Researchers discover link between expression of GATM and pain associated with statins

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(Medical Xpress)—A large team with members from several research institutions across the U.S. has found a possible link between the expression of the gene for glycine amidinotransferase (GATM) and pain experienced by patients who take statins to help lower their cholesterol levels. In their paper published in the journal *Nature*, the team describes their findings and what it might mean for patients in the near future.

People across the world are prescribed statins to help lower levels of cholesterol in their blood—the hope is that such a reduction will reduce the risk of heart attack and stroke. Statins generally do their work on the liver, helping to prevent cholesterol from being released into the bloodstream. In many instances, however, the use of statins in patients has led to muscle pain (known as myopathy) and an increased risk of developing Type II diabetes. In this new effort the researchers sought to learn if there might be a genetic difference between patients who experience pain when using statins and those who do not.

Rather than looking for genetic differences in the livers of patients, the researchers used lymphoblastoid cell lines that had been obtained from a patients prescribed simvastatin (Zocor) as part of trial testing—lymphoblastoids are a type of immune cell that can serve as a proxy for liver cells.

The researchers treated the cells they had obtained with the statin and then searched for changes to expressions by genes that were impacted. After much work, the team began to focus on GATM—it's involved in

synthesizing creatine which is known to serve as food for muscles, particularly those that work with the skeletal system. Once GATM had been identified as a possible source, the researchers looked at medical histories of statin prescribed patients to see if they could find a link. Sure enough, those that had experienced pain also had different levels of creatine in their muscles than those that did not. Subsequent tests revealed that if GATM levels were artificially reduced, liver cell response was changed, though the researchers still aren't clear as to whether that would lead to less pain in patients.

The researchers note that while their research thus far has found a link between GATM levels and muscle pain, much more work will need to be done to determine if a way can be found to use that knowledge to reduce the painful side effects of statins in some patients.

More information: A statin-dependent QTL for GATM expression is associated with statin-induced myopathy, *Nature* (2013) DOI: 10.1038/nature12508

Abstract
Statins are prescribed widely to lower plasma low-density lipoprotein (LDL) concentrations and cardiovascular disease risk and have been shown to have beneficial effects in a broad range of patients. However, statins are associated with an increased risk, albeit small, of clinical myopathy and type 2 diabetes. Despite evidence for substantial genetic influence on LDL concentrations, pharmacogenomic trials have failed to identify genetic variations with large effects on either statin efficacy or toxicity, and have produced little information regarding mechanisms that modulate statin response. Here we identify a downstream target of statin treatment by screening for the effects of in vitro statin exposure on genetic associations with gene expression levels in lymphoblastoid cell lines derived from 480 participants of a clinical trial of simvastatin treatment7. This analysis identified six expression quantitative trait loci

(eQTLs) that interacted with simvastatin exposure, including rs9806699, a cis-eQTL for the gene glycine amidinotransferase (GATM) that encodes the rate-limiting enzyme in creatine synthesis. We found this locus to be associated with incidence of statin-induced myotoxicity in two separate populations (meta-analysis odds ratio = 0.60). Furthermore, we found that GATM knockdown in hepatocyte-derived cell lines attenuated transcriptional response to sterol depletion, demonstrating that GATM may act as a functional link between statin-mediated lowering of cholesterol and susceptibility to statin-induced myopathy.