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Researchers discover genetic risk factor for skin, prostate and brain cancers

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Scientists at deCODE Genetics and academic collaborators from Iceland, The Netherlands, Spain, Denmark, Germany, Sweden, the USA, the UK and Romania today report the discovery of a variant in the sequence of the human genome associated with risk of developing basal cell carcinoma of the skin (BCC), as well as prostate cancer and glioma, the most serious form of brain cancer. The study was done in collaboration with Illumina, Inc., and is published today in the online edition of *Nature Genetics*.

Using Illumina sequencing technology, deCODE scientists determined the sequences of the entire genomes of 457 Icelanders, and identified 16 million single nucleotide polymorphisms (SNPs). Through a combination of SNP genotyping and computational techniques utilizing the extensive Icelandic genealogy, they were able to propagate those 16 million variants into over 40,000 Icelanders for use in this study.

The researchers discovered a single letter variant located in TP53, a gene known to play a central role in tumor biology and for accumulating so called somatic mutations, during the development of cancer in patients. Until now, however, individuals who are born with defective copies of the gene (germline variants) have been found extremely rarely, only in families with cancer predisposition syndromes, Li Fraumeni syndrome (LFS) and Li-Fraumeni-like syndrome (LFL). The variant found in the present study is an unusual type of mutation that appears to affect the way the gene's messenger RNA is processed; the messenger RNA in patients with the mutant TP53 gene appears to lack proper termination

and polyadenylation.

This is the first evidence of a germline variant in TP53 associated with cancer predisposition beyond LFS and LFL. While the mutations causing LFS and LFL syndromes are very rare (occuring 1:5)(000 to 1:20)(000 to 1:000 births), the variant described in this paper occurs in ~ 1 in 25 individuals in Iceland, and at comparable frequencies in US and UK populations.

"This mutation is one of a growing number of deCODE discoveries of relatively low frequency sequence variants with large effect," said Kari Stefansson, deCODE's CEO and senior author of the study. "The discovery of such variants is made possible through the breadth and quality of the data that the Icelandic population provides."

Dr. Stefansson emphasized, "We will, together with our collaborators, including Illumina, extend ourselves to turn this discovery into benefit for patients and those at risk of cancer."

BCC is the most common cancer in people of European ancestry. Sun exposure is the primary risk factor for BCC, but genetic predisposition also plays a substantial role. Until now, no mechanistic causal connection between cancers as diverse as BCC, prostate cancer, glioma, and colorectal adenoma was known.

More information: The paper, "A Germline Variant in the TP53 Polyadenylation Signal Confers Cancer Susceptibility" is published online in *Nature Genetics* at DOI:10.1038/ng.926 and will appear in an upcoming print edition of the journal.

Provided by DeCODE Genetics Inc.