors, (v) vascular factors, (vi) social factors and (vii) genomic factors (nutrigenetics, nutrigenomics, pharmacogenetics, pharmacogenomics). Among genomic factors, nutrigenetics/nutrigenomics and pharmacogenetics/pharmacogenomics may account for more than 80% of efficacy-safety outcomes in current therapeutics.

To achieve substantial goals, genomic medicine has to rely on structural genomics, transcriptomics, functional genomics, proteomics, epigenetics, and metabolomics, together with bioinformatics and high-tech diagnostic tools. Structural genomics would define the cartographic disposition and polymorphic variation of genes associated with human disease. Over 12,000 of the 35,000 genes which integrate the human genome might be assigned to specific traits; either Mendelian or susceptibility traits. Functional genomics would show the influence of genes on disease pathogenesis and phenotype expression. Transcriptomics and proteomics would help to elucidate the role of abnormal gene expression in the pathogenesis of a particular disease. The study of genotype-phenotype correlations is essential for the evaluation of the actual impact of specific polymorphic variants of a particular gene on the clinical manifestation of a disease and/or biological markers reflecting the disease condition or different biological states of the individual. Epigenetics is the study of how the environment can affect the genome of the individual during his or her development as well as the development of his/her descendants, all without changing the DNA sequence, but inducing modifications in gene expression through DNA methylation-demethylation or through modification of histones by processes of methylation, deacetylation, and phosphorylation. More than 150 post-translational modifications of histones have been reported, including methylations, acetylations, ubiquitinations, SUMOylations and phosphorylations. Epigenetic changes are probably involved in the pathogenesis of many complex disorders. The metabolome is the repertoire of biochemicals present in cells, tissues, and body fluids, whose dysfunctional interactions may lead to disease pathogenesis. Mitochondrial DNA abnormalities and aberrant interactions between mtDNA and nuclear DNA products are also subtle fields to be investigated in genomic medicine with repercussions in human disease.

Our understanding of the pathophysiology of complex disorders (cardiovascular disorders, cancer, or CNS disorders, representing 60-80% of the major causes of death) has advanced dramatically over the last 30 years, especially in terms of their molecular pathogenesis and genetics. The drug treatment of complex disorders has also made remarkable strides, with the introduction of many new drugs. Improvement in terms of clinical outcome, however, has fallen short of expectations, with up to one third of the patients continuing to experience clinical relapse or unacceptable medication-related side-effects in spite of efforts to identify optimal treatment regimens with one or more drugs. Potential reasons to explain this historical setback might be that: (i) the molecular pathology of most complex disorders is still poorly understood; (ii) drug targets are inappropriate, not fitting into the real etiology of the disease; (iii) most treatments are symptomatic, but not anti-pathogenic; (iv) the genetic component of most complex disorders is poorly defined; and (v) the understanding of genome-drug interactions is very limited.

The optimization of therapeutics requires the establishment of new postulates regarding (i) novel strategies for drug development (a reduction in the time to reach the market, identification of optimal targets, pharmacogenetic-oriented methodologies), (ii) the cost of medicines, (ii) the assessment of protocols for multifactorial treatment in chronic disorders, (iii) the implementation of novel therapeutics addressing causative factors, and (iv) the setting-up of pharmacogenomic strategies for drug development and drugs in current use.

Pharmacogenetics/Pharmacogenomics relates to the application of genomic technologies, such as genotyping, gene sequencing, gene expression, genetic epidemiology, transcriptomics, proteomics, metabolomics and bioinformatics, to drugs in clinical development and on the market, applying the large-scale systematic approaches of genomics to speed up the discovery of drug response markers, whether they act at the level of drug target, drug metabolism, or disease pathways.

The potential implications of pharmacogenomics in clinical trials and molecular therapeutics are that a particular disease could be treated according to genomic and biological markers, selecting medications and diseases which are optimized for individual patients or clusters of patients with a similar genomic profile. For many medications, interindividual differences are mainly due to SNPs in genes encoding drug-metabolizing enzymes, drug transporters, and/or drug targets (e.g. genome-related defective enzymes, receptors and proteins, which alter metabolic pathways leading to disease phenotype expression).

The pharmacogenomic outcome depends upon many different determinant factors including (i) genomic profile, (ii) disease phenotype, (iii) concomitant pathology, (iv) genotype-phenotype correlations, (v) nutritional conditions, (vi) age and gender, (vii) pharmacological profile of the drugs, (viii) drug-drug interactions, (ix) gene expression profile, (x) transcriptomic cascade, (xi) proteomic profile and (xii) metabolomic networking. The dissection and further integration of all these factors is of paramount importance for the assessment of the pharmacogenomic outcome in terms of safety and efficacy. Pharmacogenomic approaches based on genome-wide sets of SNPs associated with drug response are now feasible and may offer the potential to personalize therapeutics.

In recent times, significant advances have expedited the introduction of pharmacogenomic approaches in drug development and also in clinical practice to optimize therapeutics; however, pharmacogenomics is still in a very primitive stage. Personalized therapeutics requires a better understanding of the effects of drugs on gene expression in pathogenic cascades, and the influence that different genes and their products exert on the fate of drugs before, during and after impacting with pathogenic targets. At least 5 different categories of genes are potentially involved in the pharmacogenomic process: (i) genes associated with disease pathogenesis, (ii) genes associated with the mechanism of action of a particular drug (e.g. synthesizing enzymes, catabolizing enzymes, receptor genes), (iii) genes associated with phase I (*CYPs*) and phase II reactions (*UGTs*, *GSTs*, *SULTs*, *NATs*), (iv) genes associated with transporters (*ABCs*, *OATs*), and (v) pleiotropic genes involved in multifaceted cascades and/or genes associated with concomitant pathologies. On average, 8-10 genes (range: 1-131) may be involved in the therapeutic outcome associated with the efficacy and safety of a specific drug.

The vast majority (78%) of the 200 most prescribed drugs in the USA are metabolized via enzymes of the cytochrome P450 family (CYPs), with major contributions from CYP3A4/5 (37% of drugs) followed by CYP2C9 (17%), CYP2D6 (15%), CYP2C19 (10%), CYP1A2 (9%), CYP2C8 (6%), and CYP2B6 (4%). The genes encoding CYP2D6, CYP2C19, CYP2C9, and CYP3A4/5 isoenzymes are highly polymorphic, with great allelic variation in different ethnic groups. These genes are very promiscuous, influencing the metabolism of different drugs. Very few drugs use an exclusive metabolic pathway for their degradation and subsequent elimination. About 10,600 genes (of the 5 categories previously referred) may participate in the metabolism of 1,392 drugs approved by the FDA, EMEA, and Koseisho. CYP3A4/5 participates in the metabolism of 525 drugs (37.71%), CYP2D6 in 315 (22.63%), CYP2C9 in 287 (20.62%), CYP2C19 in 244 (17.53%), and ABCB1 in 272 (19.54%). Of 7,742 chemicals studied, 982 drugs have been related to CYP2D6 metabolism, of which 205 drugs have been characterized as major substrates, 166 as minor substrates, 75 as strong inhibitors, 183 as moderate inhibitors, 117 as weak inhibitors, and 18 drugs as inducers; 691 drugs have been related to CYP2C9 metabolism (177 major substrates, 134 minor substrates, 102 strong inhibitors, 181 moderate inhibitors, 92 weak inhibitors, and 41 inducers); 576 drugs have been related to CYP2C19 metabolism (151 major substrates, 130 minor substrates, 64 strong inhibitors, 127 moderate inhibitors, 72 weak inhibitors, and 23 inducers); and 1,937 drugs have been related to CYP3A4/5 metabolism (897 major substrates, 136 minor substrates, 141 strong inhibitors, 437 moderate inhibitors, 118 weak inhibitors, and 241 inducers). ABCB1 is a very important transporter, with 1,214 related drugs (897 major substrates, 136 minor substrates, 141 strong inhibitors, 437 moderate inhibitors, 118 weak inhibitors, and 241 inducers).

Although studies illustrating the influence of CYP enzymes on drug metabolism have been reported since the 1950s, our molecular knowledge of CYP pharmacogenetics is still very limited, with many black holes. Some examples are (i) tissue-specific metabolism (CYP expression in different tissues), (ii) age- and sex-related changes in drug metabolism, (iii) blood-brain barrier and trans-placental transport of drugs, (iv) fetal metabolism, (v) the dissociation of *in vivo* and *in vitro* results, (vi) the specificity of ligands for phenotyping studies, (vii) the influence of food in drug metabolism, (viii) the role of nuclear receptors, CYP450 oxidoreductase and cytochrome b5, in the efficiency of CYP isoenzymes, (ix) ethnic differences, and (x) drug resistance.

Numerous xenobiotics are not necessarily toxic as such, but are enzymatically transformed in the liver or in other biological organs, where CYP enzymes are expressed, to reactive and toxic intermediates. Many proteratogens, procarcinogens and promutagens are metabolically transformed by CYP enzymes into dangerous compounds with potential deleterious consequences for human health.

Age, sex, and genetic forms of CYP expression constitute relevant determinants of interindividual variability in CYP-dependent metabolism during ontogeny and throughout the life-span.

Important aspects of drug pharmacokinetics beyond genomic variants still awaiting elucidation are the effects of cytochrome b5 on catalytic activities of CYPs co-expressed with NADPH-CYP450 oxidoreductase. Mutations in CYP450 oxidoreductase can lead to reduced activities of steroidogenic P450s CYP17A1, CYP19A1, and CYP21A1. Mutations in the FMN binding domain of CYP450 oxidoreductase may reduce CYP3A4 activity, affecting drug and steroid metabolism.

Food-drug interactions can be associated with alterations in the pharmacokinetic and pharmacodynamic profile of drugs with clinical implications. In recent years, there has been an increasing application of herbal medicines and dietary supplements to treat chronic diseases and promote health. Organ toxicities associated with consumption of herbal medicines have been reported. Natural products undergoing metabolic activation may form reactive metabolites which can induce toxicity. Some herbal components may also be converted to toxic or mutagenic and carcinogenic metabolites by CYPs and Phase II conjugating enzymes. Numerous interactions between herbal medicines and commercial drugs have been documented. Over 50% of commercial ethanolic herbal extracts can cause inhibition of CYP3A4 metabolite formation. This phenomenon is extensive to all continents where herbal constituents are currently used in folk medicine and natural preparations.

Multidrug resistance is a major obstacle to successful cancer treatment. An important mechanism by which oncogenic cells may become resistant to chemotherapy is the expression of ABC transporters that use the energy of ATP hydrolysis to transport a wide variety of substrates across the cell membrane.

Clinicians currently have no way of predicting who will respond appropriately to a given drug, and the paradigm of trial-and-error is especially distressing for patients with chronic disorders and/or severe acute illness. Pharmacogenetic association studies may provide insight into which genetic polymorphisms might be clinically relevant for personalizing pharmacotherapeutic regimens. In the Western population, only 25% of its members are extensive metabolizers (EM) for the trigenic cluster integrated by *CYPs 2D6+2C19+2C9*, the most relevant genes (and enzyme products) involved in drug metabolism, together with *CYP3A4/5*. The other 75% of the population is potentially at risk for developing adverse drug events due to defective variants encoding deficient enzymes which give rise to intermediate (IM), poor (PM) or ultra-rapid metabolizers (UM). This population cluster of defective metabolizers requires dose adjustment to avoid side-effects and, in the case of PMs, the administration of another drug with alternative metabolic pathways should be the norm in order to avoid toxicity.

Ethnic differences must be taken into consideration when developing new drugs or when prescribing drugs which were tested in different ethnic groups. Although global clinical trials can enable the development of new agents efficiently, whether the results of clinical trials performed in one population can be fully extrapolated to another population remains highly questionable due to clear ethnic differences associated with genotype-related drug metabolism. Therefore, pharmacogenomic differences associated with individual responses to drugs should be carefully considered when conducting clinical trials or when prescribing drugs for chronic disorders.

To achieve a mature discipline of pharmacogenomics it would be convenient to accelerate the following processes: (i) educating physicians and the public on the use of genetic/genomic screening in the daily clinical practice; (ii) the standardization of genetic testing for major categories of drugs; (iii) the validation of pharmacogenomic procedures according to drug category and pathology; (iv) the regulation of ethical, social, and economic issues; and (v) the incorporation of pharmacogenomic procedures to both drugs in development and drugs on the market, in order to optimize therapeutics.

The World Guide of Pharmacogenomics

The World Guide for Drug Use and Pharmacogenomics (WGPGx) is a multidisciplinary, systematic exercise to put in order a myriad of data organized in selected databases and thousands of reports scattered throughout the international literature on genetics, genomics, pharmacology, drug metabolism, therapeutics, and pharmacogenomics, to provide the reader (physicians, geneticists, pharmacists, researchers, health professionals, regulators, etc.) with a body of practical information which is not available in other publications as a whole.

The Guide is divided into 5 main parts: (i) Drugs, (ii) Genes, (iii) References, (iv) Appendix and (v) Index.

The section of Drugs includes 1,395 drugs classified in alphabetical order from A to Z. Each entry contains the following headings: Drug Name; Brand Names [in 27 European countries (Austria, Belgium, Bulgaria, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, UK), North America (Canada and USA), Latin America (Argentina, Brazil, Mexico), and Asia (Japan)]; Drug Combinations; Chemistry; Pharmacological Category; Mechanism of Action; Therapeutic Use; Unlabeled Use; Pregnancy and Lactation Implications; Contraindications; Warnings and Precautions; Adverse Reactions (cardiovascular, central nervous system, dermatologic, endocrine and metabolic, gastrointestinal, genitourinary, hematologic, hepatic, local, neuromuscular and skeletal, renal, respiratory, miscellaneous); Pharmacogenetics (genotypes of risk, genes involved in drug metabolism, condition of substrate, inhibitor or inducer, when appropriate); Drug Interactions; Nutrition/Nutraceutical Interactions; Dosage; Pharmacokinetics and Pharmacodynamics (absorption, distribution, protein binding, metabolism, bioavailability, half-life, time to peak, excretion); Special Considerations (diet, age, sex, monitoring parameters).

The section of Genes includes 447 genes of relevance in pharmacogenomics. Each entry contains the following headings: Gene Name; Alternative Names; Alternative Symbols; Locus; Codes (OMIM, PharmGKB); Gene Structure; RNA; Protein; Function; Related Diseases (list of diseases investigated; in bold face those diseases potentially associated); Related Drugs (list of drugs investigated; when appropriate, major substrates, minor substrates, strong inhibitors, moderate inhibitors, weak inhibitors, and inducers); Animal Models; Allelic Variants; Selected SNPs; Evolution; Genomics and Pharmacogenomics (description of relevant findings in genomics and pharmacogenomics according to the international literature); Drug-Gene Interactions.

The section of References includes two categories: (i) Websites and International Databases, and (ii) 17,947 References alphabetically classified by author and by gene. The List of References is included in the attached CD-ROM. Due to the length of said list of references, it has been omitted in the book. The Guide's authors have respected the data and opinions of the referenced original authors where contradictory results on drugs or genes are reported. Data included in the WGPGx have been strictly extracted from the referenced authors, avoiding personal interpretations. Approximately 100,000 references have been reviewed, of which 17,947 were finally selected for this edition.

The Appendix includes 4 sub-sections: (i) Classification of Drugs, (ii) Genes-Diseases (a list of genes associated with specific diseases), (iii) Diseases-Genes (a list of diseases associated with specific genes), and (iv) Pharmacogenomic synopsis (a list of internationally-used drugs with those genes potentially involved in the metabolism of each drug).

The Index contains approximately 52,000 entries divided into 5 sections: (i) Drugs (approx. 7,750 entries), (ii) Brand names (approx. 31,750 entries), (iii) Pharmacological categories (1,891 entries), (iv) Genes (approx. 4,450 entries), and (v) Diseases (approx. 9,200 entries).

As Editor-in-Chief of the 1st Edition of the ***World Guide for Drug Use and Pharmacogenomics***, in 3 formats (Book, CD-ROM, and EuroPharmaGenics Database), it is a pleasure for me to present this monumental work to the scientific and medical communities from whom I would greatly appreciate to receive any feedback and constructive criticism in order to improve the quality and accuracy of the information released in this volume. I would like to thank all referenced authors and the entities responsible for the databases from which we necessarily obtained the documentation bulk, later to be assembled in this Guide. The final goal of this incipient, extensive, and systematic work is to efficiently serve our patients, by improving diagnostic procedures with the aid of genomic tools, personalizing treatments and minimizing undesirable drug effects by using pharmacogenomic strategies, and, in the end, optimizing therapeutics for a better healthcare model in our society.

Ramón Cacabelos, M.D., Ph.D., D.M.Sci.
Editor-in-Chief

Contents

WorldGuide for Drug Use and Pharmacogenomics

Drugs

A

Abacavir

Brand Names

Europe

Austria: Ziagen; **Belgium**: Ziagen; **Bulgaria**: Ziagen; **Cyprus**: Ziagen; **Czech Republic**: Ziagen; **Denmark**: Ziagen; **Estonia**: Ziagen; **Finland**: Ziagen; **France**: Ziagen; **Germany**: Ziagen; **Greece**: Ziagen; **Hungary**: Ziagen; **Ireland**: Ziagen; **Italy**: Ziagen; **Latvia**: Ziagen; **Lithuania**: Ziagen; **Luxembourg**: Ziagen; **Malta**: Ziagen; **Netherlands**: Ziagen; **Poland**: Ziagen; **Portugal**: Ziagen; **Romania**: Ziagen; **Slovakia**: Ziagen; **Slovenia**: Ziagen; **Spain**: Ziagen; **Sweden**: Ziagen; **UK**: Ziagen.

North America

Canada: Ziagen; **USA**: Ziagen.

Latin America

Argentina: Abacavir, Filabac, Finecil, Panka, Plusabcir, Zepril, Ziagenavir; **Brazil**: Ziagenavir; **Mexico**: Ziagenavir.

Asia

Japan: Ziagen.

Drug Combinations

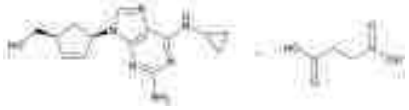
Abacavir and Lamivudine

Abacavir, Lamivudine, and Zidovudine

Chemistry

Abacavir Sulfate: $(C_{14}H_{18}N_6O)_2\ H_2SO_4$. Mw: 670.74. (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1). CAS-188062-50-2 (1997).

Abacavir Succinate: $C_{14}H_{18}N_6O\ C_4H_6O_4$. Mw: 404.42. 2-Cyclopentene-1-methanol, 4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl]-, (1S-cis)-, butanedioate (1:1). CAS-168146-84-7; CAS-136470-78-5 (abacavir)(1996).



Pharmacologic Category

Anti-Infective Agents; Antiretrovirals; Nucleoside and Nucleotide Reverse Transcriptase Inhibitors. (ATC-Code: J05AF06).

Mechanism of Action

Abacavir is phosphorylated to carbovir triphosphate, which interferes with HIV viral RNA-dependent DNA polymerase, inhibiting viral replication.

Therapeutic Use

Treatment of HIV infections in combination with other antiretroviral agents.

Pregnancy and Lactation Implications

Risk of lactic acidosis and liver damage in pregnant women. Contraindicated during lactation.

Contraindications

Hypersensitivity to abacavir (or carbovir) or any component of the formulation. Hepatic impairment.

Warnings and Precautions

Hypersensitivity reactions have occurred (increased risk in patients with *HLA-B*5701* allele). Lactic acidosis and severe hepatomegaly with steatosis have been reported (caution in risk factors for liver disease). Caution in hepatic dysfunction (contraindicated in moderate-to-severe dysfunction) or in risk factors for coronary heart disease. Immune reconstitution syndrome may develop. May cause redistribution of fat. Should always be used as part of a multidrug regimen.

Adverse Reactions

Cardiovascular: Myocardial infarction.

Central Nervous System: Abnormal dreams, anxiety, depression, dizziness, fatigue, headache, insomnia, lethargy, malaise, paresthesia.

Dermatologic: Erythema multiforme, rash, Stevens-Johnson syndrome, toxic epidermal necrolysis.

Endocrine and Metabolic: Fat redistribution, increased triglycerides, lactic acidosis.

Gastrointestinal: Diarrhea, increased amylase, nausea, pancreatitis, vomiting.

Hematologic: Thrombocytopenia.

Hepatic: Hepatic steatosis, hepatomegaly, hepatotoxicity, increased AST, increased GGT.

Neuromuscular and Skeletal: Musculoskeletal pain.

Miscellaneous: Chills, fever, hypersensitivity reactions, infection.

Pharmacogenetics

Caution and personalized dose adjustment in patients with the following genotypes:

HCP5: rs2395029

HLA-B: *HLA-B*5701*, *HLA-B*1502*, *HLA-B*5801*, *HLA-B18* subtype, *HLA-B39* subtype, *HLA-B44* subtype

HSPA1L: Thr493Met

Other genes that may be involved:

ABCB1; *ABCC6*; *ADHs*; *CRP*; *TERT*; *UGT1A1*; *UGT2B7*

Inhibits:

ABCC1; ABCC2

Induces:

CYP2B6

Drug Interactions

Ganciclovir-valganciclovir may enhance the adverse/toxic effect of reverse transcriptase inhibitors (nucleoside)(hematologic toxicity). Protease inhibitors may decrease the serum concentration of abacavir. Ribavirin may enhance the hepatotoxic effect of reverse transcriptase inhibitors (nucleoside)(lactic acidosis).

Nutrition/Nutraceutical Interactions

Ethanol: May increase risk of toxicity.

Dosage

Dosage Forms: Solution, oral: 20 mg/mL (240 mL)(strawberry-banana flavor). Tablet: 300 mg. [Oral administration].

Pharmacokinetics and Pharmacodynamics

Absorption: Rapid and extensive.

Distribution: V_d: 0.86 L/kg.

Protein binding: 50%.

Metabolism: Via alcohol dehydrogenase and glucuronosyltransferase to inactive carboxylate and glucuronide metabolites.

Bioavailability: 83%.

Half-life: 1.5 hours.

Time to peak: 0.7-1.7 hours.

Excretion: Urine (primarily), feces.

Special Considerations

Diet: May be taken with or without food.

Monitoring Parameters: CBC, serum creatine kinase, CD4 count, HIV RNA plasma levels, serum transaminases, triglycerides, serum amylase, *HLA-B*5701* genotype status prior to initiation of therapy, signs and symptoms of hypersensitivity.

Abacavir and Lamivudine

Brand Names

Europe

Austria: Kivexa; **Belgium**: Kivexa; **Bulgaria**: Kivexa; **Cyprus**: Kivexa; **Czech Republic**: Kivexa; **Denmark**: Kivexa; **Estonia**: Kivexa; **Finland**: Kivexa; **France**: Kivexa; **Germany**: Kivexa; **Greece**: Kivexa; **Hungary**: Kivexa; **Ireland**: Kivexa; **Italy**: Kivexa; **Latvia**: Kivexa; **Lithuania**: Kivexa; **Luxembourg**: Kivexa; **Malta**: Kivexa; **Netherlands**: Kivexa; **Poland**: Kivexa; **Portugal**: Kivexa; **Romania**: Kivexa; **Slovakia**: Kivexa; **Slovenia**: Kivexa; **Spain**: Kivexa; **Sweden**: Kivexa; **UK**: Kivexa.

North America

Canada: Kivexa; **USA**: Epzicom.

Latin America

Argentina: Kivexa; **Brazil**: Kivexa; **Mexico**: Kivexa.

Asia

Japan: Epzicom.

Drug Combinations

Abacavir, Lamivudine, and Zidovudine

Chemistry

Abacavir Sulfate: $(C_{14}H_{18}N_6O)_2\ H_2SO_4$. Mw: 670.74. (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1). CAS-188062-50-2 (1997).

Lamivudine: $C_8H_{11}N_3O_3S$. Mw: 229.26. (1) 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-,(2R-cis)-; (2)(-)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. CAS-134678-17-4 (1992).

Pharmacologic Category

Anti-infective Agents, Antiretrovirals, Nucleoside and Nucleotide Reverse Transcriptase Inhibitors. (ATC-Code: J05AR02).

Mechanism of Action

Abacavir phosphorylated to carbovir triphosphate interferes with HIV viral RNA-dependent DNA polymerase, inhibiting viral replication. Triphosphorylated lamivudine inhibits HIV reverse transcription via viral DNA chain termination. Inhibits RNA-dependent DNA polymerase activities of reverse transcriptase.

Therapeutic Use

Treatment of HIV infections in combination with other antiretroviral agents.

Contraindications

Hypersensitivity to abacavir, lamivudine, or any component of the formulation. Renal (CrCl <50 mL/minute) and hepatic impairment.

Warnings and Precautions

May cause redistribution of fat. Hypersensitivity reactions have occurred (increased risk in patients with *HLA-B*5701* allele). Immune reconstitution syndrome might be developed. Lactic acidosis and hepatomegaly with steatosis have been reported. Clinical exacerbations after discontinuing therapy for chronic hepatitis B in HIV patients have occurred. Caution in combination with interferon alfa with or without ribavirin in HIV/HBV-coinfected patients. Caution in renal dysfunction (contraindicated in CrCl <50 mL/minute or in risk factors for coronary heart disease). Avoid use in children.

Adverse Reactions
Central Nervous System: Paresthesia, peripheral neuropathy, seizure.
Dermatologic: Alopecia, erythema multiforme, urticaria.
Endocrine and Metabolic: Fat redistribution, hyperglycemia, lactic acidosis, Stevens-Johnson syndrome.
Gastrointestinal: Pancreatitis, stomatitis.
Hematologic: Anemia, aplastic anemia.
Hepatic: Hepatic steatosis, hepatitis B exacerbation.
Neuromuscular and Skeletal: Increased CPK, muscle weakness, rhabdomyolysis, weakness.
Respiratory: Abnormal breath sounds, wheezing.
Miscellaneous: Anaphylaxis, hypersensitivity reaction, lymphadenopathy, splenomegaly.

Pharmacogenetics
Caution and personalized dose adjustment in patients with the following genotypes:
HCP5: rs2395029
HFE: C187G
HLA-B: *HLA-B*5701*, *HLA-B*1502*, *HLA-B*5801*, *HLA-B18* subtype, *HLA-B39* subtype, *HLA-B44* subtype
HSPA1L: Thr493Met
Other genes that may be involved:
ABCB1; *ABCC6*; *ABCG2*; *ADHs*; *CRP*; *ICAM1*; *UGT1A1*; *UGT2B7*
Inhibits:
ABCC1; ABCC2
Induces:
CYP2B6

Drug Interactions
Ganciclovir-valganciclovir may enhance the adverse/toxic effect of reverse transcriptase inhibitors (nucleoside)(hematologic toxicity). Protease inhibitors may decrease the serum concentration of abacavir. Ribavirin may enhance the hepatotoxic effect of reverse transcriptase inhibitors (nucleoside)(lactic acidosis). Trimethoprim may decrease the excretion of lamivudine. Lamivudine may diminish the therapeutic effect of zalcitabine.

Dosage
Dosage Forms: Tablet: Abacavir 600 mg and lamivudine 300 mg. [Oral administration].
Dose adjustment in special conditions: In renal (use not recommended) or hepatic (use contraindicated) impairment.

Abacavir, Lamivudine, and Zidovudine

Brand Names
Europe
Austria: Trizivir; **Belgium**: Trizivir; **Bulgaria**: Trizivir; **Cyprus**: Trizivir; **Czech Republic**: Trizivir; **Denmark**: Trizivir; **Estonia**: Trizivir; **Finland**: Trizivir; **France**: Trizivir; **Germany**: Trizivir; **Greece**: Trizivir; **Hungary**: Trizivir; **Ireland**: Trizivir; **Italy**: Trizivir; **Latvia**: Trizivir; **Lithuania**: Trizivir; **Luxembourg**: Trizivir; **Malta**: Trizivir; **Netherlands**: Trizivir; **Poland**: Trizivir; **Portugal**: Trizivir; **Romania**: Trizivir; **Slovakia**: Trizivir; **Slovenia**: Trizivir; **Spain**: Trizivir; **Sweden**: Trizivir; **UK**: Trizivir.
North America
Canada: Trizivir; **USA**: Trizivir.
Latin America
Argentina: Tricivir, Trivudin, Zidomuv; **Mexico**: Trizivir.

Chemistry
Abacavir Sulfate: $(C_{14}H_{18}N_6O)_2 \cdot H_2SO_4$. Mw: 670.74. (1S,4R)-4-[2-Amino-6-(cyclopropylamino)-9H-purin-9-yl]-2-cyclopentene-1-methanol sulfate (2:1). CAS-188062-50-2 (1997).
Lamivudine: $C_8H_{11}N_3O_3S$. Mw: 229.26. (1) 2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-,(2R-cis)-; (2)(-)-1-[(2R,5S)-2-(Hydroxymethyl)-1,3-oxathiolan-5-yl]cytosine. CAS-134678-17-4 (1992).

Zidovudine: $C_{10}H_{13}N_5O_4$. Mw: 267.24. (1) Thymidine, 3'-azido-3'-deoxy-; (2) 3'-Azido-3'-deoxythymidine. CAS-30516-87-1 (1987).

Pharmacologic Category
Anti-infective Agents, Antiretrovirals, Nucleoside and Nucleotide Reverse Transcriptase Inhibitors. (ATC-Code: J05AR04).

Mechanism of Action
Inhibition of reverse transcriptase via DNA chain termination after incorporation of the nucleoside analog as well as delay of emerging mutations conferring resistance.

Therapeutic Use
Treatment of HIV infections in combination with other antiretroviral agents.

Contraindications
Hypersensitivity to abacavir, lamivudine, zidovudine, or any component of the formulation. Renal (CrCl ≤50 mL/minute) or hepatic impairment.

Warnings and Precautions
May cause redistribution of fat. Hematologic toxicity may occur (neutropenia, anemia; use with caution in bone marrow compromise). Hypersensitivity reactions have occurred (increased risk in patients with *HLA-B*5701* allele). Immune reconstitution syndrome may develop. Lactic acidosis and severe hepatomegaly with steatosis have been reported (caution in risk factors for liver disease). Clinical exacerbations after discontinuing therapy for chronic hepatitis B in HIV patients have occurred. Caution in risk factors for coronary heart disease. Risk of myopathy and myositis (with prolonged use). Should always be used as part of a multidrug regimen. Should not be used in CrCl ≤50 mL/minute. Caution in combination with interferon alfa with or without ribavirin in HIV/HBV coinfected patients. Avoid use in children.

Adverse Reactions
Central Nervous System: Anxiety, depression, fatigue, headache, malaise.
Dermatologic: Rash.
Endocrine and Metabolic: Fat redistribution, increased triglycerides.
Gastrointestinal: Diarrhea, increased amylase, nausea, pancreatitis, vomiting.
Hematologic: Neutropenia.
Hepatic: Increased ALT, increased GGT.
Neuromuscular and Skeletal: Increased CPK.
Miscellaneous: Ear/nose/throat infection, chills, fever, hypersensitivity (based on abacavir component), immune reconstitution syndrome, viral infection.

Pharmacogenetics
Caution and personalized dose adjustment in patients with the following genotypes:
ABCC4: C1612T, G3463A, G3724A, T4131G
ABCG2: C421A and G34A
CYP2A6: *CYP2A6*4*, *CYP2A6*7*, *CYP2A6*9*
CYP2C9: *CYP2C9*2*, *CYP2C9*3*, *CYP2C9*5*
CYP2C19: *CYP2C19*2*, *CYP2C19*3*, *CYP2C19*4*, *CYP2C19*5*, *CYP2C19*6*, *CYP2C19*7*, *CYP2C19*8*, *CYP2C19*17*
CYP3A4: *CYP3A4*1*, *CYP3A4*1B*, *CYP3A4*2*, *CYP3A4*3*, *CYP3A4*4*, *CYP3A4*5*, *CYP3A4*6*, *CYP3A4*8*, *CYP3A4*11*, *CYP3A4*12*, *CYP3A4*13*, *CYP3A4*15*, *CYP3A4*17*, *CYP3A4*18*, *CYP3A4*19*
HCP5: rs2395029
HFE: C187G
HLA-B: *HLA-B*5701*, *HLA-B*1502*, *HLA-B*5801*, *HLA-B18* subtype, *HLA-B39* subtype, *HLA-B44* subtype
HSPA1L: Met493Thr
UGT2B7: *UGT2B7*2* (His268Tyr)
Other genes that may be involved:
ABCB1; *ABCC6*; *ADHs*; *ICAM*; *UGT1A1*
Inhibits:
ABCC1; ABCC2
Induces:
CYP2B6

Drug Interactions
Acyclovir-valacyclovir may enhance the CNS-depressant effect of zidovudine. Doxorubicin and interferons may enhance the adverse/toxic effect of zidovudine. Doxorubicin may diminish the therapeutic effect of zidovudine. Fluconazole and probenecid may decrease the metabolism of zidovudine. Ganciclovir-valganciclovir may enhance the adverse/toxic effect of reverse transcriptase inhibitors (nucleoside). Interferons and valproic acid may decrease the metabolism of zidovudine. Methadone may increase the serum concentration of zidovudine. Protease inhibitors may decrease the serum concentration of zidovudine, and of abacavir. Ribavirin may enhance the hepatotoxic effect of reverse transcriptase inhibitors (nucleoside). Rifamycin derivatives may increase the metabolism of zidovudine (exceptions: rifabutin). Zidovudine may diminish the therapeutic effect of stavudine. Trimethoprim may decrease the excretion of lamivudine. Lamivudine may diminish the therapeutic effect of zalcitabine.

Dosage
Dosage Forms: Tablet: Abacavir 300 mg, lamivudine 150 mg, and zidovudine 300 mg. [Oral administration].
Dose adjustment in special conditions: In renal (CrCl ≤50 mL/minute: avoid use) or hepatic (use contraindicated) impairment.

Abarelix

Brand Names
Europe
Austria: Plenaxis; **Germany**: Plenaxis; **Netherlands**: Plenaxis.

Chemistry
Abarelix: $C_{72}H_{95}ClN_{14}O_{14}$. Mw: 1416.06. N-Acetyl-3-(2-naphthyl)-D-alanyl-4-chloro-D-phenylalanyl-3-(3-pyridyl)-D-alanyl-L-seryl-N-methyl-L-tyrosyl-D-asparaginyl-L-leucyl-N^6-isopropyl-L-lysyl-L-prolyl-D-alaninamide. CAS-183552-38-7 (1997).

Pharmacologic Category
Antineoplastic Agents; Endocrine Therapy; Gonadotropin Releasing Hormone Antagonists. (ATC-Code: L02BX01).

Therapeutic Use
Palliative treatment of advanced symptomatic prostate cancer.

Pregnancy and Lactation Implications
Should not be used in women.

Contraindications
Hypersensitivity to abarelix or any ingredient in the formulation. Not indicated in women or pediatric patients.

Warnings and Precautions
Risk of allergic reactions. May cause fetal harm. Increases in serum AST (SGOT) or ALT (SGPT) concentrations. Prolongation of QTc interval. Risk of decreased bone mineral density following chronic therapy with GnRH antagonists and agonists.

Adverse Reactions
Cardiovascular: Hot flushes, peripheral edema.
Central Nervous System: Dizziness, fatigue, headache, sedation, sleep disturbance.
Gastrointestinal: Constipation, diarrhea, nausea.
Neuromuscular and Skeletal: Back pain.
Renal: Dysuria, frequent urination, urinary retention, urinary tract infection.
Respiratory: Upper respiratory tract infection.
Miscellaneous: Breast enlargement, breast pain or nipple tenderness.

Pharmacogenetics
Genes that may be involved:
GNRHR

Drug Interactions
No formal drug interaction studies to date. Metabolism unlikely to involve CYP isoenzymes.

Dosage
Dosage Forms: Injection, powder for reconstitution. [I.M. administration].

Pharmacokinetics and Pharmacodynamics
Absorption: Slow.
Distribution: Extensive (approximately 4040 L).
Protein binding: 96-99%.
Metabolism: Unlikely to involve CYP isoenzymes.
Half-life: 13 days.
Time to peak: About 3 days after a single 100 mg dose.
Excretion: In urine, mainly as unchanged drug.

Special Considerations
In Women: Not for use in women.
In Elderly Subjects: No substantial differences in safety relative to younger adults.

Abatacept

Brand Names

Europe

Austria: Orencia; **Belgium**: Orencia; **Czech Republic**: Orencia; **Denmark**: Orencia; **Estonia**: Orencia; **Finland**: Orencia; **France**: Orencia; **Germany**: Orencia; **Greece**: Orencia; **Hungary**: Orencia; **Ireland**: Orencia; **Italy**: Orencia; **Latvia**: Orencia; **Luxembourg**: Orencia; **Netherlands**: Orencia; **Poland**: Orencia; **Portugal**: Orencia; **Romania**: Orencia; **Slovakia**: Orencia; **Spain**: Orencia; **Sweden**: Orencia; **UK**: Orencia.

North America

Canada: Orencia; **USA**: Orencia.

Latin America

Argentina: Orencia.

Chemistry

Abatacept: ($C_{1965}H_{3080}N_{479}O_{695}S_{16}$). Mw: approx. 92000.01 (46000.01 per chain). 1-25-Oncostatin M (human precursor) fusion protein with CTLA-4 (antigen)(human) fusion protein with immunoglobulin G_1 (human heavy chain fragment). CAS-332348-12-6 (2004).

MGVLLTQRTL	LSLVLALLFP	SMASMAMHVA	QPAVVLASSR	GIASFVCEYA
SPGKATEVRV	TVLRQADSQV	TEVCAATYMM	GNELTFLDDS	ICTGTSSGNQ
VNLTIQGLRA	MDTGLYICKV	ELMYPPPYYL	GIGNGTQIYV	IDPEPCPDSD
QEPKSSDKTH	TSPPSPAPEL	LGGSSVFLFP	PKPKDTLMIS	RTPEVTCVVV
DVSHEDPEVK	FNWYVDGVEV	HNAKTKPREE	QYNSTYRVVS	VLTVLHQDWL
NGKEYKCKVS	NKALPAPIEK	TISKAKGQPR	EPQVYTLPPS	RDELTKNQVS
LTCLVKGFYP	SDIAVEWESN	GQPENNYKTT	PPVLDSDGSF	FLYSKLTVDK
SRWQQGNVFS	CSVMHEALHN	HYTQKSLSLS	PG**K*	

** -C-terminus (predominant species)

* -C-terminus (cDNA)

Underlined: -N-glycosylation

Pharmacologic Category

Antirheumatic Drugs. (ATC-Code: L04AA24).

Mechanism of Action

Blocks CD28 interaction between antigen-presenting cells and T cells. Decreases T-cell proliferation and inhibits production of TNF, interferon-gamma, and interleukin-2. Suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen-specific production of interferon gamma.

Therapeutic Use

Treatment of adult rheumatoid arthritis (as monotherapy or in combination with other disease-modifying anti-rheumatic drugs) or juvenile idiopathic arthritis (as monotherapy or in combination with methotrexate).

Pregnancy and Lactation Implications

Should be used during pregnancy only if clearly needed (risk of autoimmune disease in fetus). Not recommended during lactation.

Contraindications

Hypersensitivity to abatacept or any component of the formulation.

Warnings and Precautions

Hypersensitivity, anaphylaxis or anaphylactoid reactions might occur. May affect defenses against malignancies. Risk of lymphoma. Caution with chronic obstructive pulmonary disease (COPD). Screening for viral hepatitis prior to use. Live vaccines should not be given concurrently or within 3 months of discontinuation of therapy.

Adverse Reactions

Cardiovascular: Hypertension, hypotension.
Central Nervous System: Dizziness, headache.
Dermatologic: Cellulitis, pruritus, rash, urticaria.
Gastrointestinal: Abdominal pain, diarrhea, diverticulitis, dyspepsia, nausea.
Genitourinary: Pyelonephritis, urinary tract infection.
Hematologic: Acute lymphocytic leukemia.
Neuromuscular and Skeletal: Back pain, limb pain.
Respiratory: Bronchitis, COPD exacerbation, cough, dyspnea, lung cancer, nasopharyngitis, pneumonia, rhinitis, rhonchi, sinusitis, upper respiratory tract infection, wheezing.
Miscellaneous: Anaphylaxis, anaphylactoid reactions, antibody formation, disease flare, fever, flushing, herpes simplex and influenza infections, hypersensitivity, infusion-related reactions, joint wear, lymphoma, malignancies (including bile duct, bladder, breast, cervical, melanoma, myelodysplastic syndrome, prostate, renal, skin, thyroid and uterine), ovarian cyst, varicella infection.

Pharmacogenetics

Genes that may be involved:
CD28; *CD80*; *CD86*; *CTLA4*; *IFNG*; *IL2*; *TNF*

Drug Interactions

Should not be used in combination with anakinra or TNF-blocking agents (risk of infections). Live vaccines should not be administered during treatment or for 3 months following completion of the same. Concomitant use with SSRIs, lithium, valproic acid and carbamazepine may produce additive effects.

Nutrition/Nutraceutical Interactions

Herbs/Nutraceuticals: Avoid echinacea (immunostimulant properties).

Dosage

Dosage Forms: Injection, powder for reconstitution: 250 mg (contains maltose). [I.V. administration].

Pharmacokinetics and Pharmacodynamics

Absorption: Following multiple I.V. infusions, steady-state serum concentrations reached at 60 days. Systemic accumulation does not appear to occur.
Distribution: V_{ss}: 0.02-0.13 L/kg.
Half-life: 8-25 days.

Special Considerations

In Elderly Subjects: Use with caution (higher incidence of infections and malignancies).
Monitoring Parameters: Signs and symptoms of infection and infusion reaction, hepatitis and tuberculosis screening prior to therapy initiation.

Abciximab

Brand Names

Europe

Austria: Reopro; **Belgium**: Reopro; **Bulgaria**: Reopro; **Czech Republic**: Reopro; **Denmark**: Reopro; **Finland**: Reopro; **France**: Reopro; **Germany**: Reopro; **Greece**: Reopro; **Hungary**: Reopro; **Ireland**: Reopro; **Italy**: Reopro; **Luxembourg**: Reopro; **Netherlands**: ReoPro; **Poland**: ReoPro; **Portugal**: ReoPro; **Romania**: ReoPro; **Slovenia**: Reopro; **Spain**: Reopro; **Sweden**: Reopro; **UK**: Reopro.

North America

Canada: Reopro; **USA**: Reopro.

Latin America

Brazil: Reopro; **Mexico**: Reopro.

Chemistry

Abciximab: Mw: approx. 47600.01. (1) Immunoglobulin G_1, (human-mouse monoclonal c7E3 clone p7E3VHhCg1 Fab fragment anti-human glycoprotein IIb/IIIa receptor), disulfide with human-mouse monoclonal c7E3 clone p7E3VkhCk light chain; (2) Immunoglobulin G_1 (human-mouse monoclonal c7E3 clone p7E3VHhCg1 Fab fragment anti-human glycoprotein IIb/IIIa receptor), disulfide with human-mouse monoclonal c7E3 clone p7E3VkhCk light chain. CAS-143653-53-6 (1994).

Pharmacologic Category

Antithrombotic Agents; Platelet-aggregation Inhibitors; Glycoprotein IIb/IIIa Inhibitor. (ATC-Code: B01AC13).

Mechanism of Action

Fab antibody fragment of the chimeric human-murine monoclonal antibody 7E3. Inhibits platelet aggregation by binding to IIb/IIIa receptors.

Therapeutic Use

Prevention of acute cardiac ischemic complications in patients at high risk for abrupt closure of the treated coronary vessel and patients at risk of restenosis. Adjunct with heparin to prevent cardiac ischemic complications in patients with unstable angina not responding to conventional therapy when a percutaneous coronary intervention is scheduled within 24 hours.

Unlabeled Use

Myocardial infarction. Acute ischemic stroke.

Pregnancy and Lactation Implications

Not known whether fetal harm can be caused or if reproduction capacity can be affected. Caution during lactation.

Contraindications

Hypersensitivity. Active internal hemorrhage or recent GI or GU bleeding. History of cerebrovascular accident. Clotting abnormalities or recent administration of oral anticoagulants (within 7 days). Thrombocytopenia. Recent major surgery or trauma. Intracranial tumor. Arteriovenous malformation. Aneurysm. Severe uncontrolled hypertension. Vasculitis. Use of dextran before percutaneous transluminal coronary angioplasty. Concomitant use of another parentheral GP IIb/IIIa inhibitor.

Warnings and Precautions

Anaphylaxis/hypersensitivity reactions, thrombocytopenia as well as diminished efficacy might occur due to human antichimeric antibody formation. Bleeding complications (use with extreme caution in platelet counts <150,000/mm^3, hemorrhagic retinopathy, previous history of gastrointestinal disease, recent thrombolytic therapy and in chronic dialysis. Use caution with administration of other drugs affecting hemostasis. Diminished drug efficacy (human antichimeric antibody formation). Use with caution in patients weighing <75 kg or >65 years of age (increased risk of bleeding).

Adverse Reactions

Cardiovascular: Arteriovenous fistula, bradycardia, chest pain, complete AV block, embolism, hypotension, incomplete AV block, nodal arrhythmia, palpitation, peripheral edema, pseudoaneurysm, stroke, thrombophlebitis, ventricular tachycardia.
Central Nervous System: Abnormal thinking, abnormal vision, agitation, anxiety, coma, confusion, diplopia, dizziness, headache, intracranial hemorrhage.
Dermatologic: Bullous eruption, cellulites, increased diaphoresis, petechiae, pruritus.
Endocrine and Metabolic: Diabetes mellitus, hyperkalemia.
Gastrointestinal: Abdominal pain, diarrhea, dyspepsia, gastroesophageal reflux, ileus, nausea, vomiting, xerostomia.
Genitourinary: Dysuria, prostatitis.
Hematologic: Anemia, leukocytosis, minor and major bleeding, thrombocytopenia.
Local: Injection site pain.
Neuromuscular and Skeletal: Back pain, hypertonia, muscle contractions, myalgia, weakness.
Respiratory: Bronchitis, bronchospasm, pleural effusion, pneumonia, pulmonary embolism.
Renal: Urinary incontinence, urinary retention.
Miscellaneous: Allergic reactions/anaphylaxis, cystalgia, inflammation, pain, peripheral coldness.

Pharmacogenetics

Caution and personalized dose adjustment in patients with the following genotypes:
ITGB3: Ex.2/Leu33Pro
Other genes that may be involved:
CYP1A2; *CYP2C19*; *ITGA2*; *P2RY1*

Drug Interactions

Antiplatelet agents may enhance the anticoagulant effect of anticoagulants. Antiplatelet agents and dasatinib may enhance the anticoagulant effect of other antiplatelet agents. Dextran may enhance the anticoagulant effect of abciximab. Antiplatelet agents may enhance the adverse/toxic effect of drotrecogin alpha (risk of bleeding), and of ibritumomab (impaired platelet function and risk of bleeding). Abciximab may enhance the potential for allergic or hypersensitivity reactions to monoclonal antibodies (thrombocytopenia or diminished therapeutic effects. Exceptions: alefacept). Nonsteroidal anti-inflammatory agents may enhance the adverse/toxic effect of antiplatelet agents (risk of bleeding). ω-3-Acid ethyl esters, and prostacyclin analogs may enhance the antiplatelet effect of antiplatelet agents. Pentosan polysulfate sodium may enhance the adverse/toxic effect of antiplatelet agents (risk of bleeding). Antiplatelet agents may enhance the adverse/toxic effect of salicylates (risk of bleeding). Antiplatelet agents may enhance the adverse/toxic effect of tositumomab and iodine ^{131}I tositumomab (bleeding-related adverse events).

Nutrition/Nutraceutical Interactions

Herbs/Nutraceuticals: Herbs with anticoagulant/antiplatelet properties (e.g. alfalfa, anise, bilberry) may enhance the adverse/toxic effect of antiplatelet agents (risk of bleeding).

Dosage

Dosage Forms: Injection, solution: 2 mg/mL (5 mL). [I.V. administration].

Genes

A

A2M (alpha-2-macroglobulin)

Alternative Names
Alpha-2M; C3 and PZP-like alpha-2-macroglobulin domain-containing protein 5.

Alternative Symbols
A2MG, *CPAMD5*, *DKFZp779B086*, *FWP007*, *S863-7*.

Codes
OMIM: 103950. **PharmGKB**: PA24357.

Gene
Locus: 12p13.31.
Size: 48.44 kb, 36 Exons.

RNA
Transcripts/Variants: A2M-001: 4844 bp. A2M-002: 623 bp. A2M-003: 533 bp. A2M-004: 533 bp. A2M-005: 692 bp. A2M-006: 546 bp. A2M-007: 729 bp. A2M-008: 509 bp.
Expression: **Organs**: Liver. **Tissues**: Hematopoietic tissue. **Fluids**: Blood, Plasma. **Subcellular localization**: Extracellular.

Protein
Size: A2M-001: 163.3 kDa, 1474 aa. A2M-002: 18.72 kDa, 168 aa.
Family: Protease inhibitor I39 (α_2-macroglobulin) family.
Category: Transport carrier.
Motifs/domains: Peptide stretch, called "bait region" with specific cleavage sites for different proteinases.

Function
A protease inhibitor and cytokine transporter. Inhibits many proteases, including trypsin, thrombin and collagenase. A2M is implicated in Alzheimer's disease (AD) due to its ability to mediate clearance degradation of Aβ, the major component of β-amyloid deposits. It is able to inhibit all four classes of proteinases by a unique "trapping" mechanism. This protein has a peptide stretch, called "bait region", which contains specific cleavage sites for different proteinases. When a proteinase cleaves bait region, a conformational change is induced in protein which traps proteinase. The entrapped enzyme remains active against low molecular weight substrates (activity against high molecular weight substrates greatly reduced). Following cleavage in bait region, a thioester bond is hydrolyzed and mediates covalent binding of protein to proteinase. A2M is a serum protease inhibitor mediating clearance and degradation of Aβ, the major component of β-amyloid deposits; a protease inhibitor and cytokine transporter. Associates with TGFBs and forms latent complexes; associates with PDGFVB; has endopeptidase inhibitor activity; serine-type endopeptidase inhibitor activity; protein binding; wide-spectrum protease inhibitor activity; enzyme binding.

Related Diseases
Acne vulgaris; Acute kidney failure; Acute liver failure; Acute-phase reaction; Adenocarcinoma; Adrenal gland neoplasms; Adrenocortical adenoma; **Alzheimer's disease**; Amyloidosis; Arteriosclerosis; Autistic disorder; Autoimmune diseases; **Blood protein disorders**; Bone marrow neoplasms; Brain injuries; Breast neoplasms; Cardiovascular disease; Cataract; Cholangiocarcinoma; Cholangitis; Cholestasis; Colonic neoplasms; Colorectal neoplasms; Dementia; Diabetic neuropathy; Dyslipidemias; Edema; Endometriosis; **Emphysema due to A2M deficiency**; Esophageal neoplasms; Essential tremor; Ewing's sarcoma; Experimental arthritis; Experimental autoimmune encephalomyelitis; Experimental liver cirrhosis; Experimental liver neoplasms; Experimental mammary neoplasms; Fat necrosis; Fatty liver; Fever; Female genital neoplasms; Female infertility; Head and neck neoplasms; Hemolytic-uremic syndrome; Hepatic encephalopathy; Hepatitis; Hepatocellular carcinoma; Hodgkin's disease; Hyperalgesia; Hypospadias; **Inflammation**; Intrahepatic cholestasis; Iron metabolism disorders; Leishmaniasis; Liver diseases; Liver neoplasms; Lung neoplasms; Macular degeneration; Male infertility; Melanoma; Amelanotic melanoma; Metabolic syndrome; Multiple myeloma; Multiple sclerosis; *Mycobacterium* infections; Myocardial infarction; Neoplasms; **Nephrotic syndrome**; Neural tube defects; Niemann-Pick disease, type C; Non-small cell lung carcinoma; Obesity; **Obstructive lung diseases**; Osteoporosis; Ovarian neoplasms; Pain; Pancreatic neoplasms; Panic disorder; Parkinson's disease; Pneumonia; Polycystic ovary syndrome; Prostatic neoplasms; Pruritus; Adult respiratory distress syndrome; Respiratory hypersensitivity; **Rheumatoid arthritis**; Salivary gland neoplasms; Seizures; Skin neoplasms; Spermatocele; Spinal cord injuries; Spinal dysraphism; Squamous cell carcinoma; Stomach diseases; Stomach neoplasms; Stomach ulcer; Testicular neoplasms; Thrombophilia; Thrombosis; Toxic hepatitis; Traumatic brain hemorrhage; Trypanosomiasis; Tuberculosis; Urinary bladder neoplasms; Uterine cervical neoplasms; Uterine neoplasms; Vaginal neoplasms; Vascular diseases; Venous thrombosis; Vomiting.

Related Drugs
1-Naphthylisothiocyanate; 3,4-Dichloroaniline; Acetaminophen; Antimony; Antimony potassium tartrate; Bacitracin; Becaplermin; beta-Naphthoflavone; Cisplatin; Clofibrate; Clofibric acid; Corticosterone; Dexamethasone; Dimethylnitrosamine; Dimethyl sulfoxide; Ethinyl estradiol; Ethinyl estradiol-desogestrel combination; Fluticasone propionate; Furan; Glucocorticoids; Imidazolium-bis(imidazole)dimethylsulfoxideimidazotetrachlororuthenate(III); Isoniazid; Lipopolysaccharides; Mercury; Methapyrilene; Naphthalene; Nitrosobenzylmethylamine; Pirinixic acid; Progesterone; Sodium arsenite; Thioacetamide; Turpentine.

Animal Models
Chimeric mice. Herring and coworkers identified the up-regulation of *a2m* in TgCRND8 mice (carrying human APP (Swedish/Indiana)) by affecting Aβ receptor/transporter molecules, facilitating Aβ clearance by brain vascularization. The up-regulation of *a2m* was also investigated by Petrusz and colleagues in transgenic mice that overexpressed rat androgen-binding protein (ABP) in their testes, resulting in a spermatogenesis impairment. The up-regulated a2m in these transgenic mice seemed to mediate a testicular response to the reduced levels of androgens and therefore, to modulate the spermatogenesis deficit.
Transgenic mice. *A2m* knockout mice are not only viable, but more resistant to endotoxin. They produce normal-sized litters and show no obvious phenotypic abnormalities. Murine a2m binds TGF-β and inhibits TGF-β-receptor interactions, which might explain the endotoxin-insensitive phenotype of knockout mice.
A2M-deficient (*MAM*-/-) mice were reported by Hochepied and colleagues to be significantly protected against lethal systemic inflammation induced by the tumor necrosis factor (TNF). As a result, the MAM deficiency shows a high metabolic tolerance to TNF, being essential for studying the pathogenesis of Gram-negative septic shock. Also using this type of transgenic mice (*MAM*-/-), Umans et al defined *in vivo* the role of macroglobulins in pancreatitis by analyzing the clinical symptoms and the expression of different cytokines and polypeptide factors. Once acute pancreatitis was induced in A2M-deficient mice, severe clinical symptoms and high mortality were observed, together with the significant induction of interleukin-1-receptor antagonist mRNA and most polypeptide factors (tumor necrosis factor-alpha, tumor necrosis factor-beta, beta-lymphotoxin, and interferon-gamma mRNA).

Allelic Variants
Total variants: 378.

Selected SNPs
rs669. **HGVS**: NM_000014.4: c.2998A>G; NP_000005.2: p.I1000V; NT_009714.16: g.1991241T>C. Susceptibility to Alzheimer's disease. A sequence polymorphism near the thiolester site of the gene, changing Val1000 (GTC) to Ile (ATC); the 2 alleles had frequencies of 0.30 and 0.70, respectively. No difference of A2M serum levels observed for these 2 alleles. Increased frequency of G/G genotype from 0.07 in controls to 0.12 in AD. Synergistic effect with a myeloperoxidase promoter polymorphism genotype (-463G/G). **Alleles**: African: A: 0.658, G: 0.342; Asian: A: 0.875-0.967, G: 0.033-0.125; European: A: 0.658-0.750, G: 0.250-0.342; Multi-national: A: 0.778, G: 0.222. **Genotypes**: African: A/A: 0.467, A/G: 0.383, G/G: 0.150; Asian: A/A: 0.795-0.933, A/G: 0.067-0.159, G/G: 0.000-0.045; European: A/A: 0.417-0.625, A/G: 0.250-0.483, G/G: 0.100-0.125; Multi-national: A/A: 0.741, A/G: 0.074, G/G: 0.185.
rs226379. **HGVS**: NT_009714.16: g.2027559T>C. Associated with Alzheimer's disease. **Alleles**: African: A: 0.593, G: 0.407; Asian: A: 0.867-0.935, G: 0.065-0.133; European: A: 0.630-0.750, G: 0.250-0.370; North American: A: 0.543-0.625, G: 0.375-0.457. **Genotypes**: African: A/A: 0.356, A/G: 0.475, G/G: 0.169; Asian: A/A: 0.778-0.913, A/G: 0.043-0.178, G/G: 0.043-0.044; European: A/A: 0.370-0.625, A/G: 0.250-0.522, G/G: 0.109-0.125; North American: A/A: 0.348-0.375, A/G: 0.391-0.500, G/G: 0.125-0.261.
rs226380. **HGVS**: NM_000014.4: c.-28T>G; NT_009714.16: g.2027447A>C. **Alleles**: African: G: 0.850, T: 0.150; Asian: G: 0.133-0.167, T: 0.833-0.867; European: G: 0.438-0.458, T: 0.542-0.562; Multi-national: G: 0.130, T: 0.870; North American: G: 0.848, T: 0.152. **Genotypes**: African: G/G: 0.700, G/T: 0.300, T/T: 0.000; Asian: G/G: 0.022-0.067, G/T: 0.200-0.222, T/T: 0.733-0.756; European: G/G: 0.217-0.250, G/T: 0.375-0.483, T/T: 0.300-0.375; North American: G/G: 0.696, G/T: 0.304, T/T: 0.000.
rs226405. **HGVS**: NM_000014.4: c.1915G>A; NP_000005.2: p.Asp639Asn; NT_009714.16: g.2007207T>C. **Alleles**: African: A: 0.017, G: 0.983; Asian: A: 0.000, G: 1.000; European: A: 0.000, G: 1.000; Multi-national: A: 0.000, G: 1.000. **Genotypes**: African: A/G: 0.033, G/G: 0.967; Asian: A/G: 0.000, G/G: 1.000; European: A/G: 0.000, G/G: 1.000; Multi-national: A/G: 0.000, G/G: 1.000.
rs3026229. **HGVS**: NT_009714.16: g.1978874G>T. **Alleles**: African: A: 0.195, C: 0.805; Asian: A: 0.022-0.065, C: 0.935-0.978; European: A: 0.089-0.188, C: 0.812-0.911; North American: A: 0.205, C: 0.795. **Genotypes**: African: A/A: 0.051, A/C: 0.288, C/C: 0.661; Asian: A/A: 0.000-0.043, A/C: 0.043-0.044, C/C: 0.913-0.956; European: A/A: 0.000, A/C: 0.179-0.375, C/C: 0.625-0.821; North American: A/A: 0.045, A/C: 0.318, C/C: 0.636.
rs10771309. **HGVS**: NT_009714.16: g.1977580C>A. **Alleles**: Asian: A: 0.033-0.111, C: 0.889-0.967; European: A: 0.342, C: 0.658. **Genotypes**: Asian: A/A: 0.000-0.044, A/C: 0.067-0.133; European: A/A: 0.100, A/C: 0.483.
rs12309184. **HGVS**: NT_009714.16: g.2027808G>A. **Alleles**: African: A: 0.025, G: 0.975; Asian: A: 0.000, G: 1.000; European: A: 0.000, G: 1.000. **Genotypes**: African: A/G: 0.050, G/G: 0.950; Asian: A/G: 0.000, G/G: 1.000; European: A/G: 0.000, G/G: 1.000.
rs1800433. **HGVS**: NM_000014.4: c.2915G>A; NP_000005.2: p.C972Y; NT_009714.16: g.1991324C>T. A mutation within the thiolester site, changing Cys972 (TGT) to Tyr (TAT). Since activation of the internal thiolester formed between Cys972 and Gln975 in each of the subunits of the tetrameric A2M molecule is involved in the covalent crosslinking of the activating proteinase, this mutation was predicted to interfere with A2M function; however, A2M serum levels are within normal range in mutants.
rs1805667. **HGVS**: NT_009714.16: g.1978940A>C. **Alleles**: African: G: 0.583, T: 0.417; Asian: G: 0.062-0.111, T: 0.889-0.938; European: G: 0.250-0.342; T: 0.658-0.750; North American: G: 0.591, T: 0.409. **Genotypes**: African: G/G: 0.350, G/T: 0.467, T/T: 0.183; Asian: G/G: 0.044-0.042, G/T: 0.042-0.133, T/T: 0.822-0.917; European: G/G: 0.100-0.125, G/T: 0.250-0.483, T/T: 0.417-0.625; North American: G/G: 0.318, G/T: 0.545, T/T: 0.136.
rs1805688. **HGVS**: NT_009714.16: g.1979074A>G. **Alleles**: African: C: 0.092, T: 1.000; Asian: C: 0.000, T: 1.000; European: C: 0.000, T: 1.000. **Genotypes**: African: C/T: 0.183, T/T: 0.817; Asian: C/C: 0.000, T/T: 1.000. European: C/C: 0.000, T/T: 1.000.

rs3759277. **HGVS**: NG_011717.1: g.52360C>T; NM_000014.4: c.4366+137C>T; NT_009714.17: g.1981323G>A. **Alleles**: African: C: 0.183, T: 0.817; Asian: C: 0.875, T: 0.125; European: C: 0.542, T: 0.458; North American: C: 0.159, T: 0.841. **Genotypes**: African: C/C: 0.017, C/T: 0.333, T/T: 0.650; Asian: C/C: 0.833, C/T: 0.083, T/T: 0.083; European: C/C: 0.300, C/T: 0.483, T/T: 0.217; North American: C/C: 0.000, C/T: 0.318, T/T: 0.682.

Ivs1Del: A deletion of the intron that separates exons 1 and 2, resulting in fusion of the two exons that code the bait domain of the *A2M* gene.

Arg681His: A G-to-A transition in exon 17, predicting an Arg-to-His substitution at position 681. In the mutant allele a MaeII restriction site was lost and a new NspHI site was created.

Ex18Del: Susceptibility to Alzheimer's disease. A 5'-splice site deletion in exon 18 (*A2M-2*). This exon encodes 'exon II' of the bait domain of *A2M*, which functions to attract and trap proteases. The *A2M-2* deletion confers increased risk for Alzheimer's disease.

5-bp Del: A deletion of 5 bases from -7 to -3 from the 5' splice site of exon 2.

Evolution

Human α_2-macroglobulin, complement component C3 and complement component C4 contain a unique activatable β-cysteinyl-γ-glutamyl thiol ester and have a common evolutionary origin. C5 also shows sequence homology to A2M.

Genomics and Pharmacogenomics

Alzheimer's disease: *A2M* has been recognized as a candidate gene for late-onset Alzheimer's disease (AD), but the association between several polymorphisms in the *A2M* gene and risk for AD remained controversial. Moreover, little is known regarding the effects of polymorphisms in the *A2M* promoter region on AD susceptibility. Song et al set out to detect polymorphisms in the *A2M* promoter region, and then evaluate their relationship to sporadic AD (SAD). One SNP (-88A/G) in the proximal promoter region was found by sequencing, and further analyzed with an established 25T/G polymorphism in 179 SAD patients and 179 age-gender-matched controls. Allele A in the -88A/G polymorphism was more prevalent in cases, with a 1.7-folded risk for SAD, while the G allele in 25T/G was less prevalent in cases, with a 43% reduced risk for SAD. After adjusting the effects of age, gender and APOE-ε4 allele status in a logistic regression model, the protective effects of -88G and 25G on SAD still remained. Individuals who carried the haplotype -88G/25G had a significant 44% reduced risk for SAD compared to those who did not carry it, while haplotype -88A/25T carriers had an increased risk for SAD compared to those who did not carry it. This study supports the hypothesis that haplotype -88G/25G might play a protective role in the development of SAD, and the protective effects of -88G and 25G were independent of APOE-ε4 allele.

A2M is a highly plausible candidate gene for Alzheimer's disease (AD) in a region of chromosome 12 which has numerous independent reports of genetic linkage. A 5 bp deletion in *A2M* associated with AD in a subset of the National Institute of Health (NIMH) Genetics Initiative AD family sample. Efforts to replicate this association in case-control samples were largely negative, while those in family samples were more positive. Variable findings regarding this deletion, along with variable reports of association with V1000I, another polymorphism in the gene, result from linkage disequilibrium in the area as well as ascertainment differences between family-based and case-control studies. Seven novel polymorphisms were identified in the full NIMH sample of 1439 individuals in 437 families. There is genetic association of the 5 bp deletion and two novel polymorphisms with AD. Substantial linkage disequilibrium was detected across the gene as a whole, and haplotype analysis also showed significant association between AD and groups of *A2M* polymorphisms. Several of these polymorphisms and haplotypes remain significantly associated with AD even after correction for multiple testing.

A2M, the A2M receptor (LRP1), two low density lipoprotein-related protein (LRP) ligands, APOE, APP, BACE, BLMH, PS1, and PS2 are probably genetically linked in regulation of brain amyloidogenesis. A2M is a carrier protein for β-amyloid decreasing fibril formation and influencing amyloid neurotoxicity. A2M enhances clearance of β-amyloid via low-density lipoprotein receptor-related protein in primary Tg2576 transgenic mouse cortical neurons. In recent years, there have been over 100 genetic studies in different countries debating the controversial role of a five-base-pair intronic deletion in the *A2M* gene in LOAD. The sibship disequilibrium test revealed a significant association between *A2M* and AD; and the inheritance of a deletion in the *A2M* gene at the 5'-splice site of exon II of the bait region (exon 18)(*A2M-2*) confers increased risk for AD, but these findings could not be replicated by others in different populations and races, though in Koreans the *A2M*-D allele might represent a modest risk factor for LOAD. The *A2M*-V1000I polymorphism (GTC/ATC) was also found to be associated with AD, but no association was found between the A2M polymorphisms (intronic 5-bp deletion, Ile1000Val) and AD. *A2M* G2998A mutation is not associated with AD in the Chinese population. In addition, *A2M* is not associated with age at onset, duration of illness, senile plaques, dystrophic neurites or NFT in AD. No change in *A2M* mRNA, protein, or protein expression could be found in AD and it appears that *A2M* is not genetically associated with LOAD. In Spanish patients, the *A2M*-G/G genotype is more frequent in AD (8.1%) than in controls (3.79%), and the homozygous *A2M* deletion (A2M-D/D) is absent in controls and appears in 5.21% of AD patients. The integration of *A2M*-related polymorphic variants in single clusters revealed clear differences in the distribution of the *A2M* genotypes between AD and controls. Data indicate that the *A2M* gene polymorphism can confer an increased risk for AD with an estimated Mantel-Haenszel ratio of 1.5 and no age- or gender-dependent increase in *A2M* gene allele frequencies. Plasma from patients homozygous for the *A2M* deletion show normal A2M subunit size, conformation, and proteinase inhibitory activity. In some cases, A2M exhibits a marked increase in TGFB1 binding. Methylamine-treated A2M mutant samples show modest elevations in β-amyloid binding to A2M compared with samples from patients lacking the deletion, suggesting a possible functional basis by which *A2M* deletion may influence multifactorial AD pathogenesis.

Genetic association with LOAD susceptibility studied in 738 Caucasian families (4704 individuals) and an independent case-control dataset with 296 cases and 566 controls explored 11 candidate genes (47 SNPs common to both samples). In addition to tests for main effects and haplotypes, MDR-PDT was used to search for gene-gene interactions in the family data. Significant haplotype effects in *ACE* in family and case-control samples using standard and cladistic haplotype models were observed. *ACE* was also part of significant 2 and 3-locus MDR-PDT joint effects models with A2M, which mediates the clearance of β-amyloid, and leucine-rich repeat transmembrane-3 (*LRRTM3*), a nested gene in α-3catenin (*CTNNA3*) which binds presenilin-1. These genes are related to β-amyloid clearance; thus this constellation of effects might constitute an axis of susceptibility for LOAD.

A panel of 15 proteins, including complement factor-H (CFH) and A2M, validated as AD-specific plasma biomarkers. Both CFH and A2M show positive correlations with hippocampal metabolite ratio N-acetylaspartate/myo-inositol (NAA/mI) in AD. Association of plasma CFH and A2M with hippocampal NAA/mI in AD subjects suggests that these proteins may reflect disease progression in early AD.

Fluticasone propionate: In patients with asthma, fluticasone induces reduction in A2M plasma levels. No pharmacogenetic data are available.

Glucocorticoids: A detailed time course of the assembly and disassembly of a STAT3-dependent, glucocorticoid-supplemented enhanceosome for the *A2M* gene has been described and compared with a detailed time course of transcription of the gene by run-on analysis. The glucocorticoid receptor (GR) can associate with the enhanceosome without STAT3. The enhanceosome contains c-Jun/c-Fos and OCT-1 constitutively. All these factors (GR, c-Jun, OCT-1) have transcription activation domains, but STAT3 is required for the observed transcriptional increase. The time course of enhanceosome occupation by GR and tyrosine-phosphorylated STAT3 shows that these transcription factors precede the arrival of RNA polymerase II (Pol II) by approximately 5-10 min. The enhanceosome remains assembled for approximately 90 min in the continued presence of both inducers. When IL6 and dexamethasone are removed (after 30 min of treatment), the disappearance within an additional 30 min of the established enhanceosome indicates that renewal of STAT3 and GR binding must occur in the continued presence of IL6+Dex. Compared with the total nuclear tyrosine-phosphorylated STAT3 capable of binding DNA, the chromatin-associated STAT3 resists dephosphorylation and appears to recycle to maintain the enhanceosome. Run-on transcription shows a lag after full enhanceosome occupation that can be largely but not completely explained by the approximately 30 min transit time of Pol II across the *A2M* locus.

Inflammation: Acute-phase protein synthesis in liver during inflammation is regulated via cytokines and glucocorticoids. Using quantitative reverse transcription (RT)-PCR analysis and immunoassay, it has been shown that the acute-phase protein, A2M, is activated after systemic inflammation induced by lipopolysaccharide (LPS) or localized inflammation induced by turpentine oil (TO). Addition of heme during LPS-induced inflammation can boost the expression of A2M, whereas blocking heme synthesis (by succinyl acetone) or enhancing its consumption in parallel biosynthetic pathways (cytochrome P450 induction by phenobarbital) decreases A2M expression. This decrease is abolished by exogenous heme supplementation. Heme supplementation is also able to increase A2M response in female rats to a level similar to that in male rats providing a new insight into the puzzling sexual dimorphism observed previously during localized inflammation. Heme might be considered a regulatory element in controlling liver A2M expression during inflammation.

Nephrotic syndrome: In both nephrotic syndrome (NS) and hereditary analbuminemia in the Nagase analbuminemic rat (NAR), the plasma protein concentration is nearly normal since albumin is replaced by several high molecular weight proteins. In rats these include protease inhibitors A2M, a 720 kDa positive acute phase protein (APP) and α_1-inhibitor 3 (α_1-I3), a 180 kDa negative APP. There is no known stimulus to increase α_1-I3 synthesis, but like albumin and other negative APPs its synthesis decreases during inflammation by transcriptional down-regulation. In hypoalbuminemic states gene transcription of other positive and negative APPs is increased. A2M is increased significantly (12-fold) in NAR and by approximately 50-fold in rats with NS compared to control. The α_1-I3 concentration is twice normal in NAR or NS compared to controls, providing approximately half of the total plasma protein. Hepatic *A2M* mRNA increases only 30% in NAR and twofold in NS, suggesting post-transcriptional regulation.

Rheumatoid arthritis: Genetic associations of *TNFR2*, *VDR* (*Bsm* I and *Fok I*), *A2M*, *GSTT1*, *GSTM1* and *ACE* in South Asian and Caucasian patients with rheumatoid arthritis (RA) were assessed in a study by Ghelani et al. DNA samples from South Asians (134 cases, 149 controls) and Caucasians (137 cases, 150 controls) from the East Midlands of the United Kingdom were genotyped for seven polymorphisms. All cases were rheumatoid-factor positive. Significant genetic associations were observed with *TNFR2* R-R, *A2M* 1-1 and *GSTT1*-null among Caucasian patients. In South Asians, *VDR Bsm* I B-B genotype, *A2M* 2-2 genotype, and *GSTT1*-null genotype were associated with RA. In the majority of cases, recessive and multiplicative modes of inheritance explained the observed associations. The study demonstrated that ethnicity affects the genetic associations in RA.

Drug-Gene Interactions

1-Naphthylisothiocyanate: Increases expression of *A2M* mRNA. **3,4-Dichloroaniline**: Decreases expression of *A2M* mRNA. **Acetaminophen**: Increases expression of *A2M* mRNA. **Antimony**: Decreases expression of *A2M* mRNA. **Antimony potassium tartrate**: Decreases expression of *A2M* mRNA. **beta-Naphthoflavone**: Decreases expression of *A2M* mRNA. **Cisplatin**: Binds to A2M protein. **Clofibrate**: Increases expression of *A2M* mRNA. **Clofibric acid**: Affects expression of *A2M* mRNA. **Corticosterone**: Increases expression of *A2M* mRNA. **Dexamethasone**: Decreases expression of *A2M* mRNA. **Dimethylnitrosamine**: Decreases expression of *A2M* mRNA. **Dimethyl sulfoxide**: Increases expression of *A2M* mRNA. **Ethinyl estradiol**: Decreases expression of *A2M* mRNA. **Ethinyl estradiol-desogestrel combination**: Increases expression of A2M protein. **Furan**: Decreases expression of *A2M* mRNA. **Imidazolium-bis(imidazole)di methylsulfoxideimidazotetrachlororuthenate(III)**: Binds to A2M protein. **Isoniazid**: Increases expression of *A2M* mRNA. **Lipopolysaccharides**: Increase expression of *A2M* mRNA. **Mercury**: Decreases expression of *A2M* mRNA. **Methapyrilene**: Decreases expression of *A2M* mRNA. **Naphthalene**: Binds to A2M protein. **Nitrosobenzylmethylamine**: Increases expression of *A2M* mRNA. **Pirinixic acid**: Decreases expression of *A2M* mRNA. **Progesterone**: Affects expression of *A2M* mRNA. **Sodium arsenite**: Increases expression of *A2M* mRNA. **Thioacetamide**: Increases expression of *A2M* mRNA. **Turpentine**: Increases expression of *A2M* mRNA.

L Fernández-Novoa, I Carrera, L Corzo, A Bello, C Fraile, A McKay, R Cacabelos

ABCA1 (ATP-binding cassette, sub-family A (ABC1), member 1)

Alternative Names

ATP-binding cassette 1; ATP binding cassette transporter 1; ATP-binding cassette transporter A1; ATP-binding cassette, sub-family A member 1; ATP-binding cassette, sub-family A (ABC1), member 1; Cholesterol efflux regulatory protein; High density lipoprotein cholesterol level quantitative trait 13; High density lipoprotein deficiency, OTTHUMP00000021833; Tangier disease; Tangier type, 1.

Alternative Symbols

ABC-1, *ABC1*, *CERP*, *FLJ14958*, *HDLCQ13*, *HDLDT1*, *MGC164864*, *MGC165011*, *TGD*, *Tangier*.

Codes

OMIM: 600046. **PharmGKB**: PA24373.

Gene

Locus: 9q31.1.

Size: 147.15 kb, 50 Exons.

Regulatory sequence: Promoter (CAAT box), binding site. In the promoter region of *ABCA1* there are 7 putative SP1-binding sites, four sterol regulatory elements (SREs) similar to the SRE of the low density lipoprotein receptor (LDLR) promoter region, a CpG island, a possible weak TATA box, 2 distal CCAAT sequences, and binding sites for several other transcription factors.

Motifs/domains: Repetitive sequence ALU.

Structure: Numerous SP1 and putative sterol regulatory elements, binding sites for NFKB and activator proteins, conserved non coding sequences.

RNA

Transcripts/Variants: ABCA1-001: 1540 bp. ABCA1-002: 10494 bp. ABCA1-004: 923 bp. ABCA1-201: 1556 bp. ABCA1-003: 807 bp.

Expression: **Organs**: Brain, Liver, Mammary gland, Placenta, Prostate, Testis, Uterus (*Highly*); Adrenal gland, Kidney, Lung, Skin, Small intestine (*Moderately*); Bladder, Heart, Large intestine, Lymph node, Ovary, Pancreas, Spleen, Stomach, Thymus, Thyroid. **Tissues**: Bone marrow, Connective, Epithelial, Secretory, Striated/skeletal muscle (*Moderately*). **Cells**: Digestive, Leukocyte, Monocyte, Macrophage, Sertoli cell. **Subcellular localization**: Intracellular (cytoplasm, organelle, endosome); Plasma membrane.

Protein

Size: ABCA1-001: 41.12 kDa, 363 aa. ABCA1-002: 254.30 kDa, 2261 aa. ABCA1-004: 13.83 kDa, 123 aa. ABCA1-201: 13.64 kDa, 121 aa.

Family: ATP binding cassette superfamily; ABC transporter family; ABCA subfamily. Complete sequence of the yeast genome predicts the existence of 29 proteins belonging to the ubiquitous ATP-binding cassette (ABC) superfamily.

Using binary comparison, phylogenetic classification, and detection of conserved amino acid residues, the yeast ABC proteins have been classified in a total of 6 clusters, including 10 subclusters of distinct predicted topology and presumed distinct function. Study of the yeast ABC proteins provided insight into the physiologic function and biochemical mechanisms of their human homologs, such as those involved in cystic fibrosis, adrenoleukodystrophy, Zellweger syndrome, multidrug resistance, and the antiviral activity of interferons.

Category: Regulatory, transport carrier.

Motifs/domains: N terminal extracellular domain containing a segment homologous to the autoantigen SSN; two ATP binding (NBF) sites; two transmembrane (2TM) domains (2 x 6 segments) separated by a linker region; PEST sequence involved in internalization and cholesterol efflux from late endosomes; contains 2 highly conserved ATP-binding cassettes including Walker A and B motifs.

Post-translational modifications: Phosphorylation on Ser-2054 regulates phospholipid efflux.

Function

ABCA1 functions as a cholesterol efflux pump in the cellular lipid removal pathway. ABC1 is a key gatekeeper influencing intracellular cholesterol transport, named "cholesterol efflux regulatory protein" (CERP). ABCA1 binds ATP in the presence of Mg^{2+} and shows that *ABCA1* expression supports apolipoprotein A-I (APOA1)-mediated release of cholesterol and choline-phospholipids. ABC transporter, traffic ATPase, facilitator of cellular efflux of cholesterol and phospholipid and key regulator of high density lipoprotein (HDL) metabolism; a leukocyte factor that controls the recruitment of inflammatory cells and protects against atherosclerosis; plays a key role in the first steps of the reverse cholesterol transport pathway by mediating lipid efflux from macrophages; plays an important role in lipid transport in Sertoli cells and influences male fertility; contributes to transport of maternal cholesterol to the developing fetus. Binding of APOA1 leads to the formation of phospholipid-APOA1 complexes which subsequently promote cholesterol efflux; binds to FADD, required for its function; carries cholesterol out of the cell for uptake into sterol dependent HDL particles regulated in monocytes and macrophages; inhibited by: SREBF2 in endothelial cells and PDGFA in vascular smooth muscle cells.

The membrane-associated protein encoded by this gene is a member of the superfamily of ATP-binding cassette (ABC) transporters. ABC proteins transport various molecules across extra- and intracellular membranes. ABC genes are divided into seven distinct subfamilies (*ABC1*, *MDR/TAP*, *MRP*, *ALD*, *OABP*, *GCN20*, White). This protein is a member of the ABC1 subfamily. Members of the ABC1 subfamily comprise the only major ABC subfamily found exclusively in multicellular eukaryotes. With cholesterol as its substrate, this protein functions as a cholesterol efflux pump in the cellular lipid removal pathway. Mutations in this gene have been associated with Tangier's disease and familial high-density lipoprotein deficiency. A cAMP-dependent and sulfonylurea-sensitive anion transporter. A key gatekeeper influencing intracellular cholesterol transport. ABCA1 participates in the statin pathway (cholesterol and lipoprotein transport PD), PID pathways (RXR and RAR heterodimerization with other nuclear receptor), and reactome pathways (HDL-mediated lipid transport).

Related Diseases

Acute kidney failure; Acute myeloid leukemia; Acute promyelocytic leukemia; Adenoma; Alopecia; **Alzheimer's disease**; Analphalipoproteinemia; Animal mammary neoplasms; **Arteriosclerosis**; Asthma; **Atherosclerosis**; Autistic disorder; **Autosomal dominant hypercholesterolemia**; Barrett's esophagus; B-cell chronic lymphocytic leukemia; B-cell lymphoma; Blood coagulation disorders; Brain ischemia; Breast neoplasms; Bronchopulmonary dysplasia; Bullous pemphigoid; Cachexia; **Cardiovascular diseases**; Cataract; **Cerebral amyloid angiopathy**; Cervical intraepithelial neoplasia; Choriocarcinoma; **Chronic kidney disease**; **Chronic renal insufficiency**; Cleft lip; Cleft palate; Colitis; Colonic neoplasms; **Colorectal cancer**; **Colorectal neoplasms**; Congenital abnormalities; **Coronary heart disease**; **Coronary artery disease**; **Coronary disease**; Craniofacial abnormalities; Diabetes mellitus (type 2); Diabetic nephropathy; Diabetic nephropathy; Drug eruptions; Drug-induced abnormalities; **Dyslipidemias**; Edema; Embryonal carcinoma; Endometrial hyperplasia; Endometrial neoplasms; Epidermolysis bullosa; Epilepsy; Experimental arthritis; Experimental autoimmune encephalomyelitis; Experimental diabetes mellitus; Experimental liver cirrhosis; Experimental mammary neoplasms; Experimental neoplasms; Eye abnormalities; **Familial high density lipoprotein deficiency**; **Familial hypercholesterolemia**; Fatty liver; Fetal death; Fever; Fibrosis; Gingival hyperplasia; Gingival overgrowth; Glioblastoma; **HIV infection**; Head and neck neoplasms; **Heart diseases**; Hemolytic-uremic syndrome; Hepatocellular carcinoma; Hepatomegaly; Herpes simplex; **High density lipoprotein deficiency type 1 (HDLD1)**; **High density lipoprotein deficiency type 2 (HDLD2)**; Human influenza; Hyperalgesia; **Hyperalphalipoproteinemia**; **Hypercholesterolemia**; Hypereosinophilic syndrome; Hyperhomocysteinemia; **Hyperlipidemia**; Hyperlipoproteinemia (type II); Hyperlipoproteinemia (type IIA); Hypertension; Hypoalphalipoproteinemia; Inflammation; Insulin resistance; Interstitial nephritis; Intestinal diseases; Iron metabolism disorders; Ischemic stroke; **Kidney diseases**; Learning disorders; Left ventricular dysfunction; Left ventricular hypertrophy; Leukemia; Lewis lung carcinoma; Leydig's cell tumor; Lipoprotein deficiencies; Lipoprotein disorder; Liver diseases; Liver neoplasms; Lung neoplasms; Medulloblastoma; Melanoma; Meningomyelocele; Metabolic diseases; Middle cerebral artery infarction; Multiple myeloma; Muscular diseases; *Mycobacterium* infections; Myeloid leukemia; Myocardial infarction; Myocardial ischemia; Myocardial reperfusion injury; Myocarditis; Myositis; Myotonia congenita; Necrotizing enterocolitis; Neoplasms; Neurodegenerative diseases; Neurogenic inflammation; **Niemann-Pick type C disease**; Noise-induced hearing loss; Non-Hodgkin lymphoma; **Obesity**; Osteomalacia; Ovarian neoplasms; Pain; Pancreatic neoplasms; Partial epilepsies; Peritonitis; Pneumonia; Porokeratosis; Postmenopausal osteoporosis; Prenatal exposure delayed effects; Primary hypoalphalipoproteinemia; Prion diseases; Progressive myoclonic epilepsies; **Prostate cancer**; Prostatic hyperplasia; **Prostatic neoplasms**; Pseudolymphoma; Pterygium; Reperfusion injury; Respiratory hypersensitivity; Rhabdomyolysis; Rhabdomyosarcoma; Rheumatoid arthritis; **Scott syndrome**; Seborrheic keratosis; Skin neoplasms; **Smith-Lemli-Opitz syndrome**; **Smoking**; Spinal muscular atrophy; Squamous cell carcinoma; Stomach neoplasms; **Stroke**; **Tangier disease**; **Thalidomide-related neuropathy**; Thyroid neoplasms; Tongue neoplasms; Toxic hepatitis; Tuberculosis; Uterine cervical neoplasms; Uterine neoplasms; Uveal neoplasms; Vitiligo; Wilms' tumor.

Related Drugs

1-Butanol; 1-Oleoyl-2-acetylglycerol; 1-Palmitoyl-2-(5-oxovaleroyl)-sn-glycero-3-phosphorylcholine; 4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid disodium salt; 9,11-Linoleic acid; 22-Hydroxycholesterol; 25-Hydroxycholesterol; AGN 193109; alpha-Lipoic acid; Alitretinoin; Arachidonic acid; Arsenic; Aspirin; Atorvastatin; ATI-111; Berberine; Calcitriol; Calmodulin; Charcoal-stripped fetal bovine serum; Cholesterol; Cholic acid; Chromium; Cilostazol; Daidzein; Dietary cholesterol; Dietary fats; Eicosapentaenoic acid; Ezetimibe; Fatty acids; Fenofibrate; Fluvastatin; Genistein; Ghrelin; *Ginkgo biloba* L.; Glyburide; Glycitein; GSK 3987; GW 1929; GW 3965; HDL-cholesterol; Honokiol; Ht31; Ibrolipim; Linoleic acid; Lipids; Lipopolysaccharides; Lithocholic acid; Liver X receptor agonists; Lovastatin; Low-density lipoproteins (LDL); Lycopene; Mastoparan; Methotrexate; Methyl-3β-hydroxy-5α,6α-epoxycholanate (MHEC); miR-33; Mitoxantrone; Naringenin; N-(2,2,2-Trifluoro-ethyl)-N-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-benzenesulfonamide (TO-901317); N-3-Oxo-dodecanoyl-l-homoserine lactone (3OC12-HSL); Obestatin; Oleic acid; Ozone; Palmitoleic acid; *Panax notoginseng* saponins; Perfluorooctanoic acid; Phenylsulfone-substituted quinoxaline (WYE-672); Phenytoin; Phosphatidylcholine; Phosphodiesterase (PDE) type 4 inhibitors; Phospholipids; Pirinixic acid; Platelet Activating Factor; PPARG agonists; Pravastatin; Pregnenolone carbonitrile; Resveratrol; Retinoids; Rexinoid LG268; Rifampin; Ritonavir; Rolipram; Rosiglitazone; Rosuvastatin; Simvastatin; Soy protein; Statins; Stigmasterol; Synthetic steroidal liver X receptor agonists; tert-Butylhydroperoxide; Tetracycline; Torcetrapib; trans-10,cis-12-Conjugated linoleic acid; Tretinoin; Triacsin C; Tributyltin chloride (TBTC); Visfatin; Wogonin.

Substrates: Apolipoproteins; Aspirin; Cholesterol; Lipids; Lipoproteins; LXR/PXR Ligands.

Inhibitors: 4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid disodium salt; Atorvastatin; Ezetimibe; Glyburide; GW 1929; miR-33; Naringenin; Phenytoin; Phosphatidylcholine; PPARG agonists; Rifampin; Simvastatin; Statins; Visfatin.

Inducers: ATI-111; Berberine; Charcoal-stripped fetal bovine serum; Cilostazol; GW 3965; Honokiol; Hormone Replacement Therapy; Ht31; Ibrolipim; Low-density lipoproteins (LDL); Lycopene; Methotrexate; Methyl-3β-hydroxy-5α,6α-epoxycholanate (MHEC); N-(2,2,2-Trifluoro-ethyl)-N-[4-(2,2,2-trifluoro-1-hydroxy-1-trifluoromethyl-ethyl)-phenyl]-benzenesulfonamide (TO-901317); N-3-Oxo-dodecanoyl-l-homoserine lactone (3OC12-HSL); *Panax notoginseng* saponins; Phosphodiesterase (PDE) type 4 inhibitors; Phenylsulfone-substituted quinoxaline (WYE-672); PPARG agonists; Rexinoid LG268; Ritonavir; Rolipram; Simvastatin; SIRT1; Statins; Stigmasterol; Tributyltin chloride (TBTC); Wogonin.

Animal Models

Humanized transgenic mouse line. Transgenic mice that express human *abca1* have been developed. Increased total *abca1* expression did not alter the pattern of abca1 distribution, but resulted in increased cholesterol efflux, elevated HDL-C levels, and increased apoA1 and apoA2 expression. The *abca1* gene contains an internal promoter with LXR elements within intron 1. Activation of this functional internal promoter by oxysterols *in vivo* directly contributed to an increase in human-specific mRNA and protein levels.

Transgenic mice. Mice with a targeted inactivation of *abc1* display morphologic abnormalities and perturbations in their lipoprotein metabolism concordant with Tangier disease. *Abc1* is expressed on the plasma membrane and the Golgi complex, mediates apolipoprotein AI APOA1-associated export of cholesterol and phospholipids from the cell, and is regulated by cholesterol flux. Structural and functional abnormalities in caveolar processing and the trans-Golgi secretory pathway of cells lacking functional ABC1 indicated that lipid export processes involving vesicular budding between the Golgi and the plasma membrane were severely disturbed. Lipid profiles in the knockout mice revealed a reduction of approximately 70% in cholesterol, markedly reduced plasma phospholipids, and an almost complete lack of high density lipoproteins, when compared with wild-type littermates. Dramatic alterations in HDL-C and near absence of APOA1 were found. Inactivation of the *abc1* gene led to an increase in the absorption of cholesterol in mice fed a chow or a high fat and high cholesterol diet. Histopathologic examination of knockout mice showed a striking accumulation of lipid-laden macrophages and type II pneumocytes in the lungs. The findings demonstrated that the knockout mice had pathophysiologic hallmarks of human Tangier disease and highlighted the capacity of *abc1* transporters to participate in the regulation of dietary cholesterol absorption.

Abc1 is expressed in Purkinje and cortical pyramidal neurons in the CNS, as well as in astrocytes and microglia. Astrocytes and microglia from *abca1*-null mice showed impaired ability to efflux cholesterol to exogenous apolipoprotein E (APOE), although residual efflux was present. The mutant cells showed increased intracellular lipid accumulation compared to wild-type cells. In addition, *Abca1*-null mice showed a 65% decrease in brain levels of APOE as a consequence of reduced secretion from mutant glial cells, with the hippocampus and striatum being the most severely affected brain regions. *Abca1* may play a role in cholesterol transport and APOE metabolism in the CNS. By analyzing brain tissue, cerebrospinal fluid, plasma, and primary astrocyte cultures from wild-type, *abca1*+/-, and *abca1*-/- mice, it was observed that deletion of *abca1* markedly affects metabolism of apoe and cholesterol in the CNS and in nascent lipoprotein particles secreted by cultured astrocytes.

Intestine-specific *abca1*-null mice were generated. Approximately 30% of the steady-state plasma HDL pool is contributed by intestinal *abca1* in mice. HDL derived from intestinal abca1 appeared to be secreted directly into the circulation. Analysis of lymph from liver-specific *abca1*-null mice with very low plasma HDL showed that HDL in lymph was predominantly derived from the plasma compartment. Intestinal abca1 may play a critical role in plasma HDL biogenesis *in vivo*.

Mice with specific inactivation of *abca1* in pancreatic β-cells have been generated. In this model, markedly impaired glucose tolerance and defective insulin secretion but normal insulin sensitivity was observed. Islets isolated from these mice showed altered cholesterol homeostasis and impaired insulin secretion *in vivo*. Rosiglitazone, a thiazolidinedione, requires β-cell abca1 for its beneficial effects on glucose tolerance. Abca1 plays a role in β-cell cholesterol homeostasis and insulin secretion. Cholesterol accumulation may contribute to β-cell dysfunction in type 2 diabetes.

5' missense mutations were expressed at the plasma membrane but produced little or no apoA1-stimulated cholesterol efflux when transfected into HEK293 cells. All mutants except one showed a marked decline in interaction between the abca1 mutant and apoA1. The deficits shown by these mutations establish their causality in Tangier disease, and binding of apoA1 by abca1 is necessary, but not sufficient, to stimulate cholesterol efflux. 3 mutations in the first extracellular domain of *abca1* showed little or no apoA1-mediated HDL assembly when expressed in HEK293 cells. Two of these mutations were associated with impaired glycosylation, retention in the endoplasmic reticulum or the cis-Golgi complex, and failure to localize to the plasma membrane.

Allelic Variants

Total variants: 1532.

Selected SNPs

rs2230806. **HGVS**: NG_007981.1: g.74570G>A; NM_005502.2: c.656G>A; NP_005493.2: p.Arg219Lys; NT_008470.18: g.14942072C>T. Protection against coronary heart disease in familial hypercholesterolemia. In heterozygous familial hypercholesterolemia (FH) patients, the clinical expression of FH is highly variable in terms of the severity of hypercholesterolemia and the age at onset and severity of coronary heart disease (CHD). ABCA1 may play a key role in the onset of premature CHD in FH. The presence of the Arg219Lys variant in the *ABCA1* gene in FH patients influences the risk of CHD. The K allele of the R219K variant was significantly more frequent in FH patients without premature CHD than in those with premature CHD, suggesting that the genetic variant may influence development and progression of atherosclerosis in FH patients. The K allele of the R219K polymorphism seemed to modify CHD risk without important modification of plasma HDL-C levels, and it appeared to be more protective for smokers than nonsmokers. In a large Swedish population-based study of 1177 individuals with a first myocardial infarction event and 1526 healthy controls, an association between the R219K polymorphism and increased serum levels of apolipoprotein B (APOB) and LDL cholesterol was found among smokers, but not among nonsmokers. The *ABCA1*: Arg219Lys; K allele frequency differs markedly between blacks and whites, and the variant-allele modulates the association between age and HDL cholesterol, as well as body fatness and triglycerides in a beneficial manner only in whites. Mutations in the *ABCA1* gene have been established as the molecular defect in Tangier disease and familial hypoalphalipoproteinemia, uncommon genetic disorders characterized by deficient or depressed high-density lipoprotein (HDL) cholesterol and increased triglycerides. Information regarding the frequency of common variants, including R219K within the coding region of the *ABCA1* gene and their effect on these phenotypes in the general population is limited. The frequency of the variant allele (K219) was higher in blacks than in whites (0.595 *vs* 0.262), with carriers (KK+RK) representing 83.8% of blacks *vs* 44.2% of whites. After adjusting for age, body mass index (BMI), and sex, the genotype effect on HDL-C and natural logarithm of triglycerides was not apparent in whites or blacks. However, significant interaction effects of genotype and age on HDL-C and genotype and BMI on triglycerides were found in whites. The *ABCA1* R219K polymorphism is associated with a higher HDL-C level in Asians and a protective role for CAD risk both in Asians and Caucasians.

Carriers (KK+RK), unlike noncarriers (RR) showed a positive relationship between age and HDL-C. Carriers of the KK genotype had higher levels of HDL-C than those of the RR genotype. Patients with the RR genotype had significantly higher serum triglyceride levels and lower HDL-C levels than those with the KK genotype. The effects of pravastatin in increasing HDL-C levels were significantly greater in patients with the KK genotype compared with those with the RR genotype. The R219K polymorphism was associated with altered lipoprotein levels and the R219K variant significantly modulated the HDL-C response to pravastatin in Chinese patients with CHD.

Carriers of the G1051A allele were associated only with increased concentrations of HDL cholesterol.

ABCA1 polymorphisms were combined in haplotypes possessing G1051A, G2706A, G2868A and -565C/T; (AAGC) seemed to be most protective against significant stenosis, whereas GGAT was probably the most atherogenic. AAGC seems to be a protective haplotype whereas GGAT has an atherogenic effect in a Tunisian population.

Alleles: African: A: 0.688-0.797, G: 0.203-0.312; Asian: A: 0.398-0.467, G: 0.533-0.602; European: A: 0.158, G: 0.842; Multi-national: A: 0.250-0.487, G: 0.513-0.750; North American: A: 0.193-0.680, G: 0.320-0.807; Pacific: A: 0.521, G: 0.479. **Genotypes**: African: A/A: 0.417-0.444, A/G: 0.305-0.542, G/G: 0.041-0.051; Asian: A/A: 0.159-0.222, A/G: 0.477-0.489, G/G: 0.289-0.364; European: A/A: 0.017, A/G: 0.283, G/G: 0.700; Multi-national: A/A: 0.231-0.250, A/G: 0.000-0.513, G/G: 0.256-0.750; North American: A/A: 0.032, A/G: 0.323, G/G: 0.645; Pacific: A/A: 0.292, A/G: 0.458, G/G: 0.250.

rs3890182. **HGVS**: NG_007981.1: g.47782C>T; NM_005502.2: c.161-806C>T; NT_008470.18: g.14968860G>A. High density lipoprotein cholesterol level quantitative trait locus 13. Association of rs3890182 (74A-G) in the *ABCA1* gene with HDL-C levels. **Alleles**: African: A: 0.192, G: 0.808; Asian: A: 0.056-0.067, G: 0.933-0.944; European: A: 0.093, G: 0.907. **Genotypes**: African: A/A: 0.067, A/G: 0.250, G/G: 0.683; Asian: A/A: 0.000, A/G: 0.111-0.133, G/G: 0.867-0.889; European: A/A: 0.017, A/G: 0.153, G/G: 0.831.

rs3905000. **HGVS**: NG_007981.1: g.38367C>T; NM_005502.2: c.67-5594T>C; NT_008470.18: g.14978275G>A. Coronary heart disease. Risk allele: rs3905000-G. **Alleles**: African: A: 0.217-0.225, G: 0.775-0.783; Asian: A: 0.000-0.067, G: 0.933-1.000; European: A: 0.000-0.093, G: 0.907-1.000; Multi-national: A: 0.104, G: 0.896; North American: A: 0.090-0.167, G: 0.833-0.910. **Genotypes**: African: A/A: 0.050-0.067, A/G: 0.317-0.333, G/G: 0.617; Asian: A/A: 0.000, A/G: 0.000-0.133, G/G: 0.867-1.000; European: A/A: 0.000-0.017, A/G: 0.000-0.153, G/G: 0.831-1.000; Multi-national: A/A: 0.000, A/G: 0.208, G/G: 0.792; North American: A/A: 0.167, A/G: 0.000, G/G: 0.833.

rs1883025. **HGVS**: NG_007981.1: g.31136G>A; NM_005502.2: c.66+1594A>G; NT_008470.18: g.14985506C>T. Polygenic dyslipidemia. Risk allele: rs1883025-T. **Alleles**: African: A: 0.300-0.302, G: 0.698-0.700; Asian: A: 0.167-0.256, G: 0.744-0.833; European: A: 0.200-0.202, G: 0.798-0.800. **Genotypes**: African: A/A: 0.117-0.121, A/G: 0.362-0.367, G/G: 0.517; Asian: A/A: 0.000-0.044, A/G: 0.333-0.422, G/G: 0.533-0.667; European: A/A: 0.033-0.035, A/G: 0.333, G/G: 0.632-0.633.

rs28933692. **HGVS**: NG_007981.1: g.114326G>T; NM_005502.2: c.3295G>T; NP_005493.2: p.Asp1099Tyr; NT_008470.18: g.14902316C>A. High density lipoprotein deficiency. Cerebral amyloid angiopathy. A 3295G-T transversion, predicted to result in an Asp1099Tyr (D1099Y) mutation.

rs28937313. **HGVS**: NG_007981.1: g.110636A>G; NM_005502.2: c.2804A>G; NP_005493.2: p.Asn935Ser; NT_008470.18: g.14906006T>C. Tangier disease. A 3199A-G transition in exon 19 of the *ABCA1* gene, leading to an Asn935Ser missense mutation.

rs28937314. **HGVS**: NG_007981.1: g.110635A>C; NM_005502.2: c.2803A>C; NP_005493.2: p.Asn935His; NT_008470.18: g.14906007T>G. Tangier disease. A 3198A-C transversion in exon 19 of the *ABCA1* gene, resulting in an Asn935His missense mutation. This and the Asn935Ser mutation involved the Walker A motif of the first nucleotide-binding fold.

rs2066714. NG_007981.1: g.108684A>G; NM_005502.2: c.2649A>G; NP_005493.2: p.Ile883Met; NT_008470.19: g.36751285T>C. Coronary artery disease. **Alleles**: African: A: 0.450-0.562, G: 0.438-0.550; Asian: A: 0.267-0.500, G: 0.500-0.733; European: A: 0.500-0.867, G: 0.133-0.500; Multi-national: A: 0.681-0.763, G: 0.237-0.319; North American: A: 0.520-0.903, G: 0.097-0.480; Pacific: A: 0.396, G: 0.604. **Genotypes**: African: A/A: 0.200-0.250, A/G: 0.500-0.625, G/G: 0.125-0.300; Asian: A/A: 0.089-0.273, A/G: 0.356-0.455, G/G: 0.273-0.556. European: A/A: 0.000-0.733, A/G: 0.267-1.000, G/G: 0.000; Multi-national: A/A: 0.490-0.632, A/G: 0.263-0.382, G/G: 0.105-0.128; North American: A/A: 0.000-0.806, A/G: 0.000-0.194, G/G: 0.000; Pacific: A/A: 0.167, A/G: 0.458, G/G: 0.375.

rs2066715. **HGVS**: NG_007981.1: g.107404G>A; NM_005502.2: c.2473G>A; NP_005493.2: p.Val825Ile; NT_008470.19: g.36752565C>T. Coronary artery disease. The subjects with AA genotype in Bai Ku Yao had higher serum TC levels than the subjects with GG and GA genotypes. V825I polymorphism is associated with male serum HDL-C and ApoAI levels in the Han, and the serum TC levels in the Bai Ku Yao populations. **Alleles**: Multi-national: A: 0.013, G: 0.987. **Genotypes**: Multi-national: A/G: 0.026, G/G: 0.974.

rs2575879. **HGVS**: NC_000009.11: g.107668825G>C; NG_007981.1: g.26612C>G; NM_005502.3: c.-92-2773C>G. Associated with higher serum HDL-C concentrations.

rs1800978. **HGVS**: NC_000009.11: g.107665978C>G; NG_007981.1: g.29459G>C; NM_005502.3: c.-18G>C. Associated with lower HDL-C concentrations.

rs9282541. **HGVS**: NC_000009.11: g.107620835G>A; NG_007981.1: g.74602C>T; NM_005502.3: c.688C>T; NP_005493.2: p.Arg230Cys. In individuals with the R230C/C230C genotypes, lower HDL-C levels were observed compared to those with the R230R genotype. The C230 allele was associated with an increased risk for hypoalphalipoproteinemia. The non-synonymous Arg230Cys variant of *ABCA1* is associated with low levels of HDL cholesterol levels in Mexican adults. The variant R230C, apparently exclusive to Native American individuals, was associated with low HDL-C levels, obesity and type 2 diabetes in Mexican Mestizos.

The C230 allele was found in 29 of 36 Native American groups, but not in European, Asian or African individuals.

c.5398A>C and c.2369G>A: Associated with HDL cholesterol deficiency in serum.

110-bp Ins/14-bp Del: Tangier disease. An insertion of a 110-bp DNA fragment structurally related to the Alu sequence family of repetitive sequences and deletion of 14 bp in exon 12 of the *ABC1* gene. This insertion/deletion predicted deletion of 6 aa and an in-frame insertion of 38 residues. This mutation does not allow the synthesis of the normal ABC1 transporter.

1-bp Del, 1764G: Tangier disease. A 1-bp deletion, removing guanine at nucleotide 1764. This mutation, localized in codon 548, created a frameshift that led to a premature translation stop 26 aa downstream of the deletion site. The translation product was predicted to be nonfunctional because it lacked 75% of the amino acid sequence, including all transmembrane regions and both ATP-binding cassettes.

1-bp Del, 2665C: Tangier disease.

2-bp Del, 3283TC: Tangier disease. A dinucleotide deletion in exon 22: 3283-3284TC. The deletion resulted in a frameshift mutation and a premature stop codon starting at position 3375. The gene product was predicted to encode a nonfunctional protein of 1084 aa, which is approximately half the size of the full-length ABC1 protein.

3-bp Del: High density lipoprotein deficiency, type 2. A 3-bp deletion that resulted in loss of nucleotides 2017-2019 and deletion of a leucine at position 633, which is conserved in mouse and *C. elegans*.

4-bp Del, 3787CGCC: Familial high density lipoprotein deficiency. A 4-bp deletion (CGCC) at nucleotide 3787, resulting in premature termination by frameshift at codon 1224.

Ala877Val: Tangier disease. A2750C-T transition, changing alanine to valine (missense mutation).

Arg1680Trp: Tangier disease, variant. An Arg1680Trp missense mutation.

Arg2021Trp: Tangier disease. A 6181C-T transition in exon 47, resulting in an Arg2021Trp (R2021W) substitution.

Asn875Ser: Tangier disease. A 2744A-G transition that changes asparagine to serine in the highly conserved Walker A motif of the amino terminal ATP-binding fold.

Asp1229Asn: Tangier disease. A 3805G-A transition in exon 27 of the *ABCA1* gene, resulting in an Asp1229Asn change.

Cys1417Arg: Tangier disease. T-to-C transition in exon 30 resulting in a Cys1417Arg substitution.

Gln537Arg: Tangier disease. An A-to-G transition at nucleotide 1730 in exon 13, resulting in the substitution of arginine for a conserved glutamine at residue 537.

Int12-14 Del, Int16-31 Del: Tangier disease. A double deletion in the *ABCA1* gene: 1.2 kb from intron 12-14 and 19.9 kb from intron 16-31, which encodes the sixth transmembrane region (a linker region) and the seventh transmembrane region of the putative secondary structure. The 3'-deletion junction had an insertion of 21 bp. The 16 bp within the 21-bp insertion was not found in the original sequence, but was complementary to the proximal sequence of the 5'-deletion junction. The same oriented Alu sequence was found in both intron 14 and intron 31, facilitating the stabilization of the folding of the *ABCA1* gene to promote nonhomologous intragenic recombination. Double deletions in the same gene previously reported for dystrophin; in the beta-globin gene (*HBB*); in the growth hormone gene (*GH1*); and in the *GALNS* gene, which is mutant in mucopolysaccharidosis type IVA. A simultaneous event of double deletions was proposed for the case of thalassemia patients with changes in the *HBB* gene due to inversion between deletions.

Ivs24DS, G-C: Tangier disease. A G-to-C transversion in the splice donor site of exon 24, predicted to cause alternative splicing, deleting a significant part of the transcript.

Phe2009Ser: High density lipoprotein deficiency. Cerebral amyloid angiopathy. A 5966T-C transition, predicted to result in a Phe2009Ser mutation.

Ser1446Leu: Tangier disease. Ser1446Leu missense amino acid substitution.

Trp530Ser: Tangier disease. A 1709G-C transversion, resulting in a Trp530Ser aa substitution (missense mutation).

Tyr573Ter: Tangier disease. A 2033C-A transversion in exon 12 of the *ABCA1* gene, resulting in conversion of codon 573 from TAC (Tyr) to TAA (Ter)(Y573X).

Pro85Leu: Low HDL-C levels.

Arg1851Gln: Low HDL-C levels.

Arg1925Gln: Scott syndrome.

Ivs46: **Del T-39-46**: Low HDL-C levels.

The variants: **219K** (rs2230806), **883I** (rs2066714), and **1587R** (rs2230808), or promoter variant **(14T)** in concert with the *APOE-4* allele, increase the risk of Alzheimer's disease.

-14C>T: Associated with high baseline gene-expression levels.

C69T: Influences CHD risk and response to statin treatment. The TT genotype was associated with 1.7 times higher CHD risk than the CC genotype.

R1587K (rs2230808-KK) and **R219K** (rs2230806-RK) polymorphisms were associated with significantly increased small HDL. The R1587KKK genotype and the R219K KK genotype were also associated with increased HDL particle concentrations.

Other selected SNPs

rs1800976. **HGVS**: NG_007981.1: g.4728G>C; NT_008470.18: g.15011914C>G. **Frequency**: C: 0.485, G: 0.515.

rs2246298. **HGVS**: NG_007981.1: g.4704C>T; NT_008470.18: g.15011938G>A. **Frequency**: C: 0.804, T: 0.196.

rs2740483. **HGVS**: NG_007981.1: g.4902C>G; NT_008470.18: g.15011740G>C. **Frequency**: C: 0.253, G: 0.747.

rs56064613. **HGVS**: NG_007981.1: g.4896C>T; NT_008470.18: g.15011746G>A. **Frequency**: C: 0.989, T: 0.011.
rs4149338. **HGVS**: NG_007981.1: g.149534C>T; NM_005502.2: c.*693C>T; NT_008470.18: g.14867108G>A. **Alleles**: African: C: 0.610, T: 0.390; Asian: C: 0.193-0.300, T: 0.700-0.807; European: C: 0.716, T: 0.284; Multi-national: C: 0.530, T: 0.470. **Genotypes**: African: C/C: 0.373, C/T: 0.475, T/T: 0.153; Asian: C/C: 0.045-0.111, C/T: 0.295-0.378, T/T: 0.511-0.659; European: C/C: 0.552, C/T: 0.328, T/T: 0.121.
rs13306080. **HGVS**: NG_007981.1: g.149209A>G; NM_005502.2: c.*368A>G: NT_008470.18: g.14867433T>C. **Alleles**: African: A: 1.000, G: 0.000; Asian: A: 0.989-1.000, G: 0.000-0.011; European: A: 1.000, G: 0.000. **Genotypes**: African: A/A: 1.000, A/G: 0.000; Asian: A/A: 0.978-1.000, A/G: 0.000-0.022; European: A/A: 1.000, A/G: 0.000.
rs10991377. **HGVS**: NG_007981.1: g.152061A>G; NM_005502.2: c.*3220A>G; NT_008470.18: g.14864581T>C.
rs34879708. **HGVS**: NG_007981.1: g.148784C>A; NM_005502.2: c.6729C>A; NP_005493.2: p.Asp2243Glu; NT_008470.18: g.14867858G>T. **Alleles**: North American: G: 0.987, T: 0.013. **Genotypes**: North American: G/G: 0.974, G/T: 0.026.
rs363717. **HGVS**: NG_007981.1: g.150737G>A; NM_005502.2: c.*1896G>A; NT_008470.18: g.14865905C>T. Associated with thalidomide-related peripheral neuropathy. **Alleles**: African: A: 0.933, G: 0.067; Asian: A: 0.740-0.833, G: 0.167-0.260; European: A: 0.793-0.847, G: 0.153-0.207; Multi-national: A: 0.820-0.880, G: 0.120-0.180; North American: A: 0.790-0.933, G: 0.067-0.210; Pacific: A: 0.780-0.800, G: 0.200-0.220. **Genotypes**: African: A/A: 0.867, A/G: 0.133, G/G: 0.000; Asian: A/A: 0.700, A/G: 0.267, G/G: 0.033; European: A/A: 0.586-0.699, A/G: 0.295-0.414, G/G: 0.000-0.006; North American: A/A: 0.867, A/G: 0.133, G/G: 0.000; Pacific: A/A: 0.640, A/G: 0.280-0.320, G/G: 0.040-0.080.
rs1800977. **HGVS**: NG_007981.1: g.4987C>T; NT_008470.18: g.15011655G>A. **Alleles**: African: C: 0.800, T: 0.200; Asian: C: 0.678-0.682, T: 0.318-0.322; European: C: 0.642, T: 0.358; Multi-national: C: 0.630, T: 0.370; Other: C: 0.766, T: 0.234. **Genotypes**: African: C/C: 0.633, C/T: 0.333, T/T: 0.033; Asian: C/C: 0.444-0.500, C/T: 0.364-0.467, T/T: 0.089-0.136; European: C/C: 0.450, C/T: 0.383, T/T: 0.167.
rs2230808. **HGVS**: NG_007981.1: g.132633A>G; NM_005502.2: c.4760A>G; NP_005493.2: p.Lys1587Arg; NT_008470.18: g.14884009T>C. **Alleles**: African: A: 0.709-0.883, G: 0.117-0.292; Asian: A: 0.289-0.389, G: 0.611-0.711; European: A: 0.158-0.161, G: 0.839-0.842; Multi-national: A: 0.200-0.473, G: 0.527-0.800; North American: A: 0.261-0.850, G: 0.150-0.739; Pacific: A: 0.417, G: 0.583. **Genotypes**: African: A/A: 0.500-0.783, A/G: 0.200-0.417, G/G: 0.017-0.083; Asian: A/A: 0.111-0.178, A/G: 0.356-0.422, G/G: 0.400-0.533; European: A/A: 0.033-0.034, A/G: 0.250-0.254, G/G: 0.712-0.717; Multi-national: A/A: 0.200-0.405, A/G: 0.000-0.135, G/G: 0.459-0.800; North American: A/A: 0.087, A/G: 0.348, G/G: 0.565; Pacific: A/A: 0.167, A/G: 0.500, G/G: 0.333.
rs4149339. **HGVS**: NG_007981.1: g.150281C>T; NM_005502.2: c.*1440C>T; NT_008470.18: g.14866361G>A. **Alleles**: African: C: 0.608-0.610, T: 0.390-0.392; Asian: C: 0.186-0.300, T: 0.700-0.814; European: C: 0.717-0.724, T: 0.276-0.283; Multi-national: C: 0.580, T: 0.420. **Genotypes**: African: C/C: 0.367-0.373, C/T: 0.475-0.483, T/T: 0.150-0.153; Asian: C/C: 0.047-0.111, C/T: 0.279-0.378, T/T: 0.511-0.674; European: C/C: 0.550-0.552, C/T: 0.333-0.345, T/T: 0.103-0.117.
rs4149340. **HGVS**: NG_007981.1: g.150752C>T; NM_005502.2: c.*1911C>T; NT_008470.18: g.14865890G>A. **Alleles**: African: C: 0.925, T: 0.075; Asian: C: 0.800-0.852, T: 0.148-0.200; European: C: 1.000, T: 0.000; Multi-national: C: 0.960, T: 0.040. **Genotypes**: African: C/C: 0.850, C/T: 0.150, T/T: 0.000; Asian: C/C: 0.622-0.705, C/T: 0.295-0.356, T/T: 0.000-0.022; European: C/C: 1.000, C/T: 0.000, T/T: 0.000.
rs2482432. **HGVS**: NG_007981.1: g.152265A>G; NT_008470.18: g.14864377T>C. **Alleles**: African: C: 0.200, T: 0.800; Asian: C: 0.057-0.078, T: 0.922-0.943; European: C: 0.425, T: 0.575. **Genotypes**: African: C/C: 0.017, C/T: 0.367, T/T: 0.617; Asian: C/C: 0.000-0.023, C/T: 0.068-0.156, T/T: 0.844-0.909; European: C/C: 0.200, C/T: 0.450, T/T: 0.350.
rs2066718. **HGVS**: NG_007981.1: g.106182G>A; NM_005502.2: c.2311G>A; NP_005493.2: p.Val771Met; NT_008470.18: g.14910460C>T. **Alleles**: African: A: 0.075, G: 0.925; Asian: A: 0.022-0.057, G: 0.943-0.978; European: A: 0.000, G: 1.000; Multi-national: A: 0.051-0.070, G: 0.930-0.949. **Genotypes**: African: A/G: 0.150, G/G: 0.850; Asian: A/G: 0.044-0.114, G/G: 0.886-0.956; European: A/G: 0.000, G/G: 1.000; Multi-national: A/G: 0.103, G/G: 0.897.
rs9282543. **HGVS**: NG_007981.1: g.96061T>C; NM_005502.2: c.1196T>C; NP_005493.2: p.Val399Ala; NT_008470.18:g.14920581A>G. **Alleles**: African: C: 0.000, T: 1.000; Asian: C: 0.000, T: 1.000; European: C: 0.009, T: 0.991; Multi-national: C: 0.010, T: 0.090; North American: C: 0.000-0.033, T: 0.967-1.000; Pacific: C: 0.000, T: 1.000. **Genotypes**: African: C/T: 0.000, T/T: 1.000; Asian: C/T: 0.000, T/T: 1.000; European: C/T: 0.017, T/T: 0.983; Multi-national: C/T: 0.020, T/T: 0.980; North American: C/T: 0.000-0.065, T/T: 0.935-1.000; Pacific: C/T: 0.000, T/T: 1.000.

Evolution

The *ABC1* and *ABCA2* genes map to 9q22-q31 and 9q34, respectively. In the mouse, the homologs map to chromosomes 4 and 2, respectively, in regions showing homology of synteny to human 9q. The ancestral chromosome split in the mouse lineage at an evolutionary breakpoint situated between hexabrachion and gelsolin, both of which map to human chromosome 9 and to mouse chromosomes 4 and 2, respectively. Thus, *ABC1* and *ABC2* probably originated through a duplication event that took place before speciation and predated the splitting of the ancestral chromosome equivalent to human 9q. Their degree of sequence similarity, less impressive than that of the P-glycoprotein isoforms, also argues for a duplication event occurring at an earlier evolutionary stage.

Genomics and Pharmacogenomics

ABCA1 and ACAT2 mutant phenotypes: Cholesterol homeostasis in the enterocyte is regulated by the interplay of multiple genes that ultimately determines the net amount of cholesterol reaching the circulation from the small intestine. The effect of deleting these genes, particularly acyl CoA:cholesterol acyl transferase 2 (*ACAT2*), on cholesterol absorption and fecal sterol excretion is well documented. The intestinal mRNA level for adenosine triphosphate-binding cassette transporter A1 (*ABCA1*) increases in *Acat2*-/- mice. Turley et al measured the expression of numerous genes and related metabolic parameters in the intestine and liver of *ACAT2*-deficient mice fed diets containing either added cholesterol or ezetimibe, a selective sterol absorption inhibitor. Cholesterol feeding raised the concentration of UC in the small intestine, and this was accompanied by a significant reduction in the relative mRNA level for Niemann-Pick C1-like 1 (*NPC1L1*) and an increase in the mRNA level for both *ABCA1* and *ABCG5/8*. All these changes were reversed by ezetimibe. When mice deficient in both *ACAT2* and *ABCA1* were fed a high-cholesterol diet, the increase in intestinal UC levels was no greater than it was in mice lacking only *ACAT2*. This resulted from a combination of compensatory mechanisms including diminished *NPC1L1*-mediated cholesterol uptake, increased cholesterol efflux via *ABCG5/8*, and possibly rapid cell turnover.

ABCA7: ATP-binding cassette transporter (ABC) A7 is an ABC family protein that is a so-called full-size ABC transporter, highly homologous to ABCA1, which mediates the biogenesis of high-density lipoprotein (HDL) with cellular lipid and helical apolipoproteins. ABCA7 mediates the formation of HDL when exogenously transfected and expressed; however, endogenous ABCA7 was shown to have no significant impact on the generation of HDL and was found to be associated with phagocytosis regulated by sterol regulatory element binding protein 2. Since phagocytosis is one of the fundamental functions of animal cells as an important responsive reaction to infection, injury and apoptosis, ABCA7 seems to be one of the key molecules linking sterol homeostasis and the host defense system. According to data reported by Tanaka et al, HDL apolipoproteins were shown to enhance phagocytosis by stabilizing ABCA7 against calpain-mediated degradation and increasing its activity, shedding light on a new aspect of the regulation of the host-defense system.
The ATP-binding cassette transporter (ABC)A7 strongly associates with phagocytic function of, rather than biogenesis of high-density lipoprotein (HDL), being regulated by sterol-regulatory element binding protein (SREBP)2. Phagocytic activity was found enhanced by apolipoprotein (apo)A-I and apoA-II more than twice the maximum in J774 and mouse peritoneal macrophages. Tanaka et al investigated the molecular basis of this reaction in association with the function of ABCA7. Similar to ABCA1, ABCA7 was degraded, probably by calpain, and apoA-I and apoA-II stabilized ABCA7 against degradation. Cell surface biotinylation experiments demonstrated that endogenous ABCA7 predominantly resides on the cell surface and that the apolipoproteins increase the surface ABCA7. The increase of phagocytosis by apolipoproteins was retained in the J774 cells treated with *ABCA1* siRNA and in the peritoneal macrophages from *ABCA1*-knockout mice, but it was abolished in the J774 cells treated with *ABCA7* siRNA and in the peritoneal macrophages from *ABCA7*-knockout mice. Phagocytosis was decreased in the cells in the peritoneal cavity of the *ABCA7*-knockout mouse compared with the wild-type control. Extracellular helical apolipoproteins augment ABCA7-associated phagocytosis by stabilizing ABCA7.
ABCG1: ATP binding cassette transporter G1 (*ABCG1*) mediates the transport of cellular cholesterol to HDL, and it plays a key role in maintaining macrophage cholesterol homeostasis. During inflammation, HDL undergoes substantial remodeling, acquiring lipid changes and serum amyloid A (SAA) as a major apolipoprotein. de Beer et al investigated whether remodeling of HDL that occurs during acute inflammation impacts ABCG1-dependent efflux. Lipid-free SAA acts similarly to apolipoprotein A-I (apoA-I) in mediating sequential efflux from ABCA1 and ABCG1. Compared with normal mouse HDL, acute phase (AP) mouse HDL containing SAA exhibited a modest but significant 17% increase in ABCG1-dependent efflux. Interestingly, AP HDL isolated from mice lacking SAA (SAAKO mice) was even more effective in promoting ABCG1 efflux. Hydrolysis with Group IIA secretory phospholipase A_2 (sPLA$_2$-IIA) significantly reduced the ability of AP HDL from SAAKO mice to serve as a substrate for ABCG1-mediated cholesterol transfer, indicating that phospholipid (PL) enrichment, and not the presence of SAA, is responsible for alterations in efflux. AP human HDL, which is not PL-enriched, was somewhat less effective in mediating ABCG1-dependent efflux compared with normal human HDL. Inflammatory remodeling of HDL impacts ABCG1-dependent efflux independent of SAA.
Endothelin-1 (ET-1), a potent proatherogenic vasoconstrictive peptide, is known to promote macrophage foam cell formation via mechanisms that are not fully understood. Excessive lipid accumulation in macrophages is a major hallmark during the early stages of atherosclerotic lesions. Cholesterol homeostasis is tightly regulated by scavenger receptors (SRs) and ATP-binding cassette (ABC) transporters during the transformation of macrophage foam cells. Lin et al investigated the possible mechanisms by which ET-1 affects lipid accumulation in macrophages. Oxidized low density lipoprotein (oxLDL) treatment increases lipid accumulation in rat bone marrow-derived macrophages. Combined treatment with ET-1 and oxLDL significantly exacerbated lipid accumulation in macrophages as compared to treatment with oxLDL alone. ET-1 markedly decreased the ABCG1 levels via ET type A and B receptors and activation of the phosphatidylinositol 3-kinase pathway; however, ET-1 had no effect on the protein expression of CD36, SR-BI, SR-A, or ABCA1. ET-1 treatment did not affect *ABCG1* mRNA expression. ET-1 decreases ABCG1 possibly due to the enhancement of the proteosome/calpain pathway-dependent degradation of ABCG1. ET-1 significantly reduced the efficiency of the cholesterol efflux in macrophages. ET-1 may impair cholesterol efflux and further exacerbate lipid accumulation during the transformation of macrophage foam cells.
Lipid and cholesterol metabolism in the postprandial phase is associated with both quantitative and qualitative remodeling of HDL particle subspecies that may influence their anti-atherogenic functions in the reverse cholesterol transport pathway. Julia et al evaluated the capacity of whole plasma or isolated HDL particles to mediate cellular free cholesterol (FC) efflux, cholesteryl ester transfer protein (CETP)-mediated cholesteryl ester (CE) transfer, and selective hepatic CE uptake during the postprandial phase in subjects displaying type IIB hyperlipidemia. Postprandial, large HDL2 displayed an enhanced capacity to mediate FC efflux via both scavenger receptor class B type I (SR-BI)-dependent (+12%) and ATP binding cassette transporter G1 (ABCG1)-dependent (+31%) pathways in *in vitro* cell systems. The capacity of whole postprandial plasma (4 h and 8 h postprandially) to mediate cellular FC efflux via the ABCA1-dependent pathway was significantly increased (+19%). Concomitantly, postprandial lipemia was associated with elevated endogenous CE transfer rates from HDL2 to apoB lipoproteins and with attenuated capacity (-17%) of total HDL to deliver CE to hepatic cells. Postprandial lipemia enhanced SR-BI and ABCG1-dependent efflux to large HDL2 particles. Postprandial lipemia is equally associated with deleterious features by enhancing formation of CE-enriched, triglyceride-rich lipoprotein particles through the action of CETP and by reducing the direct return of HDL-CE to the liver.
Adiponectin: Expression of the activator protein (AP) 2β is closely associated with type-2 diabetes and negatively regulates expression of the adiponectin gene. Iwamoto and Yokoyama reported that AP-2α negatively regulates the ATP-binding cassette A1 (*ABCA1*) gene through its Ser-phosphorylation by protein kinase (PK) D. The phosphorylation site of AP-2α located in the basic domain, a critical site for its DNA binding, is conserved among species and five subtypes of AP-2. Knockdown of *PKD* by its siRNA led to the increase in the mRNA and the promoter activity of adiponectin, and resulted in increase of adiponectin secretion and decrease of fat accumulation in cultured cells. PKD activators decreased expression of the adiponectin gene, and its inhibition by *PKD* siRNA and by a selective inhibitor GO6983 canceled this effect. ChIP analysis demonstrated that inhibition of PKD activity decreased the DNA binding of AP-2β to the adiponectin promoter. *PKD* is a common modulator of the DNA binding activity of AP-2α and AP-2β through their phosphorylation for negative regulation of the *ABCA1* and adiponectin genes expression, respectively.
alpha-Lipoic acid: α-Lipoic acid (α-LA), a key cofactor in cellular energy metabolism, has protective activities in atherosclerosis. Cheng et al examined whether α-LA affects foam cell formation and its underlying molecular mechanisms in murine macrophages. Treatment with α-LA markedly attenuated oxidized low-density lipoprotein (oxLDL)-mediated cholesterol accumulation in macrophages, which was due to increased cholesterol efflux. Additionally, α-LA treatment

dose-dependently increased protein levels of ATP-binding cassette transporter A1 (ABCA1) and ABCG1 but had no effect on the protein expression of SR-A, CD36, or SR-BI involved in cholesterol homeostasis. α-LA increased the mRNA expression of *ABCA1* and *ABCG1*. α-LA-mediated suppression of oxLDL-induced lipid accumulation was abolished by *GGPP* or *LXRα* siRNA treatment. LXRα-dependent upregulation of ABCA1 and ABCG1 may mediate the beneficial effect of α-LA on foam cell formation.

Alzheimer's disease: Variant (219K, 883I, and 1587R), or promoter variant (14T) in concert with the *APOE-4* allele, increase the risk of Alzheimer's disease. Both single marker alleles and haplotypes of *ABCA1* contribute to variable cerebrospinal fluid tau and β-amyloid protein levels, and brain β-amyloid load. Results indicate that variants of *ABCA1* may affect the risk of Alzheimer's disease (AD), providing support for a genetic link between AD and cholesterol metabolism. In 42 individuals with AD, an association was found between increased CSF cholesterol and β-amyloid protein levels. In a separate study of a Swedish population of 1177 individuals with a first myocardial infarction event and 1526 controls, an association between the R219K polymorphism and serum levels of apolipoprotein B (APOB) and LDL-C was found among smokers, but not among nonsmokers.

Aberrant cholesterol metabolism has been implicated in Alzheimer's disease (AD). Underexpression of NPC1 in concert with under-expression of ABCA1 would result in increased cholesterol accumulation and increased AD risk. Rodríguez-Rodríguez examined a functional polymorphism in the *ABCA1* promoter region (-477, rs2422493), and four *NPC1* polymorphisms in exon 6 (rs18050810), intron 20 (rs4800488), intron 22 (rs2236707), and intron 24 (rs2510344) capturing 85% of genetic variability in the Hap Map Caucasian (CEU) population, in a group of 631 Spanish AD patients and 731 controls. Subjects carrying both the *ABCA1* (-477) TT genotype and the *NPC1* (exon 6) GG genotype, *NPC1* (intron 20) AA genotype, *NPC1* (intron 22) AA genotype or *NPC1* (intron 24) GG genotype may have higher risk of developing AD than subjects without these risk genotypes.

ATP-binding cassette transporter A1 (ABCA1) reduces amyloid-beta burden in transgenic mouse models of AD. Associations between *ABCA1* polymorphisms and AD risk are also established. Kim et al assessed *ABCA1* mRNA and protein expression in the hippocampus of AD cases compared to controls. *ABCA1* was clearly expressed in hippocampal neurons and expression was increased two- to three-fold in AD cases. The increased hippocampal *ABCA1* expression was associated with increased *APOE* and *PUMA* gene expression, implying an association with neuronal stress. Consistent with this, treatment of SK-N-SH neurons with amyloid-beta peptide resulted in a 48% loss in survival and a significant upregulation of *ABCA1*, *APOE*, and *PUMA* gene expression. Studies in young (2 month) and old (12 month) transgenic mice expressing a familial AD form of human amyloid-beta protein precursor and presenilin-1 revealed a significant age-dependent upregulation of hippocampal *Abca1* compared to wild-type control mice. However, hippocampal *Apoe* and *Puma* gene expression were not correlated with increased *Abca1* expression in mice. *ABCA1* is upregulated in AD hippocampal neurons potentially via an amyloid-beta-mediated pathway.

Cholesterol content of cerebral membranes is tightly regulated by elaborate mechanisms that balance the level of cholesterol synthesis, uptake and efflux. Among the conventional regulatory elements, a recent research focus has been nuclear receptors, a superfamily of ligand-activated transcription factors providing an indispensable regulatory framework in controlling cholesterol metabolism pathway genes. The mechanism of transcriptional regulation by nuclear receptors such as LXRs involves formation of heterodimers with RXRs. LXR/RXR functions as a sensor of cellular cholesterol concentration and mediates cholesterol efflux by inducing the transcription of key cholesterol shuffling vehicles, namely ATP-binding cassette transporter A1 (ABCA1) and ApoE. Akram et al provided evidence from direct analysis of human *post-mortem* brain gene and protein expression suggesting that RXRα, a key regulator of cholesterol metabolism, is differentially expressed in individuals with dementia. RXRα expression showed strong association with *ABCA1* and *ApoE* gene expression, particularly in Alzheimer's disease vulnerable regions. LXR/RXR-induced upregulation of ABCA1 and ApoE levels may be the molecular determinants of cholesterol dyshomeostasis and of the accompanying dementia observed in Alzheimer's disease.

ApoE-1 mimetic peptide D4-F: Adenosine triphosphate-binding cassette transporter A1 (ABCA1) plays a crucial role in apolipoprotein A-I (apoA-I) binding activity and promotes cellular cholesterol efflux. ApoA-I mimetic peptide D4-F has been reported to have similar ability to apoA-I. Liu et al investigated the effects of D4-F on *ABCA1* expression and *ABCA1*-dependent cholesterol efflux and examined the role of the Cdc42/cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) pathway on the regulation of ABCA1 by D4-F in THP-1 macrophage-derived foam cells. D4-F stabilized ABCA1 protein and enhanced ABCA1-dependent cholesterol efflux but had no effect on *ABCA1* messenger RNA expression. D4-F enhanced cAMP level and PKA activity and ABCA1 serine phosphorylation. Short interfering RNA of PKA led to reduction of ABCA1 serine phosphorylation and ABCA1-mediated cholesterol efflux compensated by D4-F. PKA-specific activation by PKA agonist enhanced the upregulation of ABCA1 serine phosphorylation and ABCA1-mediated cholesterol efflux by D4-F. ABCA1 expression did not change by treatment with PKA agonist or PKA-short interfering RNA. Secramine B, a Cdc42 inhibitor, reduced the cAMP level compensated by D4-F. D4-F enhances ABCA1 serine phosphorylation and ABCA1-dependent cholesterol efflux through the Cdc42/cAMP/PKA pathway in THP-1 macrophage-derived foam cells.

ARL7: Ligand activation of liver X receptors (LXRs) has been shown to impact both lipid metabolism and inflammation. One complicating factor in studies utilizing synthetic LXR agonists is the potential for pharmacologic and receptor-independent effects. Hong et al described an LXR gain-of-function system that does not depend on the addition of exogenous ligand. They generated transgenic mice expressing a constitutively active VP16-LXRα protein from the *aP2* promoter. These mice exhibit increased LXR signaling selectively in adipose tissue and macrophages. Analysis of gene expression in primary macrophages derived from two independent *VP16-LXRα* transgenic lines confirmed the ability of LXR to drive expression of genes involved in cholesterol efflux and fatty acid synthesis. VP16-LXRα expression also suppressed the induction of inflammatory genes by lipopolysaccharide to a degree comparable to that of a synthetic agonist. They further utilized VP16-LXRα-expressing macrophages to identify and validate new targets for LXRs, including the gene encoding ADP-ribosylation factor-like 7 (*ARL7*). ARL7 has previously been shown to transport cholesterol to the membrane for ABCA1-associated removal and thus may be integral to the LXR-dependent efflux pathway. The *ARL7* promoter contains a functional *LXRE* and can be transactivated by LXRs in a sequence-specific manner, indicating that ARL7 is a direct target of LXR.

Arsenic: Padovani et al set out to determine whether arsenic inhibits transcriptional activation of the liver X receptor (LXR)/retinoid X receptor (RXR) heterodimers, thereby impairing cholesterol efflux from macrophages and potentially contributing to a proatherogenic phenotype. Arsenic is an important environmental contaminant and has been linked to an increased incidence of atherosclerosis. Arsenic inhibits transcriptional activation of type 2 nuclear receptors, known to heterodimerize with RXR. Environmentally relevant arsenic doses decrease the LXR/RXR ligand-induced expression of the LXR target genes (*ABCA1* and *SREBP-1c*). Arsenic failed to decrease cAMP-induced ABCA1 expression, suggesting a selective LXR/RXR effect. This selectivity correlated with the ability of arsenic to decrease LXR/RXR ligand-induced, but not cAMP-induced, cholesterol efflux. Arsenic inhibits the ability of LXR/RXR ligands to induce activation markers on the *ABCA1* and *SREBP-1c* promoters and blocks ligand-induced release of the nuclear receptor coexpressor (NCoR) from the promoter. Arsenic did not alter the ability of LXR to transrepress inflammatory gene transcription, further supporting the hypothesis that RXR is the target for arsenic inhibition. Exposure to arsenic enhances the risk of atherosclerosis. Arsenic may promote an atherosclerotic environment by decreasing the ability of macrophages to efflux excess cholesterol, thereby favoring increased plaque formation.

Aspirin: The efflux of cellular cholesterol mediated by apolipoprotein (apo)A-I and ATP-binding cassette transporter A1 (ABCA1) is a major pathway of reverse cholesterol transport. Wang et al investigated the effect of aspirin on this process. Aspirin increased apoA-I-mediated cholesterol efflux and increased the expression of *ABCA1*. By increasing the dose of aspirin, *ABCA1* expression and function were significantly decreased. In cells transfected with a specific peroxisome proliferator-activated receptor (*PPAR*)-α small interfering RNA, the induction of *ABCA1* expression and apoA-I-mediated ^{3}H-cholesterol efflux by aspirin were substantially suppressed. Low-dose aspirin increases *ABCA1* expression via a PPAR-α-dependent mechanism and increases apoA-I-mediated cholesterol efflux.

Atherosclerosis: ABCA1 protein degradation is regulated by a PEST sequence (a sequence rich in proline, glutamic acid, serine, and threonine) in *ABCA1* and is mediated by calpain protease. In a novel form of positive feedback control, the interaction of ABCA1 with APOA1 leads to inhibition of calpain protease degradation and an increase in ABCA1 protein on the cell surface. ABCA1 degradation by calpain may represent a novel therapeutic approach to increasing macrophage cholesterol efflux and decreasing atherosclerosis.

Insulin resistance/hyperinsulinism is one of the major risks for atherosclerotic vascular diseases. Low HDL may be involved in the pathogenesis of atherosclerosis. Nonomura et al examined the effects of insulin on HDL biosynthesis, focusing on the activity of ATP-binding cassette transporter A1 (ABCA1) in culture cells and in experimental animals. Insulin impairs HDL biosynthesis through modulation of ABCA1 activity by two different mechanisms. Insulin enhances degradation of ABCA1. This effect was found due to phosphorylation of ABCA1, which leads to a decrease in its specific activity. The authors identified a novel insulin-specific phosphorylation site of ABCA1, Tyr1206, which regulates its specific activity.

A crucial step in atherogenesis is the infiltration of the subendothelial space of large arteries by monocytes where they differentiate into macrophages and transform into lipid-loaded foam cells. Macrophages are heterogeneous cells that adapt their response to environmental cytokines. Th1 cytokines promote monocyte differentiation into M1 macrophages, whereas Th2 cytokines trigger an "alternative" M2 phenotype. Chinetti-Gbaguidi et al reported the presence of CD68$^+$ mannose receptor (MR$^+$) M2 macrophages in human atherosclerotic plaques. Histological analysis revealed that CD68$^+$ MR$^+$ macrophages locate far from the lipid core of the plaque and contain smaller lipid droplets compared to CD68$^+$ MR$^-$ macrophages. Interleukin (IL)-4-polarized CD68$^+$ MR$^+$ macrophages display a reduced capacity to handle and efflux cellular cholesterol because of low expression levels of the nuclear receptor liver x receptor (LXR)α and its target genes, *ABCA1* and apolipoprotein E, attributable to the high 15-lipoxygenase activity in CD68$^+$ MR$^+$ macrophages. By contrast, CD68$^+$ MR$^+$ macrophages highly express opsonins and receptors involved in phagocytosis, resulting in high phagocytic activity. In M2 macrophages, peroxisome proliferator-activated receptor (PPAR)γ activation enhances the phagocytic but not the cholesterol trafficking pathways. These data reflect the existence of a distinct macrophage subpopulation with a low susceptibility to become foam cells but high phagocytic activity resulting from different regulatory activities of the PPARγ-LXRα pathways.

Atherosclerosis is an inflammatory disease characterized by the accumulation of macrophages in the arterial intima. The activated macrophages secrete more proinflammatory cytokines, such as tumor necrosis factor (TNF)-alpha, which promote the development of the disease. Apolipoprotein A1 (apoA1), the major component of high-density lipoprotein (HDL), is involved in reverse cholesterol transport (RCT) of lipid metabolism. ApoA1 suppresses inflammation via repression of inflammatory cytokine expression. Yin et al reported that apoA1 suppresses the expression of some inflammatory cytokines induced by lipopolysaccharide (LPS) via a specific post-transcriptional regulation process, namely mRNA destabilization, in macrophages. AU-rich elements (AREs) in the 3' untranslated region (UTR) of *TNF*-α mRNA are responsive to the apoA1-mediated mRNA destabilization. The apoA1-induced inflammatory cytokine mRNA destabilization was associated with increased expression of mRNA-destabilizing protein tristetraprolin (TTP) through a JAK2/STAT3 signaling pathway dependent manner. When blocking interaction of apoA1 with ATP-binding membrane cassette transporter A1 (ABCA1), a major receptor for apoA1 in macrophages, it almost totally abolished the effect of apoA1 on TTP expression.

Macrophages cannot limit the uptake of lipids and rely on cholesterol efflux mechanisms for maintaining cellular cholesterol homeostasis. Important mediators of macrophage cholesterol efflux are ATP-binding cassette transporter 1 (ABCA1), which mediates the efflux of cholesterol to lipid-poor apolipoprotein AI, and scavenger receptor class B type I (SR-BI), which promotes efflux to mature high-density lipoprotein. Zhao et al studied the putative synergistic roles of ABCA1 and SR-BI in foam cell formation and atherosclerosis. Low-density lipoprotein receptor knockout (*LDLr* KO) mice were transplanted with bone marrow from *ABCA1/SR-BI* double knockout mice, the respective single knockouts, or wild-type littermates. Serum cholesterol levels were lower in *ABCA1/SR-BI* double knockout transplanted animals, as compared to the single knockout and wild-type transplanted animals on Western-type diet. Despite the lower serum cholesterol levels, massive foam cell formation was found in macrophages from spleen and the peritoneal cavity. BI double knockout transplanted animals also showed a major increase in proinflammatory KC (murine interleukin-8) and interleukin-12p40 levels in the circulation. After 10 weeks of Western-type diet feeding, atherosclerotic lesion development in the aortic root was more extensive in the *LDLr* KO mice reconstituted with *ABCA1/SR-BI* double knockout bone marrow. Deletion of *ABCA1* and *SR-BI* in bone marrow-derived cells enhances *in vivo* macrophage foam cell formation and atherosclerotic lesion development in *LDLr* KO mice on Western diet, indicating that under high dietary lipid conditions, both macrophage ABCA1 and SR-BI contribute significantly to cholesterol homeostasis in the macrophage *in vivo* and are essential for reducing the risk for atherosclerosis.

Atherosclerosis has been characterized as a chronic inflammatory response to cholesterol deposition in arteries. Plasma high density lipoprotein (HDL) levels bear a strong independent inverse relationship with atherosclerotic cardiovascular disease. One central antiatherogenic role of HDL is believed to be its ability to remove excessive peripheral cholesterol back to the liver for subsequent catabolism and excretion, a physiologic process termed reverse cholesterol transport (RCT). Cholesterol efflux from macrophage foam cells, the initial step of RCT, is the most relevant step with respect to atherosclerosis. The ATP-binding cassette (ABC) transporters ABCA1 and

Pharmacogenomic Synopsis

Drug	Related Genes	Substrate	Inhibits	Induces
Abacavir				
Anti-Infective Agent, Antiretroviral, Nucleoside and Nucleotide Reverse Transcriptase Inhibitor (ATC Code: J05AF06)	ADH1, rs1230025 HLA-A, HLA-B*57:01, HLA-B*57:03, HLA-B*5701, HLA-B*5703 subtype, HLA-B5701 subtype, HLA-B5703 subtype HLA-B, TNFRSF1A ABCB1, ABCC4, ADH1C, CYP1B1, UGT1A1, UGT2B7		ABCC1 ABCC4	CYP2B6
Abacavir and Lamivudine				
Anti-Infective Agents, Antimicrobial, Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (ATC Code: J05AR02)	ADH1, rs1230025 HFE, C282Y HLA-A, HLA-B*5701, HLA-B*5703, HLA-B5701 subtype, HLA-B5703 subtype, HLA-DR4 subtype HSPA1L, Thr493Met ABCB1, ABCC4, ABCG2, ADH1B, CR1, CYP1A1, UGT2B7		ABCC1 ABCC4	CYP2B6
Abacavir, Lamivudine, and Zidovudine				
Anti-Infective Agents, Antimicrobial, Nucleoside and Nucleotide Reverse Transcriptase Inhibitors (ATC Code: J05AR04)	ABCC2, C1515T, G3563A, G3724A, T4131G ABCG2, G421A and G34A CR1, CR1*1, CR1*2, CR1*3 CYP2C9, CYP2C9*2, CYP2C9*3, CYP2C9*5 CYP2C19, CYP2C19*2, CYP2C19*3, CYP2C19*4, CYP2C19*5, CYP2C19*6, CYP2C19*7, CYP2C19*8, CYP2C19*9, CYP2C19*10 CYP3A4, CYP3A4*1, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*7, CYP3A4*8, CYP3A4*9, CYP3A4*10, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*14, CYP3A4*15, CYP3A4*16, CYP3A4*17 HFE, C282Y HLA-A, HLA-B*5701, HLA-B*5703, HLA-B5701 subtype, HLA-B5703 subtype, HLA-DR4 subtype HSPA1L, Thr493Met JUP, rs1799937 UGT2B7, rs7439366 ABCB1, ABCC1, ABCC4, ABCG2, ADH1B, CR1, CYP1A1, UGT1A1, UGT2B7		ABCC1 ABCC4	CYP2B6
Abatacept				
Antirheumatic Drug (ATC Code: L04AA24)	CD28, CTLA4, CD80, CD86, IRF5, STAT4			
Abciximab				
Antithrombotic Agent, Platelet-aggregation Inhibitor, Glycoprotein IIb/IIIa Inhibitor (ATC Code: B01AC13)	ITGB3, Ile727Leu[Phe] ITGA2, ITGB3, rs1126643			
Acamprosate				
Central Nervous System Agent, GABA Agonist/Glutamate Antagonist (ATC Code: N07BB03)	GABRA, GABRB1, GABRG2, GRM1, GRM2A, GRM3R, GRM3A, GRM5, GRM7, GRM8, GRIA1			
Acarbose				
Antidiabetic Agent α-Glucosidase Inhibitor (ATC Code: A10BF01)	ACPP, c.403G>A, c.578G>T PPARG, Pro12Ala PPARGC1A, Gly482Ser ADIPOR, rs7539542			
Acebutolol				
Cardiovascular Drug, β-Adrenergic Blocking Agent, Intrinsic Sympathomimetic Activity (ATC Code: C07AB04)	ACE, I/D ADRB1, Ser49Gly, Arg389Gly ADRB2, Gly16Arg, Arg34Gln, Gln27Glu, Thr52Ile VKORC1, 5c1013a, T/C		CYP2D6 (weak)	
Acenocoumarol				
Antithrombotic Agent, Anticoagulant, Coumarin Derivative, Vitamin K Antagonist (ATC Code: B01AA07)	ABCB1, 2677insTA/4605C haplotype APOE, APOE-4 CALU, A23590G CYP2C9, CYP2C9*2, CYP2C9*3, CYP2C9*5 VKORC1, -3673G>A, 1542G>C, 2255C>T, 2506A>T, 3730G>A, 6484C>T, 9041A>G, C1173T, G-1639A, G3730A CYP2A6, CYP4F2	ABCB1 CYP1A2 (major) CYP2A6 (major) CYP2C8 (minor) CYP2C9 (minor) CYP2E1 (major) CYP3A4 (major) ELAT1A1 ELAT1A3/4 ELET1E1 ELAT2A1 UGT1A1 UGT1A6 UGT1A9		
Acetaminophen (Paracetamol)				
Analgesic and Antipyretic, Miscellaneous (ATC Code: N02BE01)	CYP1A2, C734A, G-3364A CYP2C9, CYP2C9*2, CYP2C9*3, CYP2C9*5 CYP2E1, CYP2E1*1, CYP2E1*2, CYP2E1*3, CYP2E1*4, CYP2E1*5, CYP2E1*6 CYP3A4, CYP3A4*1, CYP3A4*2, CYP3A4*3, CYP3A4*4, CYP3A4*5, CYP3A4*6, CYP3A4*7, CYP3A4*8, CYP3A4*9, CYP3A4*10, CYP3A4*11, CYP3A4*12, CYP3A4*13, CYP3A4*14, CYP3A4*15, CYP3A4*16, CYP3A4*17 UGT1A1, Gly71Arg UGT1A1, UGT1A1*28 UGT1A6, UGT1A6*2 ABCB1, ABCB11, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC10, ABCC11, ABL1, ACADM, ACSL1, ACSL3, ACSL4, ACSL5, ADH1A, ADH1B, ADH1C, ADH4, ADH7P4, ADORA2A, ADRB1R, AGA1, AHR, ALDH1A1, ALDH2, ALDH3A1, ALDH9, ANK1, APEX1, APOA1, ARTN4, ASAH1, ASIP, ATP7A, BCHE, CALU, CBR3, CES1, CLMN1, CDA, CES1, CES2, CHRM3, CHRNA4, COMT, CRBN, CSNK1E, CYP27B1, CYP7A1, CYP7B1, DDC, DDX3X, DHFR, DPYD, DYRK1A, EIF2AK2, EPHX1, ESR1, F2, FABP2, FGD1, FTH1, FUT1, GBE1, GLB1, GLO1, GNAI2, GNB1, GNB2, GNB3, GNG2, GOT1, GOT2, GPD1, GPX1, GSTA1, GSTM1, GSTP1, HFE, HMOX1, HNF4A, HPRT1, HSD11B1, HSD17B4, HSPA1L, HSPB1, IDH1, IMPA1, INPP1, ITPA, KAT2A, KCNJ11, KCNJ5, LIPC, MAOA, MAOB, MAPK1, MCCC1, MCCC2, MDH1, MDH2, MGST1, MGST2, MGST3, MOCOS, MPO, MVD, NAAA, NCOA3, NCOA6, NFE2L2, NQO1, OPRM1, PDGFRA, PDGFRB, PEMT, PGLS, PNMT, PON1, PON2, PON3, PPARA, PPARD, PPARG, PPP1CA, PPP2CA, PPP2R1A, PPP2R5C, PTGDS, PTGS2, RARA, RGS16, SLC11A1, SLC19A1, SLC22A1, SLC22A4, SLC22A5, SOD1, SOD2, SPR, TAT, TBXAS1, TF, TGM2, TPMT, TYMS, UCHL1, UGT1A10, UGT1A3, UGT1A4, UGT2A1, UGT2A2, UGT2B10, UGT2B11, UGT2B15, UGT2B17, UGT2B4, UGT2B7, UMPS, VDR, XDH, XPA, XPC, YWHAZ, ZNF259, ZNF423, ZNF652	CYP1A2 (minor) CYP2A6 (minor) CYP2C8 (minor) CYP2C9 (minor) CYP2E1 (major) CYP3A4 (major) ELAT1A1 ELAT1A3/4 ELET1E1 ELAT2A1 UGT1A1 UGT1A6 UGT1A9	CYP3A5 (moderate) UGT1A1	CYP2E1

Drug	Related Genes	Substrate	Inhibitor	Inducer
Acetazolamide				
Antiglaucoma Agent; Antiglaucoma Agent: Diuretic (ATC Code: S01EC01)	CA1		CA CYP2A6 (weak)	
Acetylsalicylic acid				
Analgesic; Antipyretic; Platelet Aggregation Inhibitor (ATC Code: N02BA01)	PTGS1			
Acetylcholine				
Antiglaucoma Agent; Miotic; Parasympathomimetic; Neurotransmitter; Cholinergic Agonist (ATC Code: S01EB09)	ACHE; APOE 4 BCHE; KCNH2 CHRNA1; CHRNA7; CHRNB1; CHRNE; CHRND CHRM1; CHRM2; CHRM3 DNER; SNTB2 KCNH2; SNORD96A ABCC4; ACHE; APP; CHAT; CHRM1; CHRM2; CHRM3; IL1B; TYK2			
Acetylcysteine				
Antidote; Mucolytic Agent (ATC Code: R05CB01; S01XA03; V03AB23)	ABCC1; ABCC2; ALB; F7; GGT1; IL10RB; IL1RAP; IL1RL1; IL18; IL18R1; IL33; LTA; NQO1; PTGS2; SLC22A1; SLC22A2; SLC22A3; SLC22A5; TNF; TYK2; VEGFA			
Acitretin				
Antipsoriatic Agent; Retinoid Like Compound (ATC Code: D05BB02)	ARSA; CHRM3 CCND1; EMC6; KRT6			
Aciclovir				
Antiviral Agent; Nucleoside and Nucleotide (ATC Code: J05AB01; J05AB51; S01AD03)	CMPK1; TNF	SLC22A6	SLC22A1 SLC22A2 SLC22A3	
Adalimumab				
GI Drugs; Disease modifying Antirheumatic Drug; Immunosuppressant; Tumor Necrosis Factor Inhibitor; Monoclonal Antibody (ATC Code: L04AB04)	FCGR3A; NR1H4Pre TYK; ZBMG; ZBMG; ABCC1			
Adefovir				
Antiviral Agent; Nucleoside and Nucleotide; Reverse Transcriptase Inhibitor (ATC Code: J05AF08)	ABCC4; GLYAT1p; GLYAT2p; MTRR1Dys SLC22A6; MgMDHs; AgGGT1p; AsgSAS1p SLC22A1; SLC22A2		CYP2C9 (moderate) CYP3A4 (moderate)	
Adenosine				
Class V Antiarrhythmics; Therapeutic Agent; Diagnostic Agent (ATC Code: C01EB10)	ABCC1; ABCC2; ABCC4; ADA; ATOH8A; ADORA1; CPNE; DPP; HMBT; KDR1; SLC28A1; TNF; VDR1			
Agalsidase Alpha				
Enzyme; ATC Code: A16AB03;	GLA			
Agalsidase Beta				
Enzyme; ATC Code: A16AB04;	GLA			
Agomelatine				
Antidepressant; Melatonergic agonist (MT1 and MT2 receptors) and 5-HT2C antagonist (ATC Code: N06AX22)	CNR1A; HTR2C; MTNR1A; MTNR1B	CYP1A2 (major) CYP2C9 (minor) CYP2C19 (minor)		
Alemtuzumab				
Antineoplastic Agent; Immunosuppressant; Monoclonal Antibody (ATC Code: L04AA34)	CD52; CD52 G-28kDa CFDA1 and CYP3A1; CHRNA1; CHRNA7; CHRNB1; CHRND; CHRNE; CHRM1; CHRM2; CHRM3; CHRNA1; CHRNA7; CHRNB1; CHRNE; CHRND; CHRM1; CHRM2; CHRM3; CYP1A1; CYP1A2; CYP2A6; CYP2A13; CYP2B6; CYP2C8; CYP2C9; CYP2C18; CYP2C19; CYP2D6; CYP2E1; CYP2F1; CYP3A4; CYP3A5; CYP3A7; CYP4B1 ABCB1; CYP3A4	CYP1A2 (weak) CYP2C8 (major) CYP3A4 (major) PMCA	CYP1A2 (weak)	
Alkeran				
Blood Dyscrasias; Cultural Atoms; volume expander (ATC Code: B03AA01)	APOE; APOE-ε; APOE-3; APOE-4 ABCB1		CYP2C9 (moderate) CYP3A4 (moderate)	
Alkaloid (Belladonna)				
Sympathomimetic (Adrenergic) Agent; Selective β1 Adrenergic Agonist; Bronchodilator; Adrenergic Agent; Selective β2 Adrenergic Agonist (ATC Code: R03AC02)	ADRB1; Ile712Met ADRB2; Arg16Gly; Gln27Glu; Val64Met; Thr164Ile; Cys164Arg ACHE; NR3C1			
Alprostadil				
Anti-Inflammatory Agent; Topical Corticosteroid (ATC Code: D11AX01; S01BA15)	CYJ1; PLA2G1B1a			
Alcohol (Ethyl/Ethanol)				
Local Anti-Infective; Antidote (ATC Codes: D08AX08; V03AB16; V04AB01)	ADH1A; ADC+T ADH1B; ADH1B*2 ALDH2; Glu504Lys CYP2E1; CYP2E1*1B; CYP2E1*1C; CYP2E1*1D; CYP2E1*5 ADH; +ADH ABCC1; ABCC2; ALB; ALDH1A1; ADRB1A; B-LEVAT; ALDH2; BDNF; BRCA1; CYP1A1; CYP1A2; CYP2A6; CYP2A13; CYP2B6; CYP2C8; CYP2C9; CYP2C18; CYP2C19; CYP2D6; CYP2E1; CYP2F1; CYP3A4; CYP3A5; CYP3A7; CYP4B1; DRD2; FADS1; FOS; GSTM1; GSTP1; HMOX1; HRAS; IL1B; IL6; IL10; IL18; IL18R1; IL33; LTA; MAPK1; MAPK3; MTHFR; NFKB1; NOS2; NQO1; PTGS2; SLC22A1; SLC22A2; SLC22A3; SLC22A5; TNF; TYK2; VEGFA; VDR1	ADHs ALDHs CYP1A1 (major) CYP1A2 (major) CYP2A6 (major) CYP2B6 (major) CYP2C8 (major) CYP2C9 (major) CYP2C18 (major) CYP2C19 (major) CYP2E1 (major) CYP2F1 (major) CYP3A4 (major)	CYP1A1 (moderate) CYP2A6 (moderate) CYP2C8/11 (moderate) CYP2C19 (moderate) CYP3A4 (weak)	CYP1A1 CYP2A6 CYP3A4 CYP2E1
Aldesleukin				
Antineoplastic Agent; Immunostimulant; Biological Modifier (ATC Code: L03AC01)	IL2RA; IL2RB; IL2RG			
Alefacept				
Skin and Mucous Membrane Agent; Antipsoriatic; Immunosuppressive Agent; Monoclonal Antibody (ATC Code: L04AA15)	CD2; CD28; CXCC-CCR; CD3; FCGR1A; FCGR2A; FCGR3B; FCGR3C; FCGR3A; FCGR3F			
Alemtuzumab				
Antineoplastic Agent; Monoclonal Antibodies (ATC Code: L01XC04)	CD52; FCGR1A; FCGR3B			
Alendronate				
Bone Resorption Inhibitor; Bisphosphonate Derivative (ATC Code: M05BA04)	ATP-Beta CCL101; IRAK1; MMP1; TLR4rs; TLR4rs; TLR4rs			
Alentuzumab				
Analgesic and Antipyretic; Opioid Agonist; Antidyskinetics; Opioid (ATC Code: N01AH02)	CNR1; Val158Met (rs4633Met) CFDA1 and CYP3A1; CHRNA1; CHRNA7; CHRNB1; CHRND; CHRNE; CHRM1; CHRM2; CHRM3; CHRNA1; CHRNA7; CHRNB1; CHRNE; CHRND; CHRM1; CHRM2; CHRM3; CYP1A1; CYP1A2; CYP2A6; CYP2A13; CYP2B6; CYP2C8; CYP2C9; CYP2C18; CYP2C19; CYP2D6; CYP2E1; CYP2F1; CYP3A4; CYP3A5; CYP3A7; CYP4B1 ABCB1; CYP3A4	CYP3A4/5 (major) CYP2D6 (major)		

Drug	Related Genes	Substrate	Inhibitor	Inducer
Afatinib				
Tyrosine Kinase Inhibitor, Irreversible Blocking Agent, Selective ErbB Receptor Blocking Agent, Quinazoline Derivative (ATC Code: L01EB03)	ADRA1A, ADRA1B, ADRA1D	CYP3A4 (major)		
Alglucerase				
Enzyme (ATC Code: A16AB01)	GBA			
Alglucosidase Alfa				
Enzyme (ATC Code: A16AB07)	GAA, M6PR			
Aliskiren				
Renin Inhibitor (ATC Code: C09XA02)	CYP3A4 and CYP1A2, CYP2A6[1], CYP2A7[2], CYP2B6[3], CYP2C8[4], CYP2C9[5], CYP2C18[6], CYP2C19[7], CYP2D6[8], CYP2E1[9], CYP2F1[10], CYP2J2[11], CYP2R1[12], CYP2S1[13], CYP3A5[14], CYP3A7[15], CYP4F2[16] REN, SLC15A1	ABCB1, CYP3A4 (major)	CYP3A4 (moderate), REN	
Allopurinol				
Antigout Agent, Xanthine Oxidase Inhibitor (ATC Code: M04AA01)	NCAM, NCA-95/CD67, NCA-90/CD66c, NCA-50/CD66b, NCA-160/CD66a, NCA-x/CD66d subtype CDK, Arg-tRNA, PHKB Kyc, Prostatin, Arginosin, THADtide, Asn-tRNA Kyc, Pro-tRNA Arg, Cort (rRNA), NCDW XDH, SLC22A7, TAF	SLC22A8		ABCC4
Alosetron				
Antagonist Agent, Selective Serotonin Agonist, (ATC Code: A03AE03)	CYP1A1 and CYP1A2, CYP2A6[1], CYP2A7[2], CYP2B6[3], CYP2C8[4], CYP2C9[5], CYP2C18[6], CYP2C19[7], CYP2D6[8], CYP2E1[9], CYP2F1[10], CYP2J2[11], CYP2R1[12], CYP2S1[13], CYP3A5[14], CYP3A7[15], CYP4F2[16] MTHFR, MTR, TYMS, UGT1A	ALDH1, CYP2C8 (major), CYP3A4 (major), FMO3, MAOA		
Alosetron				
Anti-Inflammatory Agent, Selective 5-HT3 Receptor Antagonist (ATC Code: A03AE01)	HTR3A, SLC5A4	CYP1A2 (minor), CYP2C9 (minor), CYP3A4 (major)	CYP1A2 (weak), CYP2E1 (weak)	
Alpha1-Proteinase Inhibitor				
Antiemphysematous Agent, Protease Inhibitor (ATC Code: B02AB)	ELANE, SERPINA1, SERPINA2, SERPINA11			
Alprostadil				
Analgesic, Sedative, and Hypnotic Benzodiazepine (ATC Code: N05BA12)	CYP1A1 and CYP1A2, CYP2A6[1], CYP2A7[2], CYP2B6[3], CYP2C8[4], CYP2C9[5], CYP2C18[6], CYP2C19[7], CYP2D6[8], CYP2E1[9], CYP2F1[10], CYP2J2[11], CYP2R1[12], CYP2S1[13], CYP3A5[14], CYP3A7[15], CYP4F2[16] CYP2C19, GABRA6	CYP1A1 (minor), CYP1A2 (minor), CYP2C8 (minor), CYP3A4/5 (major)		
Apraclonidine				
Vasodilating Agent, Prostaglandin (ATC Code: C01EA01) GABBR1, GABBR2	PCSK1, Rab39B/Ac ABCC8, KCNE2, PTGER3			
Aliskiren				
Thrombolytic Agent, Enzyme (ATC Code: B01AD02, S01XA15)	SLC, InterPro (Multi) (20) CLEC1A, F13			
Aluminum Hydroxide				
Antacid and Adsorbent, Antiulcer, Emollient, Demulcent, and Protectant (ATC Code: A02AB01)	ABCC2, ATOB, CAVR, CHIP			
Alvimopan				
G-Protein Coupled, Peripheral Opioid Receptor Antagonist (ATC Code: A06AH02)	OPRM1			
Amantadine				
Antiparkinsonian Agent, Adamantanes Dopamine Agonist (ATC Code: N04BB01)	GRIN1, GRIN2A, GRIN2B, HRH3			
Ambenonium				
Parasympathomimetic (Cholinergic) Agent (ATC Code: S01EA03)	AHR, CHRNA1, CHRNB1, CHRND, CHRNE, SCN4A		ACHE	
Ambrisentan				
Vasodilating Agent, Endothelin Antagonist (ATC Code: C02KX02)	ABCB1, Cldn18.1 (126777.01.24) CYP2C8, CYP2C9[1], CYP2C9[2], CYP2C9[3] CYP3A4 and CYP1A1, CYP1A2, CYP2A6[1], CYP2A6[2], CYP2A6[3], CYP2A6[4], CYP2A6[5], CYP2A6[6], CYP2A6[7], CYP2A6[8], CYP2A6[9], CYP2A6[10], CYP2A6[11], CYP2A6[12], CYP2A6[13], CYP2A6[14], CYP2A6[15], CYP2A6[16], CYP2A6[17] ATP1A3, SLC1A6[2] EDN1, EDNRA, [3] SLC10A1[2]	ABCB1, CYP2C8 (major), CYP2C9 (major), CYP3A4 (major), DRD5, SLCO1A2, UGT1A3, UGT2B7, UGT1A9		
Amfepramone				
Central Nervous System Agent, Pyridine Derivative (ATC Code: N07BA02)	ACHE, KCNA			
Amifostine				
Protective Agent, Chemoprotective Agent, Cytoprotective Antidote (ATC Code: V03AF06)	ALPL, ALPP[1], CYP3A4, GSTM1			
Amikacin				
Antiinfective Agent, Antibacterial, Aminoglycosides (ATC Code: D06AX11, S01AB05, S01AA01)	DTD, Gluco mutations			
Amiloride				
Diuretic, Potassium-Sparing Diuretic (ATC Code: C03DB01)	SCNN1G, TYRP1[Mel] ABCB1, ACCN4, CYP1C1[1][2]			
Aminocaproic acid				
Antihemorrhagic Agent, Hemostatic (ATC Code: B02AA01)	LPA, PLG		PLAT	
Aminoglutethimide				
Antineoplastic Agent, Endocrine Therapy, Hormone Antagonist, Enzyme Inhibitor (ATC Code: L02BG01)	NR2A, NR2B, NR2C, NR2D, NR2E, NR2F, NR2F11, NR2F12, NR2F13, NR2F14		CYP11A1 (strong)	CYP1A2, CYP2B6, CYP3A4, CYP3A5
Aminolevulinic Acid				
Skin and Mucous Membrane Agent, Photosensitizing Agent, Porphyrin Precursor (ATC Code: L01XD04)	ALAD, ALAS2			
Aminophylline				
Bronchodilator, Xanthine Derivative, (ATC Code: R03DA05)	ADRB2, BRD2[Ba] CYP1A2, CYP4A, SLC28A4 ADORA1, ADRB2	CYP1A2 (major), CYP2E1 (minor), CYP3A4 (minor)		
Aminosalicylic Acid				
Antituberculosis Agent, Salicylate, (ATC Code: J04AA01)	ALOX5, FLAD1[Ac], PTGS2			

Pharmacogenomic Synopsis

Drug	Related Genes	Substrate	Inhibits	Induces
Amiodarone				
Class III Antiarrhythmic; ATC-Code C01BD01	ABCB1: C3435T, G2677T, C1236T CYP2C9: CYP2C9*3 CYP2C19: CYP2C19*2, CYP2C19*3 and CYP2C19*17 CYP2D6: [illegible] KCNE2: Gln9Glu, Met54Thr, Thr8Ala KCNH2: Arg784Trp KCNQ1: Arg583Cys SCN5A: Gly615Glu, Leu618Phe, Phe1250Leu, Leu1825Pro [illegible]	CYP1A1 (minor) CYP1A2 (minor) CYP2C8 (major) CYP2C9 (minor) CYP2C19 (minor) CYP2D6 (minor) CYP3A4 (major) CYP3A4 (major)	ABCB1 CYP1A2 (weak) CYP2A6 (moderate) CYP2B6 (weak) CYP2C8 (moderate) CYP2C9 (moderate) CYP2C19 (weak) CYP2D6 (moderate) CYP3A4 (moderate)	CYP1A2
Amitriptyline				
Antidepressant, Tricyclic and Norepinephrine-reuptake Inhibitor (ATC-Code N06AA09)	ABCB1: C3435T, G2677T, C1236T ADRA1A: Arg347Cys CYP1A2: C734A, G-2964A CYP2C9: [illegible] and [illegible] CYP2C19: [illegible] CYP2D6: [illegible] CYP3A4 and CYP3A5: [illegible] [illegible]: ATT→ATC at codon 131 [illegible]: Ser270Ser KCNE2: Gln9Glu, Met54Thr, Thr8Ala KCNH2: Arg784Trp KCNQ1: Arg583Cys SCN5A: Gly615Glu, Leu618Phe, Phe1250Leu, and Leu1825Pro TNF: 308G>A [illegible]	CYP1A2 (minor) CYP2B6 (minor) CYP2C9 (minor) CYP2C19 (minor) CYP2D6 (major) CYP3A4/5 (major)	ABCB1 ABCC2 ABCG2 CYP1A2 (moderate) CYP2C9 (moderate) CYP2C19 (moderate) CYP2D6 (moderate) CYP2E1 (weak)	
Amlodipine				
Calcium Channel Blocking Agent; Dihydropyridine (ATC-Code C08CA01)	ABCB1: C3435T, G2677T, C1236T ACE1: Gly460Trp CYP3A4 and CYP3A5: [illegible] NPPA: T2238C, G664A [illegible]	CYP3A4/5 (major)	ABCB1 CYP1A1 (moderate) CYP1A2 (moderate) CYP2A6 (weak) CYP2B6 (moderate) CYP2C8 (weak) CYP2C9 (moderate) CYP2D6 (moderate) CYP3A4/5 (moderate)	
Amobarbital				
Anxiolytic, Sedative, and Hypnotic; Barbiturate (ATC-Code N05CA02)	[illegible]			CYP2A6
Amodiaquine				
Antimalarial; Aminoquinoline (ATC-Code P01BA06)	CYP2C8: CYP2C8*2, CYP2C8*3, CYP2C8*4 [illegible]	CYP2C8 (major) CYP2C9 (minor)	ABCB1 CYP2C9 (moderate) CYP2D6 (moderate)	
Amonafide				
Antineoplastic Agent; DNA Binding Agent; Topoisomerase II Inhibitor (ATC-Code L01)	NAT2: NAT2*4, NAT2*5, [illegible]		TOP2A	
Amoxapine				
Antidepressant, Tricyclic and Norepinephrine-reuptake Inhibitor (ATC-Code N06AA17)	ADRA1A: Arg347Cys CYP2D6: [illegible] [illegible]: ATT→ATC at codon 131 [illegible]: Ser270Ser [illegible]	CYP2D6 (major)		
Amoxicillin				
Antibacterial; Aminopenicillin (ATC-Code J01CA04)	ABCB1: C3435T [illegible]			
Amphetamine				
Anorexigenic Agent and Respiratory and Cerebral Stimulant; Amphetamines (ATC-Code N06BA01)	COMT: Val158Met [illegible]: [illegible] CYP2D6: [illegible] SLC6A3: Haplotype [illegible] formed from [illegible], [illegible], and [illegible] [illegible]	COMT CYP2D6 (major) CYP3A4 (major)	CYP1A2 (moderate) CYP2D6 (moderate) CYP3A4 (moderate) MAO	
Ampicillin				
Antibacterial; Aminopenicillin (ATC-Code J01CA01, S01AA19)	[illegible]			CYP1A1
Amprenavir				
Antiretroviral; HIV Protease Inhibitor (ATC-Code J05AE05)	ABCB1: G1199A, C3435T, G2677T, C1236T CYP2C9: [illegible] CYP3A4 and CYP3A5: [illegible] [illegible]	CYP2C9 (minor) CYP2D6 (minor) CYP3A4/5 (major)	CYP2C19 (weak) CYP3A4 (strong) CYP3A5 (weak) CYP3A7 (weak)	
Amyl Nitrite				
Vasodilating Agent; Nitrates and Nitrites; Antidote (ATC-Code V03AB22)	[illegible]	ALDH2		
Anagrelide				
Antithrombotic Agent; Platelet-reducing Agent; Phosphodiesterase III Inhibitor (ATC-Code L01XX35)	[illegible]	CYP1A2 (minor)	PLA2G	
Anakinra				
Disease-modifying Antirheumatic Drug; Interleukin-1 Receptor Antagonist (ATC-Code L04AC03)	[illegible]			
[illegible]				
[illegible]	[illegible]			