Study finds genetic mutations linked with ethnic disparities in cancer

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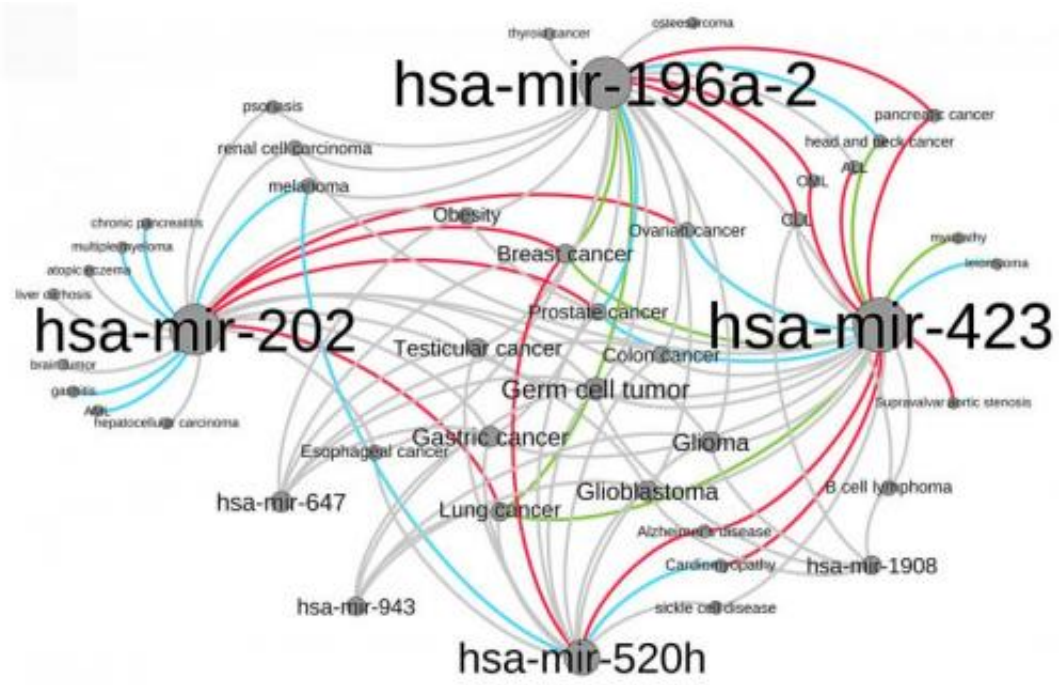

University of Pennsylvania researchers identified several miRNA mutations that were associated with particular ethnic groups and had links to cancer and other diseases. Credit: University of Pennsylvania

One of the goals of genome sequencing is to identify genetic mutations associated with increased susceptibility to disease. Yet by and large these discoveries have been made in people of European or Asian ancestry, resulting in an incomplete picture of global genetic variation in disease vulnerability.

In a new study published in the journal *BMC Medical Genomics*, researchers at the University of Pennsylvania have addressed this omission. Their investigation identified more than 30 previously undescribed mutations in important regulatory molecules called microRNAs. Many of these mutations influence whether a person develops cancer or the severity of the disease.

One variant has been associated with breast cancer mortality, and the team's discovery could help explain why, once diagnosed with breast cancer, women with African ancestry are more likely to die from the disease than other women. Knowing about these differences could inform efforts to develop diagnostic tests or even treatments for diseases like cancer.

Renata A. Rawlings-Goss, a postdoctoral fellow in the Department of Genetics in Penn's Perelman School of Medicine, led the work, collaborating with the department's Michael C. Campbell. Sarah Tishkoff, a Penn Integrates Knowledge professor with appointments in Penn Medicine's Department of Genetics and the School of Arts & Sciences' Department of Biology, was the study's senior author.

MicroRNAs, or miRNAs, are small molecules that are not translated into proteins but rather serve to regulate gene expression, usually by blocking protein production. A single miRNA can govern the expression of as many as 6,000 different genes, so a change in the way they function can have significant biological effects.

Because miRNAs have the potential to affect a host of genes, scientists have become interested in their role in disease. Several miRNAs have been implicated as biomarkers for diseases including diabetes, asthma and various cancers.

To better understand miRNA diversity across the world, the Penn team

searched for miRNA variants in the genome sequences of 69 individuals from 14 populations from Europe, Asia, the Americas and Africa. The samples included genetic material collected by Tishkoff and members of her lab from diverse African populations, including three hunter-gatherer populations.

"We wanted to try to see if there was variability in miRNA that hadn't been identified before," Rawlings-Goss said.

Overall, the researchers found that miRNA sequences were similar across the populations they sampled, likely because of how critical they are for regulating genes involved in key physiological functions. Nevertheless, they did identify 33 novel variants that appeared in more than one individual and found many that were closely associated with particular populations. Taken as a whole, African groups had more diversity of miRNA expression than the other populations they examined.

The researchers searched available databases to see which genes these miRNAs were known to inhibit. Their query turned up a large proportion of genes involved in glucose and insulin metabolism, indicating a possible connection between diabetes risk and possessing one of these variants. The search also pointed to effects on genes involved in cell division, a process that is disrupted in cancers.

"Several of the new miRNA variants we identified have been studied in correlation with cancer onset, progression and severity," Rawlings-Goss said.

Looking specifically at miRNA variants that were more frequently associated with particular ethnic populations, the Penn team found seven that have previously been connected to a variety of types of cancer.

"I was really interested to see that among the diseases that turned up were breast, ovarian and prostate cancer," Rawlings-Goss said. "All three of those cancers show a pretty systematic and well documented difference between people of African background and European or Asian background."

One mutation, miRNA 202, was of particular interest.

"There have been some studies done that show that genetic variation at this site changes the amount of miRNAs that are produced," Rawlings-Goss said. "This variant is protective against breast cancer mortality, and it appears at significantly lower frequency in African samples."

This finding could help explain the long-observed disparity in breast cancer survival rates between women of African ancestry and women of European ancestry.

"It's becoming more and more apparent that miRNAs can have a broad-reaching and global effect on our health and adaptation to disease," said Rawlings-Goss. "Learning more about differences across populations could be helpful to doing early diagnostics and treating disease across diverse populations."

Provided by University of Pennsylvania