

# Gene Mutations Linked to Statin Resistance

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(PhysOrg.com) -- Scientists at Duke University Medical Center have identified genetic mutations that may help explain why some people don't respond very well to statins, drugs taken by millions of Americans to fight high cholesterol and prevent coronary artery disease.

The findings, published in the Dec. 17 issue of *Circulation: Cardiovascular Genetics*, suggest that some patients may fail to see lower LDL cholesterol levels from taking the drugs -- no matter what the dose -- because of their genetic makeup.

Statins are generally effective in lowering low-density lipoprotein cholesterol, or LDL (the so-called "bad" cholesterol) -- even slashing LDL levels in half, in some cases. But in about 20 percent of patients, statins fail to bring LDL into target range, a phenomenon known as "statin resistance."

Geoffrey Ginsburg, MD, PhD, director of the Center for Genomic Medicine in Duke's Institute for Genome Science & Policy, says race, age and smoking status may exert modest influence on statin response, but he believes genetic variation may play a more powerful role.

To find out, Duke researchers randomly assigned 509 patients with high cholesterol to receive the lowest dose of one of three statins for eight weeks. Afterward, participants took the highest recommended dose of the same drug for a second, 8-week period. The statins tested included atorvastatin (Lipitor), simvastatin (Zocor), and pravastatin (Pravachol).

Researchers wanted to study statins at two dose levels because the results could help answer an important clinical question: If a low or moderate dose of a statin isn't lowering LDL to target levels - the definition of statin resistance - could more of the drug overcome that?

"This is the first study we know of that looked at the value of dose escalation among statin resistant patients," says Deepak Voora, MD, a cardiologist at Duke and the lead author of the study. "What the research told us, among other things, is that dose escalation is not the best choice for statin resistant patients. The better option would be to simply switch them to the most potent statin available."

Using a database of previously determined genes believed to be important in cholesterol management, researchers selected 31 genes and 489 mutations to study statin resistance in the patients at both the high and low dose levels.

In correlating the presence or absence of mutations with response to the statins, investigators found only one - a mutation in the ABCA1 gene, a gene involved in cholesterol transport - that appeared to be associated with a diminished response to statins at the lower dose level. While the low dose statins did cause the LDL levels to decline among the carriers of that mutation, their LDL levels fell far less than did the LDL levels of patients who did not carry the mutation (24 percent vs. 32 percent, respectively).

The ABCA1 mutation was also significantly associated with resistance at the higher statin dose, as was a second mutation, an alteration in the APOE gene.

Both carriers of the APOE and the ABCA1 mutations showed an improved response to the higher dose of the statins, but it was still significantly weaker than that of the non-carriers' response to the higher

drug dose.

Investigators also discovered that older patients and nonsmokers were more likely to have a more robust response to statin therapy than were younger patients and patients who smoked.

Ginsburg says this study underscores the value of genetic testing and the role it can play in selecting the most appropriate therapy for an individual patient, a key principle of predictive, or personalized medicine.

"There are likely more genes involved in statin resistance, so much more research needs to be done before we can fully understand which patients won't respond well to particular statins," says Ginsburg. "Studies like this one, however, move us one step closer to the time when we'll routinely use genetic testing to guide patient care."

Provided by Duke University

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