Study discovers 103 genes that cause inherited diseases when mutated can also increase cancer risk

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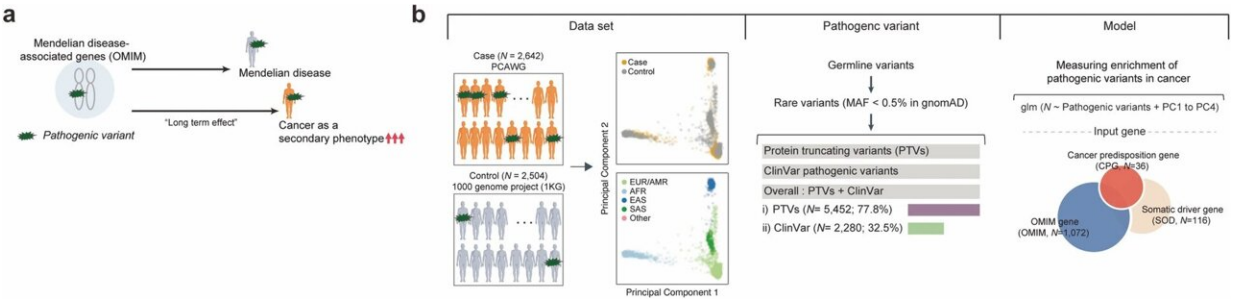

Systematic analysis of the enrichment of rare pathogenic variants in cases compared to control samples. a Proposed hypothesis that rare pathogenic variants in Mendelian disease-associated genes (OMIM genes) increase the risk of cancer. b Overview of the case–control analysis. Principal components analysis (PCA) using common variants was performed to stratify the population of cases (cancer patients) and control individuals. After defining pathogenic variants (PTVs or ClinVar pathogenic variants) from case–control samples, the linear regression model tests germline variant enrichments in cases compared to controls with the first four PC values. AFR: African, AMR: American, EAS: East Asian, EUR: European, and SAS: South Asian

About 100 cancer predisposition genes (CPGs) are known. The probability of developing cancer is greater in individuals who inherit certain altered variants of one of these genes.

"But these 100 genes account for only about 10% of cancer cases. The vast majority of other cases may be related to mutations we don't know about," says Solip Park, head of the Computational Cancer Genomics Group at the Spanish National Cancer Research Center (CNIO). Finding these other altered variants can contribute to early detection and the development of treatments to counteract their effect.

To discover them, Park decided to narrow the search to a group with an easily identifiable genetic profile: people carrying genes that, when altered, cause an inherited disease. These are monogenic diseases (caused by the alteration of a single gene), such as muscular dystrophy or Gaucher disease, in which fat accumulates in various cells.

Park, along with collaborators from several institutions in Seoul (South Korea), has discovered 103 genes in which single-gene disease-causing alterations often coexist with other cancer-predisposing alterations.

The study verified that people with single-gene inherited disease mutations in these 103 genes also had more mutations implicated in cancer than the control group of healthy individuals. While some of these mutations are associated with specific types of cancer, such as renal cell carcinoma, B-cell non-Hodgkin's lymphoma, breast adenocarcinoma and medulloblastoma; others relate to a general cancer susceptibility.

Thus, the authors propose in their study published in *Genome Medicine* that "these 103 genes whose mutations can cause Mendelian diseases may also behave as cancer predisposition genes," says Park.

In their research they also analyze how defective variants of these genes promote tumor progression and cause other diseases, and suggest various mechanisms of action, such as distortions of cellular metabolism or immune response. Some of these mechanisms had not been previously

considered in cancer, so the authors stress the need to study them in greater depth.

They have focused particularly on the PAH gene—known because some of its mutations cause the rare inherited disease phenylketonuria, which prevents the assimilation of proteins and aspartame. They selected it because it had the largest number of variants likely to give rise to several types of cancer and have discovered its relationship with squamous cell carcinoma of the lung, tumors of the liver tissue, as well as with other diseases and growth delay.

"Our study shows for the first time how genes associated with a variety of monogenic diseases can increase cancer risk. In addition, it provides new mechanisms of tumorigenesis previously unknown, by new cancer predisposition genes," says Solip Park.

Thus, the work suggests the need for further research into the role in cancer of these 103 genes, whose clinical relevance was until now limited to hereditary diseases other than cancer. The relationship of each variant to specific cancer types needs still to be explored.

However, the results point to the desirability of people carrying the alterations that cause monogenic inherited diseases to follow any cancer prevention program already available.

More information: Seulki Song et al, Systematic analysis of Mendelian disease-associated gene variants reveals new classes of cancer-predisposing genes, *Genome Medicine* (2023). DOI: 10.1186/s13073-023-01252-w

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