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Detailed Gene-Drug Report

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Adverse drug reactions (ADRs) represent the fourth leading cause of death in the US[1]. Over 90% of people carry at least 1 genetic variant that should prompt a change in dosing or medication, including pain relievers, antidepressants and blood thinners. Pharmacogenomics can help guide physicians in prescribing the best medicine for you. Pharmacogenomics combines pharmacology (the study of drugs) and genomics (the study of genes and their functions) and involves how variations in a person's DNA can affect their response to drug.

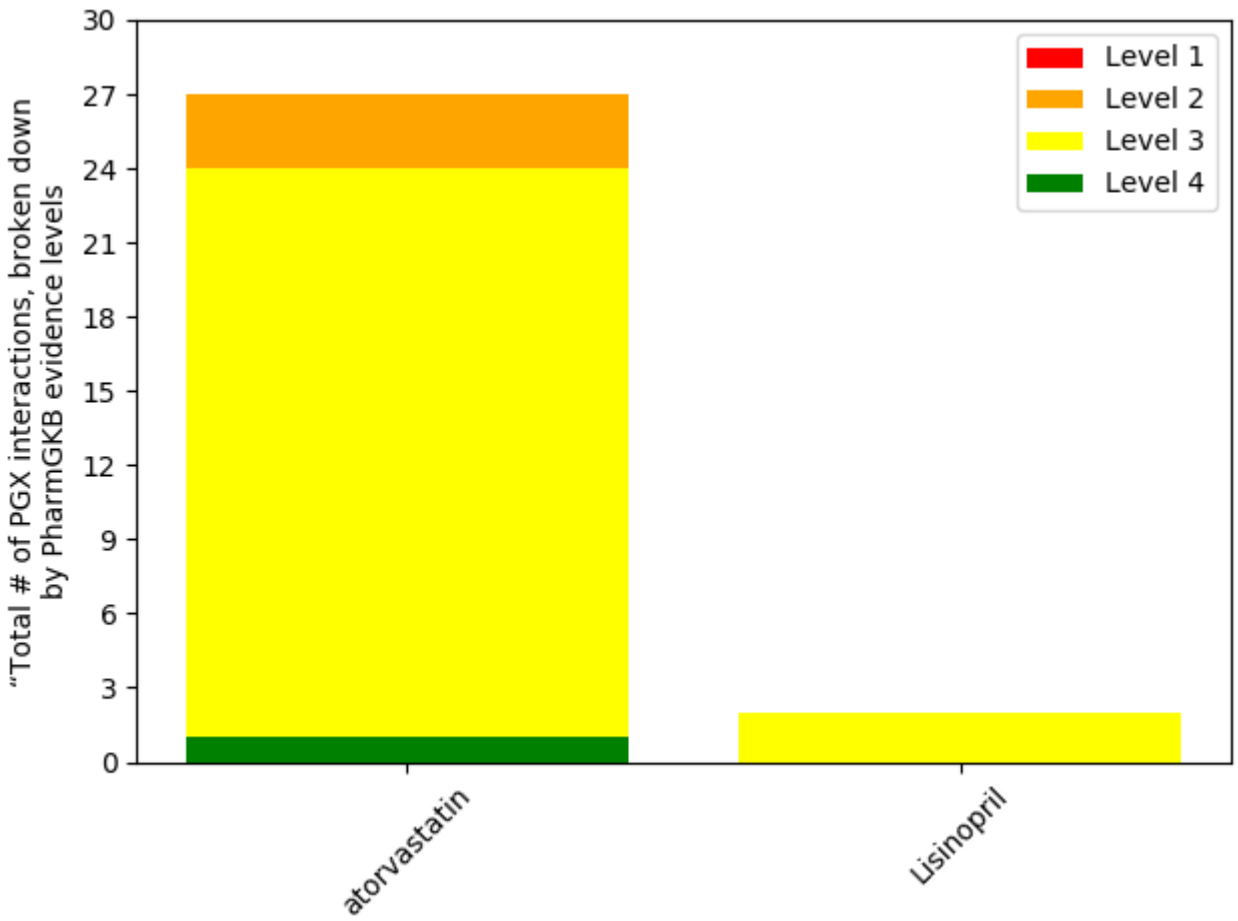
From the moment you take a drug, your body begins to process it, in an effort to eliminate it. Most medications undergo one of more chemical transformations in the body (a process known as metabolism) to facilitate their removal. Each of the chemical transformations can change a drug's pharmacological activity. Modifications can also alter how long a drug stays in your body (half-life). There can be considerable variation in how different people metabolize the same drug. That is because an individual's DNA is an important factor in determining the extent to which drugs are metabolized and the speed at which the metabolism occurs. For example, by looking at what bases are present (genotype) at certain locations (rsID) in the DNA, one can gain information about whether someone lacks an enzyme responsible for the metabolism of a drug. Such variations will influence the person’s drug exposure, clinical response, and risk for adverse effects. Using the information provided in this report, healthcare professionals can evaluate which drugs may be less effective or more effective for you.

This detailed drug-gene report provides insights into variations in your DNA that might influence your clinical response to certain medications. For most drugs, multiple genes are responsible for a person's response to a drug, the appropriate dose level, and/or the toxicity associated with taking a drug. The $\text{MyGenome}_{\text{Rx}}$ platform analyzes your DNA at over 1 million locations (rsID) from 2038 different genes to determine if there are single nucleotide polymorphisms (SNPs) or variants present. Some of the genes screened are related to how drugs are processed by the body, or pharmacokinetics (absorption, bioavailability, distribution, metabolism, and excretion). Other genes are involved in how the drug interacts with its target, or pharmacodynamics.

The potential pharmacogenomic interactions are presented in a color coded, graphic based on PharmGKB Evidence Levels 1-4. The information is ranked by PharmGKB evidence levels, with Level 1 being the highest level (with the most clinical evidence for drug-gene interaction) and Level 4 being the lowest level (with the least amount of evidence or conflicting reports on drug gene interaction). Tables for each of the drugs your provided contain detailed variant drug-gene interactions identified in your raw DNA file. Information on the ATC organ/system classification[1], gene, rsID, and PharmGKB Clinical Evidence Level is included, and the information is ranked by the PharmGKB evidence level. If no pharmacogenomic issues were identified for a given drug, this is stated. The report highlights when your DNA shows a variant genotype compared to the reference DNA (reference assemble GRCh37). There is further information on the ATC system and PharmGKB Levels at the end of the report. When combined with the Personalized Pharmacogenomic Overview, and in collaboration with healthcare

providers, MyGenome$_{Rx}$ services can help optimize your drug therapy choices. However, there are additional non-genetic factors that influence drug response such as age, weight, gender, race, diet, smoking status, comorbidities, and whether you are taking other medications.

PLEASE READ THE DISCLAIMERS BELOW. IT IS IMPORTANT THAT YOU DISCUSS THE RESULTS IN THIS REPORT WITH YOUR PHYSICIAN BEFORE STARTING, STOPPING OR MAKING ANY OTHER CHANGES TO YOUR PRESCRIPTION REGIMEN, YOUR TREATMENT OR ANY THERAPIES WITH WHICH YOU ARE INVOLVED.



The figure depicts the number of pharmacogenomic interactions for each of the drugs provided. These pharmacogenomic interactions are assigned evidence levels per PharmGKB, with Level 1 being the highest level and Level 4 being the lowest level. The potential drug-gene interactions shown above are specific to the raw DNA file and drug list that were provided.

Drugs Provided:

ATORVASTATIN

LISINOPRIL

ATORVASTATIN

Alternative Names: ['Caduet', 'Lipitor']

Evidence	Gene	rsID	Genotype	Clinical Relevance
2	APOE	rs7412	CC	If you are treated with ATORVASTATIN, then you may have a reduced response (less reduction in LDL-cholesterol).

Evidence	Gene	rsID	Genotype	Clinical Relevance
2	APOA5	rs662799	AA	If you have Hyperlipidemia and are treated with ATORVASTATIN, lovastatin or simvastatin, then you may have a higher reduction in LDL-cholesterol.
2	KIF6	rs20455	AA	You may have a lower risk of coronary disease and may be less likely to benefit from ATORVASTATIN treatment.
3	ABCB1	rs1045642	AG	If you are treated with ATORVASTATIN, then you may have a better response to treatment (as measured by an increased reduction in LDL-cholesterol or total cholesterol). If you have Coronary Artery Disease and are treated with ATORVASTATIN, then you may have a higher likelihood of developing myalgia.
3	ABCC2	rs717620	CT	If you have hypercholesterolemia and are treated with ATORVASTATIN, then you may have a lower decrease in triglycerides. You may have decreased dose of simvastatin and ATORVASTATIN.
3	ABCG2	rs2231142	GG	You may have lower plasma concentrations of ATORVASTATIN.
3	ABCG8	rs11887534	GG	If you are treated with ATORVASTATIN, then you may have a decreased response to treatment (measured by lower decreases in LDL-cholesterol).
3	AGTR1	rs5186	AC	You may have an increased exposure to ATORVASTATIN.
3	BDKRB2	rs1799722	CT	You may have increased exposure to ATORVASTATIN.
3	CETP	rs708272	AG	If you are treated with ATORVASTATIN, then you may have a decreased risk of cardiovascular disease events.
3	CYP3A4	rs2740574	TT	You may be more likely to require a decrease in dose or switch to a different drug when treated with ATORVASTATIN or simvastatin.
3	CYP3A5	rs776746	CC	If you are treated with ATORVASTATIN, then you may have a better response to treatment.

Evidence	Gene	rsID	Genotype	Clinical Relevance
3	CYP7A1	rs3808607	GT	You may have a decreased response to ATORVASTATIN.
3	FDPS	rs11264359	AA	You may have an increased response to bisphosphonate treatment, or may have an increase in bone density when treated with ATORVASTATIN .
3	HMGCR	rs17671591	CT	If you have hypercholesterolemia and are treated with ATORVASTATIN, then you may have an increased drop in LDL-C levels and rise in HDL-C levels.
3	MYLIP	rs9370867	AG	If you have hypercholesterolemia and are treated with ATORVASTATIN, then you may have decreased LDL-C responses and are less likely to achieve LDL-C levels of less than 130mg/dl.
3	PON1	rs662	TT	If you have hypercholesterolemia, then you may have a smaller increase in HDL cholesterol when treated with simvastatin or ATORVASTATIN.
3	POR	rs1057868	CC	If you have (POR *1/*1) and familial hypercholesterolemia, then you may have a greater decrease in total cholesterol and low-density lipoprotein cholesterol when treated with ATORVASTATIN.
3	RYR2	rs2819742	AG	If you have cardiovascular disease and are taking a statin, then you may have an increased likelihood of statin-associated myopathy and myalgia as compared with individuals with the GG genotypes and decreased likelihood.
3	SLCO1B1	rs2306283	AG	If you have Hypercholesterolemia and are treated with ATORVASTATIN, then you may have less reduction in LDL.
3	SLCO1B1	rs4149036	CC	You may have increased response to ATORVASTATIN.

Evidence	Gene	rsID	Genotype	Clinical Relevance
3	SLCO1B1	rs4149056	TT	Individuals with the TT genotype and who are treated with ATORVASTATIN may have 1) higher oral clearance and lower plasma concentrations of ATORVASTATIN 2) a decreased risk of composite adverse events but not a decreased risk of myalgia, as compared to individuals with the CC and CT genotypes. Other genetic and clinical factors may also influence a individual's response to ATORVASTATIN treatment and ATORVASTATIN pharmacokinetics. You may have increased plasma concentration of ATORVASTATIN when treated concomitantly with rifampin.
3	TNF	rs1800629	GG	Individuals with the GG genotype and acute coronary syndrome who are treated with ATORVASTATIN may have an increase in lumbar bone marrow density as compared to individuals with the AG genotype. Other genetic and clinical factors may also influence a individual's response to ATORVASTATIN treatment.
4	SCAP	rs12487736	CT	If you are treated with ATORVASTATIN, then you may have higher expression of SCAP.

LISINOPRIL

Alternative Names: ['Qbrelis', 'Zestoretic', 'Prinzide', 'Prinivil', 'Zestril']

Evidence	Gene	rsID	Genotype	Clinical Relevance
3	ACE	rs4291	AT	If you have hypertension, then you may have decreased fasting glucose levels when treated with amlodipine, chlorthalidone or LISINOPRIL.
3	BDKRB2	rs1799722	CT	You may have increased risk of Cough when treated with enalapril, imidapril and LISINOPRIL if you have Essential hypertension.

The MyGenome$_{Rx}$ platform analyzes over 1 million rsIDs, from 2038 different genes to generate the Personalized Pharmacogenomic Overview. Tables are provided for each drug. The tables include the ATC Level 1 system category, gene, rsID, genotype, PharmGKB evidence level, and clinical information for each variant gene-drug interaction identified in the uploaded raw DNA file. More

information on the rsIDs (reference SNP cluster ID numbers)[2] can be found using the NCBI dbSNP database (https:// www.ncbi.nlm.nih.gov/snp/). If no pharmacogenomic interactions were identified for a given drug based on the DNA sequence provided this is noted.

Information on the PharmGKB evidence level[4] for each variant drug-gene interaction is also included. PharmGKB, is an NIH funded knowledgebase (https://www.pharmgkb.org/) that aggregates, curates, integrates, and disseminates information on the impact of human genetic variation on drug response. Level 1 annotations are used for a variant-drug combination where the preponderance of evidence shows an association or has been recognized in a Clinical Pharmacogenetics Implementation Consortium (CPIC) or medical society-endorsed pharmacogenomics guideline, implemented at a Pharmacogenomics Research Network (PGRN) site, or in a major health system. The association must be replicated in more than one cohort with significant p-values, and preferably will have a strong effect size. Level 2 annotations are used for a variant-drug combination with known pharmacogenes, so functional significance is likely. Level 2 annotations are also used for a variant-drug combination with moderate evidence of an association. For example, when the association has been replicated but there may be some studies that do not show statistical significance, and/or the effect size may be small. Level 3 annotations are for drug-gene interactions that are based on a single study that showed statistical significance, or that was evaluated in multiple studies but which lacked clear evidence of an association. Level 4 annotations are for drug-gene interactions that are based on a case report, non-significant study, or in vitro, molecular or functional assay evidence only.

*** Status of Evidence Levels**

The PharmGKB Database and Evidence Levels referenced in this Report are based on information available to MyGenome$_{Rx}$ as of the date of this Report. These Evidence Levels may change over time as additional research is completed, additional links between genes and treatment outcomes are identified, studies are evaluated and confirmed by the scientific community, and additional knowledge of gene interactions with pharmaceuticals are understood.

**** General Disclaimer**

The Detailed Drug Gene Report is an educational tool, to be used in collaboration with your healthcare providers. MyGenome$_{Rx}$ services provide an individual the potential to optimize their drug therapy choices. This overview is not intended to be a substitute for professional medical advice, diagnosis, or treatment, and nothing in this Report or the services provided by MyGenome$_{Rx}$ should be construed as medical advice or the practice of medicine by MyGenome$_{Rx}$. Patients should seek the advice of their physicians, pharmacists, or other qualified health care providers with any questions they may have regarding a medical condition or a medication and before starting, stopping or making other changes to your prescription regimen, your treatment or any therapies with which you are involved.

1 Lazarou J, Pomernaz B, Corey P. Incidence of adverse drug reactions in hospitalized patients: a meta-analysis of prospective studies. Surv Anesthesiol. 1999; 43:53–4

2 Kitts, A and Sherry, S. Chapter 5. The Single Nucleotide Polymorphism Database (dbSNP) of Nucleotide Sequence Variation. The NCBI Handbook. McEntyre J, Ostell J, editors. Bethesda (MD): National Center for Biotechnology Information (US); 2002

3 The Selection and Use of Essential Medicines. World Health Organization technical report series. 2015; (994):vii-xv, 1-54. PMID: 27183787

4 Whirl-Carrillo M, McDonagh E M, Hebert J M, Gong L, Sangkuhl K, Thorn C F, Altman R B, Klein T E. Pharmacogenomics knowledge for personalized medicine. Clinical pharmacology and therapeutics. 2012. 92:414-7 PMID: 22992668