PIP Digest

Canadian Cancer Research Alliance
Alliance canadienne pour la recherche sur le cancer
Patient Involvement in Cancer Research Program
Programme de Participation des Patients à la recherche sur le cancer

This PIP Digest outlines the role of genes and the proteins they create in causing cancer.

UNDERSTANDING CANCER:
Genetics 101

Key Concepts

- DNA
- Transcription
- Genetic mutations
- Gene editing
- The International Cancer Genome Consortium

Related PIP Digests

- Understanding Cancer: Epigenetics 101
- Understanding Cancer: Biomarker Basics
- Understanding Cancer: Hallmarks of Cancer

Genes, the blocks of information that make up the strands of deoxyribonucleic acid (DNA), serve many roles in the human body (and in every other living organism.) They contain the code that allows hereditary traits to be passed down from one generation to the next. They direct the creation of proteins and other molecules that give cells, tissues, and entire people their structure and function. They also regulate cell division and growth.

When something goes wrong with a gene, it can disrupt that regulation, allowing certain cells to grow out of control, turning into cancerous tumours. Genes can be disrupted in two main ways: environmental factors can turn genes on or off, changing their behaviour, through a process called "epigenetics" or a gene can "mutate," or change its molecular structure in ways that make it behave differently.

A complex organism like a human being has trillions of cells, each of which contains an identical DNA string (or "genome,") that is unique to that individual. Genetic differences increase with evolutionary distance. Family members have distinct, but very similar genomes. Unrelated people have less in common genetically. Our genes are more similar those of a chimpanzee than, say, a dog, flea, or mushroom.

As cells divide and organisms reproduce, genes frequently mutate, creating imperfect copies of the original. Often, these mutations are benign or even beneficial — they help account for the huge variety of life on our planet. But sometimes, genetic mutation becomes a factor in illnesses like cancer.

Cells and Genetic Behaviour

Cells are the basic building blocks of all living things. The human body is composed of trillions of them. They provide structure for the body, take in nutrients from food, convert nutrients into energy, and carry out specialized functions. They also contain the body's hereditary material. Cells have many parts or organelles, each with a different function. The organelle known as the **nucleus** serves as the cell's command center, sending directions to the cell to grow, mature, divide, or die. It houses the cell's genetic material. The nucleus is surrounded by a membrane called the nuclear envelope, which protects the DNA and separates the nucleus from the rest of the cell.

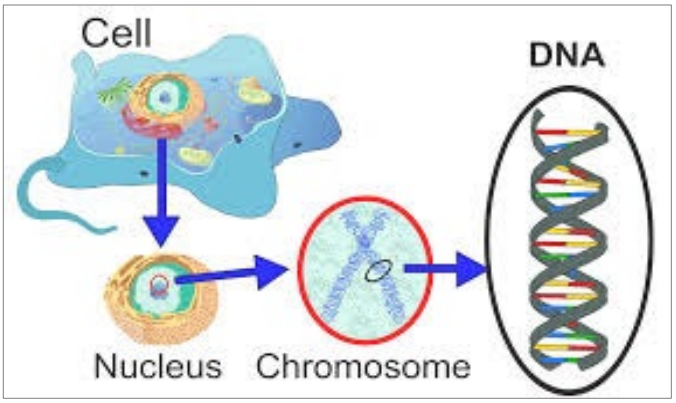
DNA – Our Unique Genetic Fingerprint

DNA molecules contain the body's instructions for making proteins. Most DNA is located in the cell nucleus (called nuclear DNA).

The information in DNA encoded using four **chemical bases**: adenine (A), guanine (G), cytosine (C), and thymine (T), which bond with each other in pairs — A always pairs with T, and C with G. One strand of human DNA consists of about 3 billion base pairs.

Each base also attaches to a sugar molecule and a phosphate molecule. Together, a base, sugar, and phosphate are called a **nucleotide**. Nucleotides join into two long, connected strands that form a spiral

called a double helix. The double helix is like a ladder, with base pairs forming the rungs and the sugar and phosphate molecules forming the sides.



From: https://commons.wikimedia.org/wiki/File:Eukaryote_DNA-en.svg

DNA can **replicate** or make copies of itself. Each half of the double helix can serve as a pattern for duplicating the complete sequence. This function is critical when cells divide, ensuring each new cell receives an exact copy of the DNA.

A DNA molecule is divided into thread-like structures called chromosomes. In humans, cells normally contain 23 pairs of chromosomes, for a total of 46. Each chromosome coils tightly many times around proteins called **histones** that govern its structure.

Chromosomal DNA becomes more tightly packed during cell division. Each chromosome has a constriction point called the **centromere**, which divides the chromosome into two sections, or "arms." The location of the centromere on each chromosome gives it its characteristic shape. The centromere can be used to help locate specific genes.

Creating Proteins[1]

Genes are segments of DNA that contain information for making a protein. In humans, genes vary in size from a few hundred DNA bases to more than 2 million. The Human Genome Project estimates that humans have between 20,000 and 25,000 genes.

Through a process called **transcription**, the DNA that makes up a gene is copied into a complementary molecule called messenger RNA (mRNA). Through a process called **translation**, mRNA is decoded into amino acids. A sequence of three mRNA bases is called a **codon**, and each codon translates into a specific amino acid. There are 20 different kinds of amino acids in humans.

Amino acids form into folded chains known as proteins. Proteins have millions of functions. The shape of a protein determines its role.

Only about 1% of DNA is made up of protein-coding genes. The other 99% — "noncoding DNA" — also affects the function of cells, including by controlling gene activity. For example, certain noncoding DNA sequences determine when and where genes are turned on and off. Such elements allow specialized proteins called **transcription factors** to activate or repress the process of turning genetic information into proteins.

Chromosomes also contain noncoding DNA. For example, repeated noncoding DNA sequences at the ends of chromosomes form **telomeres**. Telomeres protect the ends of chromosomes from damage when genetic material is copied.

Genetic Mutations

A genetic mutation is a permanent alteration in a DNA sequence. Mutations range in size from a single base pair to a large segment of a chromosome involving multiple genes. When DNA code changes, it can affect protein production. A mutated gene may create a different version of a protein, or different amount of

[1]Adapted from: https://www.cancer.gov/about-cancer/causes-prevention/genetics

protein. It may stop protein production altogether. These changes affect how the body functions.

Hereditary mutations are inherited from a parent and are present throughout a person's life in virtually every cell in the body. These mutations are also called **germline mutations** because they are present in the parent's egg or sperm cells.

Hereditary mutations, including those that change your risk of developing certain cancers, can be **recessive** or **dominant**. You need only inherit a dominant gene mutation from one parent for it to affect you. But you need two copies of a recessive mutation to cause disease.

Hereditary mutations play a major role in about five to ten percent of all cancers. To date, researchers have identified more than 50 hereditary cancer syndromes that predispose individuals to certain cancers. (See table below for some examples.)

Cancer	Major familial susceptibility syndrome	Major gene	Gene function	Mode of inheritance
Breast and ovary	Hereditary breast and ovarian cancer syndrome	BRCA1, BRCA2	Tumour suppressor	Dominant
Colon and rectum	HNPCC/Lynch syndrome	MLH1, MSH2, MSH6, PMS2	DNA repair	Dominant
Prostate	Li-Fraumeni syndrome	P53, CHEK2	Tumour suppressor	Dominant
Leukemia/lymphoma	Fanconi anemia	FANCA,B,C,D,E,F,G	DNA repair	Recessive
Pediatric cancers	Retinoblastoma	RB1	Tumour suppressor	Dominant

From: Cancer Care Ontario. (2013). *Cancer Risk Factors in Ontario: Genetic Susceptibility to Cancer.* Toronto: Cancer Care Ontario.

Acquired (or somatic) mutations occur during a person's life and are present only in certain cells, not in every cell in the body. These changes can be caused by environmental factors such as ultraviolet radiation from the sun or exposure to certain chemicals in tobacco smoke. They can also result from errors as DNA replicates during cell division. Acquired mutations in somatic cells (cells other than sperm and egg cells) cannot be passed to the next generation.

De novo (new) mutations can be either hereditary or somatic. In some cases, the mutation occurs in a person's egg or sperm cell but is not present in any of the person's other cells. In other cases, the mutation occurs in the fertilized egg shortly after the egg and sperm cells unite.

Most disease-causing gene mutations are uncommon in the general population. However, some genetic changes occur frequently. Single nucleotide **polymorphisms** (SNPs) are the most common types of human genetic variation. SNPs in genes that regulate the cell's system of identifying and fixing problems during DNA replication, the cell cycle, cell metabolism, and immunity are associated with susceptibility to cancer. Understanding how SNPs increase cancer susceptibility is critical to understanding various cancers. SNPs may also serve as potential biomarkers to aid in cancer diagnosis and treatment. Genome-wide association studies (GWAS) look at hundreds or thousands of SNPs at the same time to reveal SNPs that occur more frequently in people with a specific cancer than in people without the disease.

Gene Function Related to Cancer[2]

Most genes that contribute to cancer development fall into three broad categories: tumour suppressor genes, oncogenes and DNA repair genes.

Tumor suppressor genes are protective genes that normally limit cell growth by monitoring how quickly cells divide, repairing mismatched DNA, and controlling when cells die. When a tumor suppressor gene mutates, cells grow uncontrollably and may eventually form a tumor. Two tumor suppressor genes, p53 and TP53, are the most commonly mutated gene in people with cancer. More than 50% of cancers involve a missing or damaged p53 gene. Most p53 gene mutations are acquired. Germline p53 mutations are rare, but patients who carry them are at a high risk of developing many different types of cancer.

Germline mutations in the tumor suppressing genes BRCA1 and BRCA2 increase a woman's risk of developing breast or ovarian cancers and a man's risk of developing prostate or breast cancers. They also increase the risk of pancreatic cancer and melanoma in women and men.

DNA repair genes normally fix mistakes made when DNA is copied. Many of them function as tumor suppressor genes. BRCA1, BRCA2, and p53 are all DNA repair genes. If a person has an error in a DNA repair gene, mistakes remain uncorrected, become mutations, and may eventually lead to cancer. Mutations in DNA repair genes may be inherited or acquired.

Mutated oncogenes turn healthy cells into cancerous ones. Most mutated oncogenes are acquired not inherited. Mutated versions of HER2, a gene that controls cell growth, may be found in breast and ovarian cancer cells.

Gene Editing

Gene editing (also called genome editing) allows genetic material to be added, removed, or altered at specific places in the genome. The most famous gene editing technique, CRISPR-Cas9, (**c**lustered **r**egularly **i**nterspaced **s**hort **p**alindromic **r**epeats and **C**RISPR-**a**ssociated **p**rotein **9**) is based on a naturally occurring genome editing system in bacteria. Microbes make "edits" to their own genetic code to protect themselves from viruses.

Genome editing could revolutionize the prevention and treatment of human diseases, including cancer. Most research on genome editing has involved animal models. Recent research, though, involves editing human somatic cells (which cannot be passed on to future generations). A Phase I clinical trial sponsored by the University of Pennsylvania started in September 2018. It involves using CRISPR for to treat 18 patients with multiple myeloma, melanoma, synovial sarcoma, and liposarcoma.[3] In this study, immune system cells will be removed from patients, genetically modified in the lab, and then infused back, with the hope that the modified cells will target and destroy cancer cells.

Not surprisingly, there are a lot of major ethical concerns about this technology. Changes made to genes in egg or sperm cells (germline cells) or in the genes of an embryo could be passed to future generations. This is why the international scientific community widely condemned Chinese researcher, He Jiankui, who used CRISPR-Cas9 to edit the germline in twin girls.

[2]Adapted from: https://www.cancer.net/navigating-cancer-care/cancer-basics/genetics/genetics-cancer

[3]This trial is entitled, "NY-ESO-1-redirected CRISPR (TCRendo and PD1) Edited T Cells (NYCE T Cells)" (NCT03399448).

Françoise Baylis, a Canadian bioethicist at Dalhousie University, points out that the potential benefits of gene editing are neither guaranteed nor risk-free. Harms could include inadvertently activating cancer-causing genes or triggering an unhealthy immune response. These techniques may also "exacerbate existing inequalities resulting in human rights abuses, a new wave of eugenics, increased discrimination and increased stigmatization."[4] Currently, Canadian legislation on human germline gene editing is among the most restrictive in the world.[5]

References:

U.S. Department of Health and Human Services. *The New Genetics*. National Institute of General Medical Sciences. NIH Publication No. 10-662. Revised April 2010. https://www.nigms.nih.gov/education/Booklets/the-new-genetics/Documents/Booklet-The-New-Genetics.pdf

Genetics Home Reference, a consumer health website from the U.S. National Library of Medicine, which is part of the National Institutes of Health. The website provides information for the general public about the effects of genetic variation on human health. https://ghr.nlm.nih.gov/

The International Cancer Genome Consortium (ICGC)

The ICGC, initiated in 2007, was the first step to broadly and comprehensively map the structural aberrations of genomes and unravel the molecular basis of cancer. It involved a coordinated, global effort to sequence the genomes of 25,000 untreated primary cancers – data that really transformed cancer research around the world.

The second ICGC project, the Pan Cancer Analysis of Whole Genomes (The PCAWG Project), began in 2013 with the goal of analyzing about 2,600 of the highest quality whole genomes for 38 cancer types. This project brought together thousands of scientists. In February 2020, an entire special issue of *Nature* was dedicated to the results of this work. It makes available to the research community a comprehensive resource for cancer genomics research through different data portals. By combining sequencing of the whole cancer genome with a suite of analysis tools, it is possible to characterize every genetic change found in a cancer, all the processes that have generated those mutations, and even the order of key events during a cancer's life history.

The ICGC released a white paper on the evolution of ICGC, looking at its role in advancing genomics to the clinic. This set the stage for the launch of the ICGC-Accelerate Research in Genomic Oncology (The ARGO Project) in 2016. The focus of this project is on linking existing genomic data from more than 100,000 patients with new genomic data and clinical and health information. It includes information concerning lifestyle, co-morbidities, diagnostics, toxicity and response to therapy, and survival. With this large-scale integrated data, researchers, scientists, policymakers and clinicians will be able to work with patients, health care providers, industry, and others to advance precision medicine, develop preventative strategies, and identify markers for early detection as well as more specific criteria and methods for diagnosis and prognostication.

For more information, see https://www.icgc-argo.org/.

[4]Baylis, F. (2018). The Potential Harms of Human Gene Editing Using CRISPR-Cas9. *Clinical Chemistry*, 64(3):489-91.

[5]Knoppers, BM, Nguyen, MT, Noohi, F. & Kleiderman, E. (2018). *Human Genome Editing: Ethical and Policy Considerations. Policy Brief.* Montreal: Centre of Genomics and Policy (CGP), McGill University and Genome Quebec Innovation Centre.

Use these videos to further your understanding of genetics:

- yourgenome. From DNA to protein - 3D. (YouTube) January 7, 2015 [2:41 minutes] https://www.youtube.com/watch?v=gG7uCskUOrA [From more, see https://www.yourgenome.org/]
- Genomics Education Programme. *Introducing Genomics in Healthcare*. (YouTube) June 25, 2014 [7:43 minutes] https://www.youtube.com/watch?v=KiQgrK3tge8
- McGovern Institute. *Genome Editing with CRISPR-Cas9.* (YouTube) November 5, 2014 [4:12 minutes] https://www.youtube.com/watch?v=2pp17E4E-O8
- European Society for Medical Oncology. *Accelerating Medical Breakthroughs in Cancer with Fabien Calvo* (YouTube) October 11, 2017 [3:59 minutes] https://youtu.be/2ct1Vss_i7c

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