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Role of inherited genetic variants in rare blood cancer uncovered

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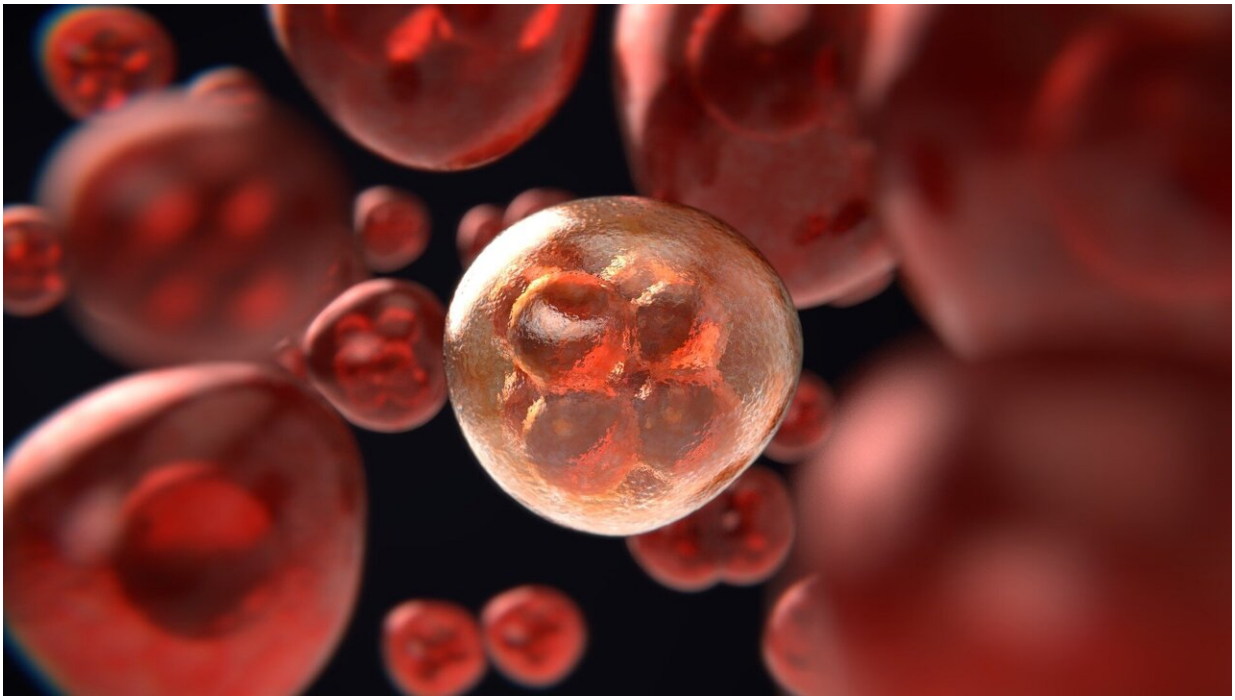

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Large-scale genetic analysis has helped researchers uncover the interplay between cancer-driving genetic mutations and inherited genetic variants in a rare type of blood cancer.

Researchers from the Wellcome Sanger Institute, the University of Cambridge, and collaborators, combined various comprehensive data

sets to understand the impact of both cancer-driving spontaneous mutations and inherited genetic variation on the risk of developing myeloproliferative neoplasms (MPN).

The study, published today (17 January) in *Nature Genetics*, describes how inherited genetic variants can influence whether a spontaneous mutation in a particular gene increases the risk of developing this rare blood cancer.

This analysis has an impact on current clinical predictions of disease development in individuals. Further research is required to understand the biological mechanisms behind how these inherited genetic variants influence the chances of developing rare blood cancer. In the future, this knowledge could aid drug development and interventions that reduce the risk of disease.

Myeloproliferative neoplasms, MPNs, are a group of rare, chronic, blood cancers. There are around 4,000 cases of MPN in the UK each year. These occur when the bone marrow overproduces blood cells, which can result in blood clots and bleeding. MPNs can also progress into other forms of blood cancer, such as leukemia.

In the population, there is a large amount of natural variation between individuals' blood cells, which can affect the amount of blood cells a person has and their particular traits. This is because multiple different genes can influence blood cell features in an individual. During routine blood tests, researchers take known information about these genes and analyze the variation to give a genetic risk score, which is how likely that individual is to develop a disease over their lifetime.

MPNs have been linked to random somatic mutations in certain genes including in a gene called JAK2. However, mutated JAK2 is commonly found in the global population, and the vast majority of these individuals

do not have or go on to develop MPN.

While previous studies have identified over a dozen associated inherited genetic variants that increase the risk of MPN, these studies insufficiently explain why most individuals in the population do not go on to develop MPN.

This new study, from the Wellcome Sanger Institute and collaborators, combined information on the known somatic driver mutations in MPN, inherited genetic variants, and genetic risk scores from individuals with MPN.

They found that the inherited variants that cause natural blood cell variation in the population also impact whether a JAK2 somatic mutation will go on to cause MPN. They also found that individuals with an inherited risk of having a higher blood cell count could display MPN features in the absence of cancer-driving mutations, thus, mimicking disease.

Dr. Jing Guo, first author from the Wellcome Sanger Institute and the University of Cambridge, said, "Our large-scale statistical study has helped fill the knowledge gaps in how variants in DNA, both inherited and somatic, interact to influence complex disease risk. By combining these three different types of datasets we were able to get a more complete picture of how these variants combine to cause blood disorders."

Professor Nicole Soranzo, co-senior author from the Wellcome Sanger Institute, the University of Cambridge and Human Technopole, Italy, said, "There has been increasing realization that human diseases have complex causes involving a combination of common and rare inherited genetic variants with different severity. Previously, we have shown that variation in blood cell parameters and function has complex genetic

variability by highlighting thousands of genetic changes that affect different gene functions.

"Here, we show for the first time that common variants in these genes also affect blood cancers, independent of causative somatic mutations. This confirms a new important contribution of normal variability beyond complex disease, contributing to our understanding of myeloproliferative neoplasms and blood cancer more generally."

Dr. Jyoti Nangalia, co-senior author from the Wellcome Sanger Institute and the Wellcome-MRC Cambridge Stem Cell Institute at the University of Cambridge, said, "We have a good understanding of the genetic causes of myeloproliferative neoplasms. In fact, many of these genetic mutations are routine diagnostic tests in the clinic. However, these mutations can often be found in healthy individuals without the disease.

"Our study helps us understand how inherited DNA variation from person to person, can interact with cancer-causing mutations to determine whether disease occurs in the first place, and how this can alter the type of any subsequent disease that emerges. Our hope is that this information can be incorporated into future disease prediction efforts."

More information: Inherited polygenic effects on common hematological traits influence clonal selection on JAK2V617F and the development of myeloproliferative neoplasms, *Nature Genetics* (2024). DOI: 10.1038/s41588-023-01638-x

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