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Well-known cancer gene NRAS produces five variants, study finds

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A new study shows that a gene discovered 30 years ago and now known to play a fundamental role in cancer development produces five different gene variants (called isoforms), rather than just the one original form, as thought.

The study of the NRAS gene by researchers at The Ohio State University Comprehensive Cancer Center – Arthur G. James Cancer Hospital and Richard J. Solove Research Institute (OSUCCC – James) identified four previously unknown variants that the NRAS gene produces.

The finding might help improve drugs for cancers in which aberrant activation of NRAS plays a crucial role. It also suggests that NRAS might affect additional target molecules in cells, the researchers say.

The isoforms show striking differences in size, abundance and effects. For example, the historically known protein (isoform 1) is 189 amino-acids long, while one of the newly discovered variants, isoform 5, is only 20 amino-acids long.

The study is published in the *Proceedings of the National Academy of Sciences*.

"We believe that the existence of these isoforms may be one reason why NRAS inhibitors have so far been unsuccessful," says corresponding author Albert de la Chapelle, MD, PhD, professor of Medicine and the

Leonard J. Immke Jr. and Charlotte L. Immke Chair in Cancer Research.

Co-senior author Clara D. Bloomfield, MD, Distinguished University Professor and Ohio State University Cancer Scholar, notes that one of the newly discovered isoforms might play a greater role in the development of some cancers than the known protein itself.

"Targeting the NRAS pathway may have been unsuccessful in the past because we were unaware of the existence of additional targets of these novel isoforms," says Bloomfield, who is also senior adviser to the OSUCCC – James and holds the William Greenville Pace III Endowed Chair in Cancer Research.

"The discovery of these isoforms might open a new chapter in the study of NRAS," says first author Ann-Kathrin Eisfeld, MD, a postdoctoral fellow in the laboratories of de la Chapelle and of Bloomfield. "Knowing that these isoforms exist may lead to the development of drugs that specifically decrease or increase the expression of one of them and provide more effective treatment for cancer patients."

For this study, de la Chapelle, Eisfeld and their colleagues analyzed expression of the NRAS isoforms in a variety of normal and matched tumor samples. Key technical findings include:

- The isoforms showed modest but significant differences in expression in normal and malignant samples;
- Each isoform had different effects on NRAS target molecules;
- Isoform 5 was the most aggressive variant in proliferation and transformation assays;
- Isoforms 3 and 5, the smallest of the isoforms (40 and 20 amino acids respectively), were found in both the cell nucleus and cytoplasm.

More information: Paper: NRAS isoforms differentially affect downstream pathways, cell growth, and cell transformation, www.pnas.org/content/early/201 … /1401727111.abstract

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