# Researchers identify inherited gene mutation linked to esophageal cancer

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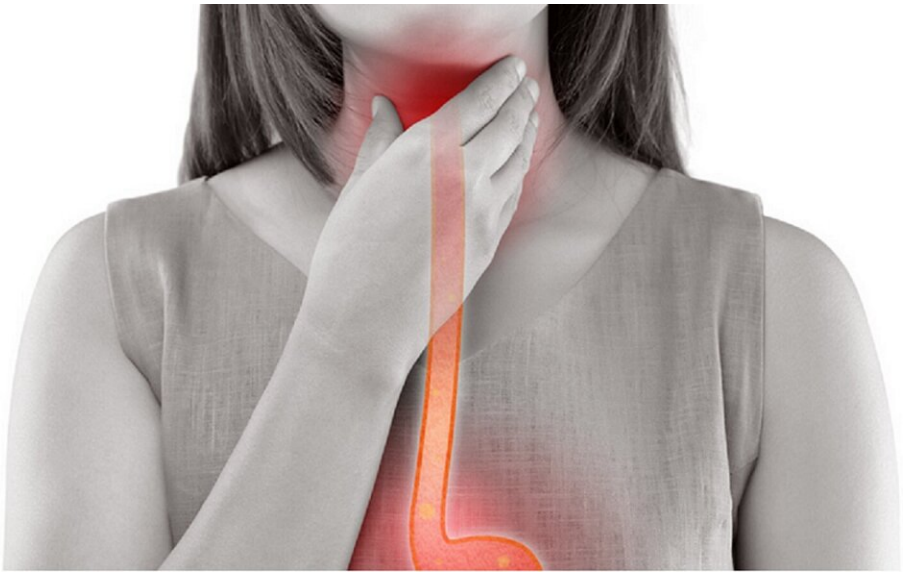

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Studying genes in families with a propensity for certain diseases has led to many critical advances in medicine, including the discovery of statins in family members who suffered heart attacks at an early age.

Now, a team of researchers at Case Western Reserve University has identified an inherited mutation in a gene linked to a highly lethal cancer called esophageal adenocarcinoma (EAC).

"With this discovery, we will be able to identify early those at a high risk of developing EAC in their lifetime, and accordingly tailor screening, lifestyle and treatment strategies to prevent cancer development," said Kishore Guda, an associate professor at the Case Western Reserve School of Medicine and member of the Case Comprehensive Cancer Center.

Guda led the study, published in the journal *Gastroenterology*, with Amitabh Chak, a professor at the School of Medicine and physician at University Hospitals Cleveland Medical Center.

Their previous studies found that up to 10% of patients with EAC or Barrett's esophagus—a precursor to EAC—have a family member with the disease, suggesting a potential genetic predisposition.

But the molecules contributing to EAC's development have been poorly understood.

By studying families with the disease, they identified the gene—Caveolin-3 (CAV3)—that plays a critical role in its development.

Caveolins (including CAV1, CAV2, CAV3) are structural components of a cell that regulate various proteins involved in the cell's ability to function properly. But until now the gene's specific role in the esophagus—and especially in EAC—was unknown.

The researchers used molecular techniques and tissues from humans and animal models to learn what CAV3 does in the esophagus.

They learned CAV3 is normally present in specialized cells—called mucosal glands—which are typically found beneath the surface of esophagus. And when the esophagus is injured, these CAV3-containing cells migrate up to heal the injury.

"In the family where we identified CAV3 mutation," Guda said, "we show that this mutation leads to loss of its normal function and wouldn't be able to repair the injured esophagus."

## Implications

Their discovery suggests:

- a new role for esophageal mucosal glands (where CAV3 is present) in normal healing of injured esophagus, and
- inherited defects in the CAV3 gene can prevent the injured esophagus from properly healing, increasing the risk of developing EAC.

"This is especially relevant to individuals suffering from chronic heartburn, where the acid and bile from the stomach reaches up and injures the lower esophagus," Guda said. "These individuals are particularly at risk of developing EAC if the injured esophagus isn't repaired and healed."

Future work will focus on screening more families who may be carrying genetic defects in CAV3 or in other Caveolin genes; figuring out how CAV3 helps in esophageal healing and identifying strategies to correct or restore normal function of defective esophageal mucosal glands to prevent cancer risk; and making ablative therapy more effective, they said. (Ablative therapy uses extremely high or low temperatures to destroy abnormal tissue or tumors.)

"There could be several reasons why normal cells become cancerous," Chak said. "By studying familial clusters of the disease, we are identifying the dangerous roads that lead to cancer so effective screening and intervention strategies can be implemented to prevent the disease before it even begins."

**More information:** Katherine S. Garman et al, Genetic Defect in Submucosal Gland–Associated Caveolin-3: A New Paradigm in Esophageal Adenocarcinoma Risk, *Gastroenterology* (2023). DOI: 10.1053/j.gastro.2023.08.039