Cholesterol-lowering gene changes may increase the risk of cataracts

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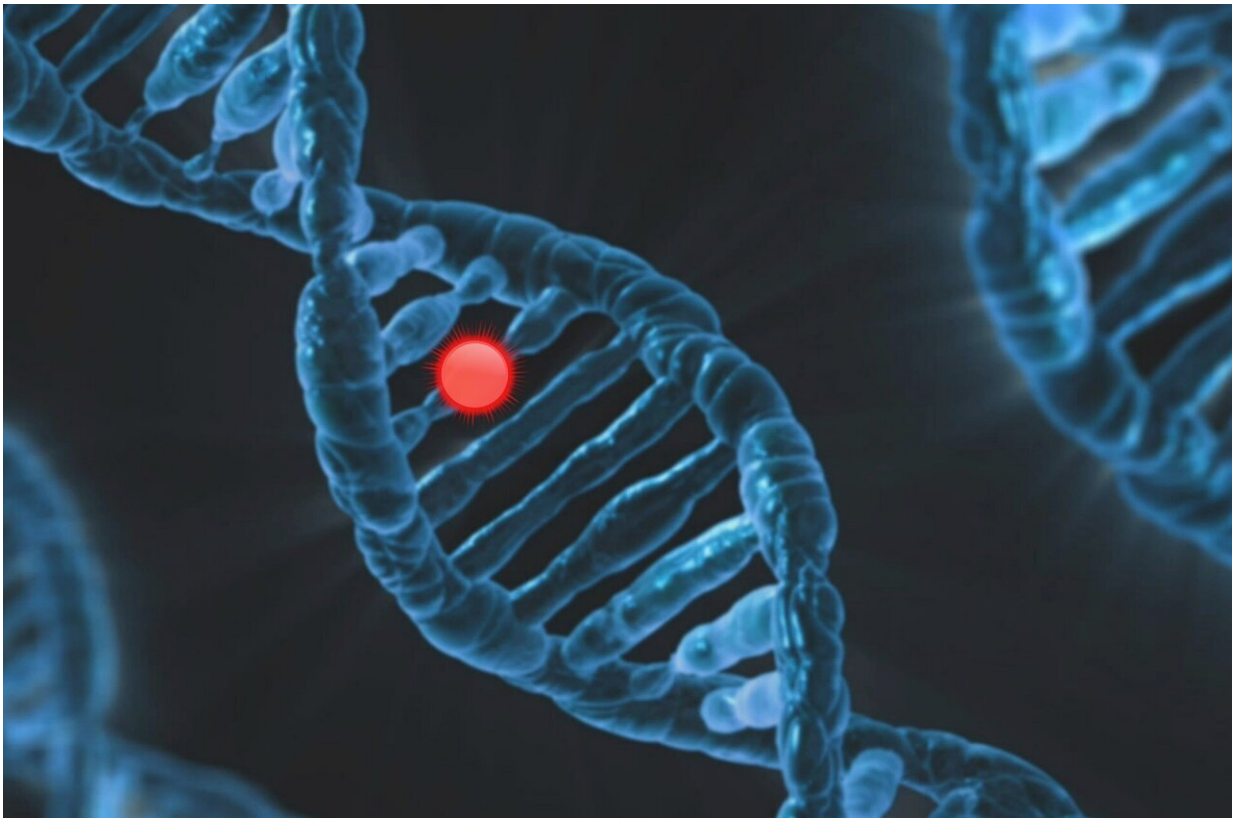

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People who have genetic variations associated with lowering LDL-cholesterol similar to statin medications appear to have an increased risk of developing cataracts and having cataract surgery, according to new

research published today in the *Journal of the American Heart Association* (*JAHA*).

Previous research has found some evidence that statin medications may increase the risk of cataracts. In this study, researchers explored whether certain genes that mimic the activity of statins may also independently increase the risk of developing cataracts.

Statin medications reduce levels of LDL-cholesterol by inhibiting an enzyme called HMG-CoA-reductase (HMGCR). Previous research efforts have confirmed that variants in the HMGCR gene region of the human genome affect how people metabolize cholesterol.

"We were able to establish a link between genetic variants that mimic inhibition of HMGCR and the development of cataracts," said lead study author Jonas Ghouse, M.D., Ph.D., a fellow in the cardiac genetics group, Laboratory for Molecular Cardiology in the department of biomedical sciences at the University of Copenhagen in Denmark. "We were not able to find any association between newer non-statin, lipid-lowering medications and cataract risk, so this effect is likely specific to statins. However, it's important to stress that the benefits of statins for lowering levels of low-density lipoproteins in people who have high blood cholesterol levels completely outweighs the small risk of cataracts, and cataract surgery is effective and safe."

Using the UK Biobank, a large database of UK residents that tracks serious health and medical conditions of nearly half a million adults, researchers analyzed genetic data for more than 402,000 people. The researchers focused on five common previously identified genetic variants that lower the level of LDL cholesterol. They then calculated genetic scores based on each variant's previously identified impact on LDL cholesterol. Genetic coding data was examined to identify carriers of a rare mutation in the HMGCR gene called a predicted loss-of-

function mutation.

"When we carry a loss-of-function mutation, the gene is less likely to work," Ghouse said. "If that gene doesn't work, the body can't produce that protein. Simply put, the loss-of-function mutation in the HMGCR gene equals taking a statin medication."

The study found:

- The HMGCR genetic risk score identified people with a higher risk of cataracts and cataract surgery. Each 38.7 mg/dL reduction in LDL cholesterol by the genetic score was associated with a 14% higher risk of cataracts and a 25% higher risk of cataract surgery.
- Among 169,172 with HMGCR sequencing data, 32 (0.02%) carried one of 17 rare HMGCR predicted loss-of-function mutations. Compared with non-carriers, carriers of these rare mutations were more than four-and-a-half times as likely to develop cataracts and over five times as likely to have cataract surgery.

Ghouse said he was surprised by the magnitude of the association. "The main difference between the two analyses is that loss-of-function mutations are really more detrimental than common variants, meaning they mimic change that is often induced by medications," he said. "We believe that the true effect lies closer to the loss-of-function mutation association than the common variant association. When taking statins, you have an almost-complete inhibition of that protein, and when you have a loss-of-function mutation you also have a significantly reduced ability to produce that protein."

According to the authors, one major limitation of the study is that while carrying these genetic variants constitutes a lifelong risk for the

development of cataracts, that risk should not be evaluated the same for people who begin taking statins later in life given the positive impact statins may have by lowering blood cholesterol levels. Further evaluation of this association in more clinical trials is needed to confirm these findings.

"Our associations reflect lifelong treatment, whereas statin treatment typically occurs later in life," Ghouse said. "However, there is a specific group of patients who are diagnosed with high cholesterol in childhood and start statin treatment at a young age, so they could be identified and followed up more closely for cataracts."

Co-authors are Gustav Ahlberg, M.Sc., Ph.D.; Anne Guldhammer Skov, M.D.; Henning Bundgaard, M.D., D.M.Sc.; and Morten S. Olesen, M.Sc., Ph.D. Authors' disclosures are listed in the manuscript.

More information: Association of Common and Rare Genetic Variation in the 3-Hydroxy-3-Methylglutaryl Coenzyme A Reductase Gene and Cataract Risk, *Journal of the American Heart Association* (2022). DOI: 10.1161/JAHA.122.025361

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