CANCER SUSCEPTIBILITY

What makes one person more likely to get cancer than another? It is known that some habits and environmental exposures predispose people to developing certain cancers, yet not all exposed individuals will develop tumors. Understanding the molecular basis of cancer susceptibility remains one of the holy grails of cancer research and will improve the ability to prevent and treat cancer.

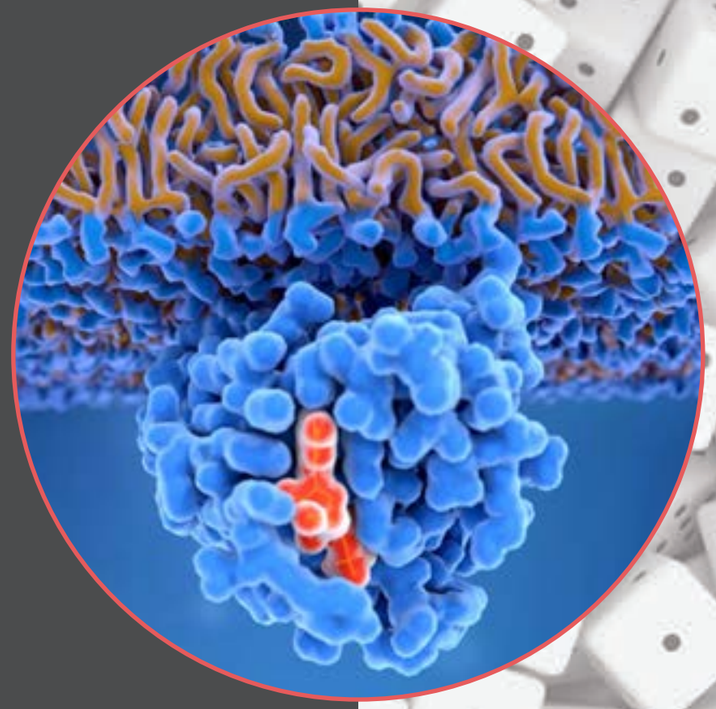
Cancer susceptibility is a complex genetic trait, and few cancers are a result of mutations in a single gene. To tease out the factors that increase risk, it is usually necessary to follow large numbers of people over many years. But the problem has become somewhat more tractable thanks to a combination of cheaper methods to sequence genomes and the development of advanced computational tools.

Advanced tools and methods allow for the detection of subtle differences in the genetic makeup of individuals and help find variations that exacerbate—or mitigate—risk.

Untangling how the environment impacts the risk of cancer is even more daunting than charting the complex effects of our genes. For example, all life on earth must cope with constant exposure to DNA damage from sources such as ultraviolet light from the sun, X-rays and various chemicals, all of which cause mutations. But several research areas promise to uncover the roles of important environmental exposures in the coming years.

To generate a more complete picture of how genetic variation impacts susceptibility, it is important to look beyond cancer cells themselves. Experts need to explore the genes that shape the immune system and tumor microenvironment to determine which elements permit cancer cells to flourish or help keep them in check. An intriguing example is the potential role of the microbiome, which is a community of microbes that mingle with human cells. The composition of the microbiome differs greatly between individuals and may be one factor that modulates the contribution of the genome to cancer risk for an individual.

The ultimate goal in the area of cancer susceptibility is to both understand the molecular basis of susceptibility and to predict who is most likely to develop certain cancers. There is also a need to understand what the specific risk factors are and which cancers are likely to be most aggressive so that steps can be taken to minimize risk and implement appropriate treatment. Deepening the understanding of genetic and environmental risk factors will also yield important clues into the biological processes that unfold as tumors develop and progress, paving the way toward new interventions.



Caption: An activated Ras protein attached to a cell membrane. More than 30 percent of all human cancers are driven by mutations of the *RAS* genes.

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The National Institutes of Health's *All of Us* Research Program, which is seeking one million or more U.S. participants from all backgrounds, will provide a rich source of data to explore susceptibility factors in a diverse group.