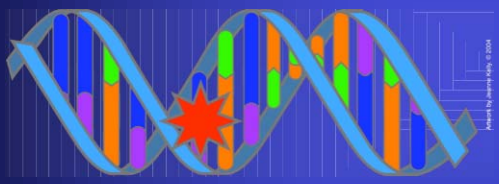
Understanding Cancer and Related Topics

Understanding Cancer Genomics



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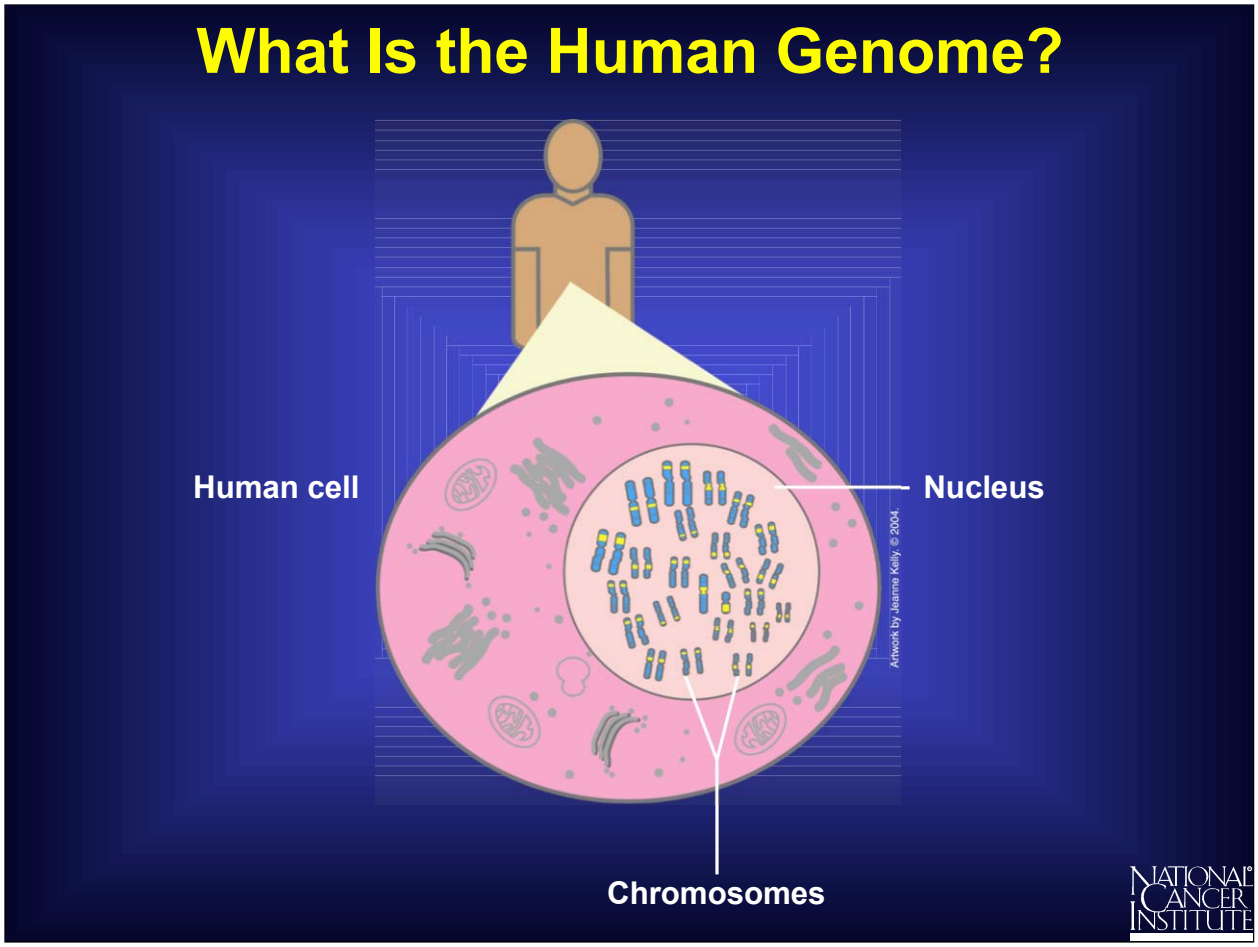
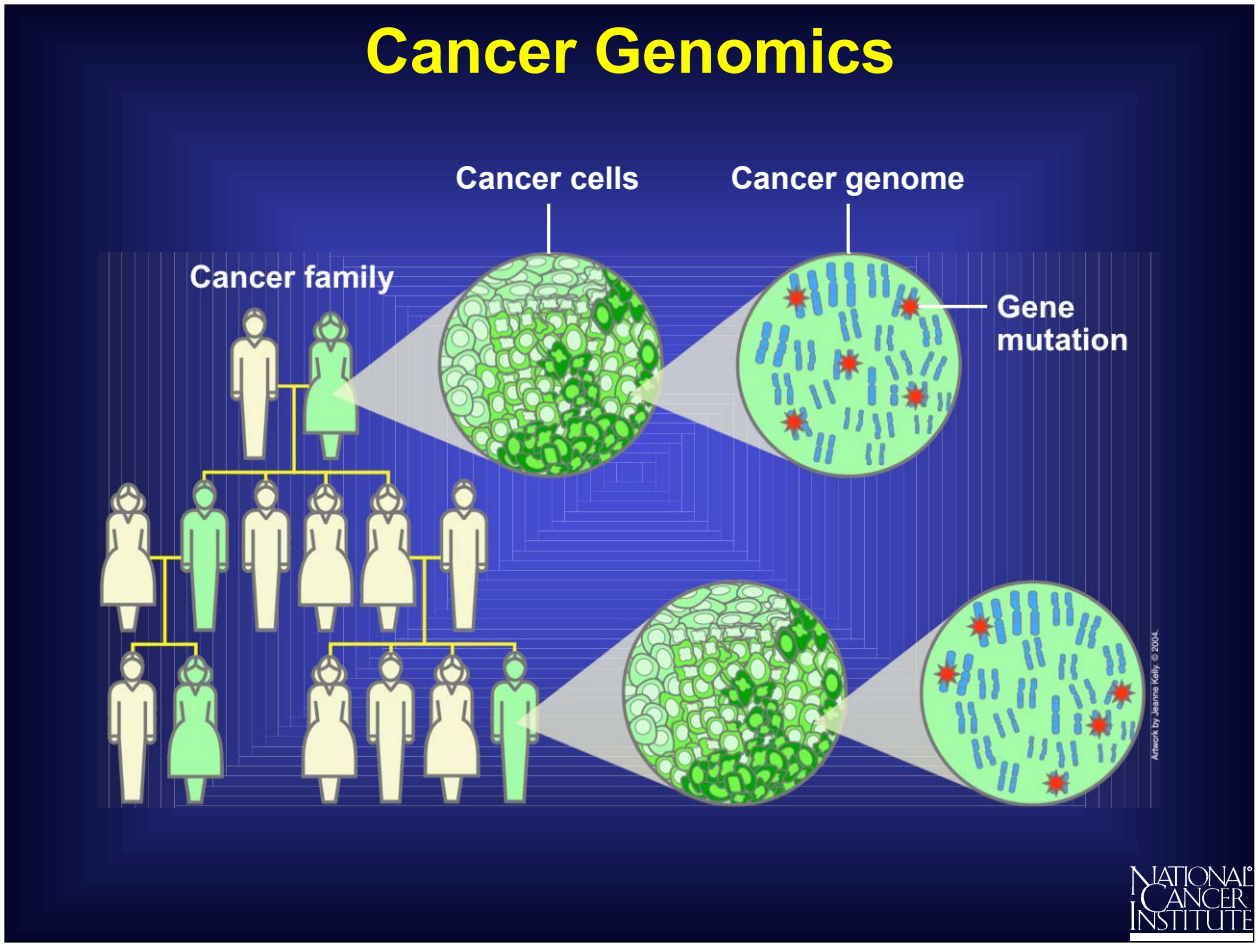
This tutorial describes some of the genes and mutations--both inherited and sporadic--in the human genome that contribute to cancer susceptibility and to the development and progression of cancer. The presentation also briefly discusses some epigenetic factors, such as methylation or imprinting, that can influence cancer-related gene expression.

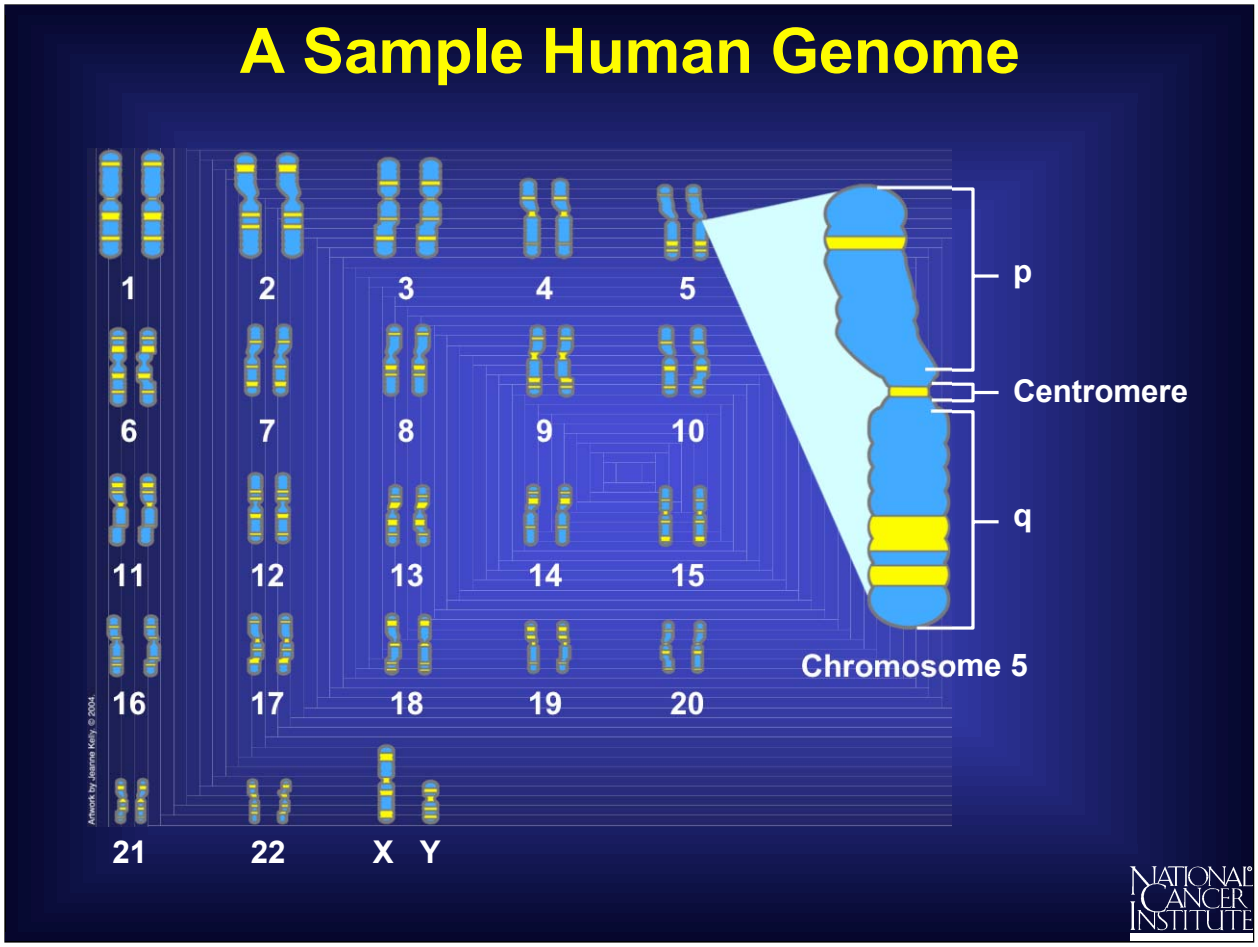


The complete supply of DNA--all the genes and spaces in between--in all the chromosomes of a species is called its genome. Except for red blood cells, which have no nucleus, the human genome is located in the nucleus of every cell in the body. There it is organized into 46 very large molecules called chromosomes; 44 are called autosomes and 2 are called the sex chromosomes.

An international collaboration known as the Human Genome Project has identified every chemical base in the human genome and has discovered that there are about 25,000 genes present.

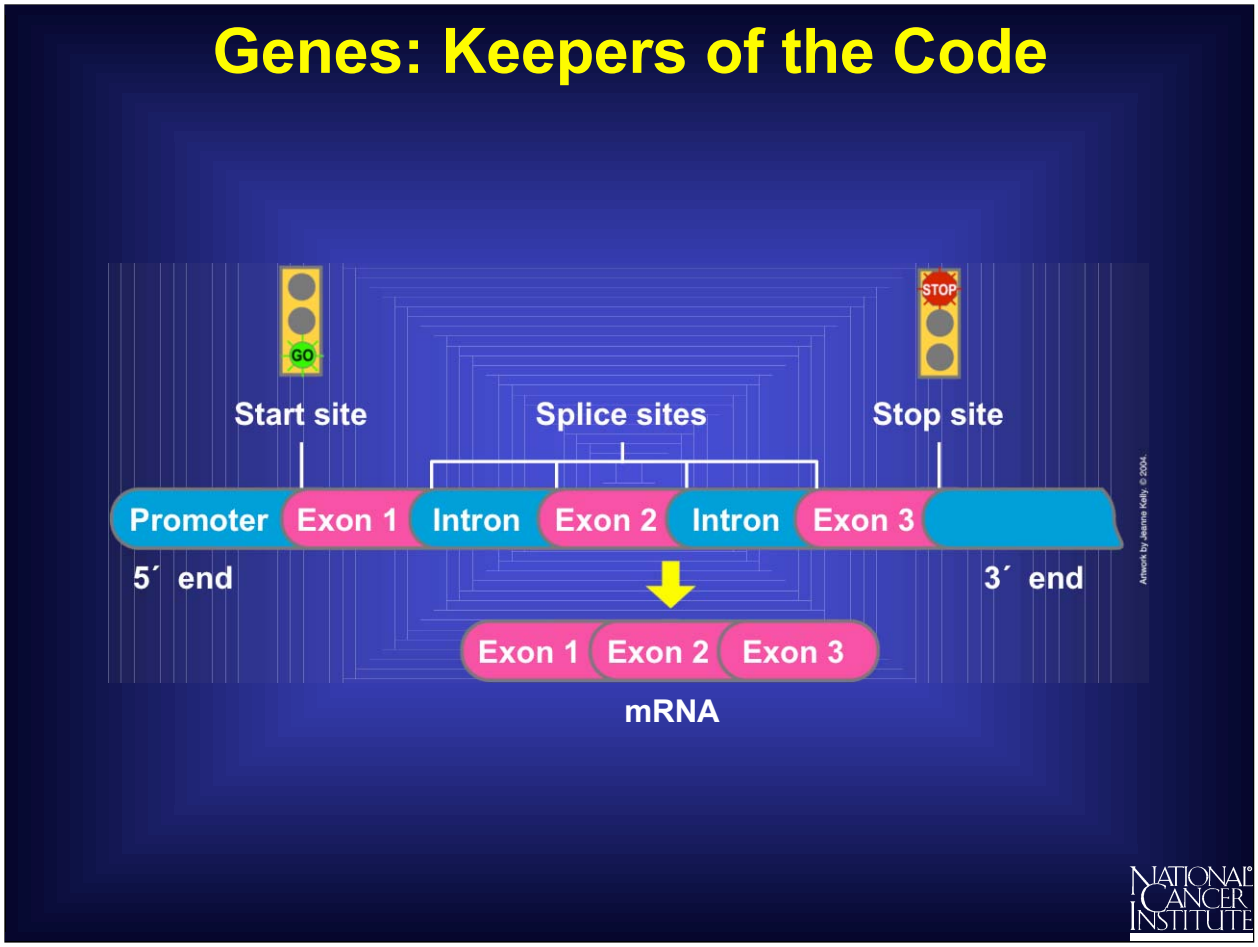


Cancer genomics is the study of the human cancer genome. It is a search within "cancer families" and patients for the full collection of genes and mutations--both inherited and sporadic--that contribute to the development of a cancer cell and its progression from a localized cancer to one that grows uncontrolled and metastasizes (spreads throughout the body).



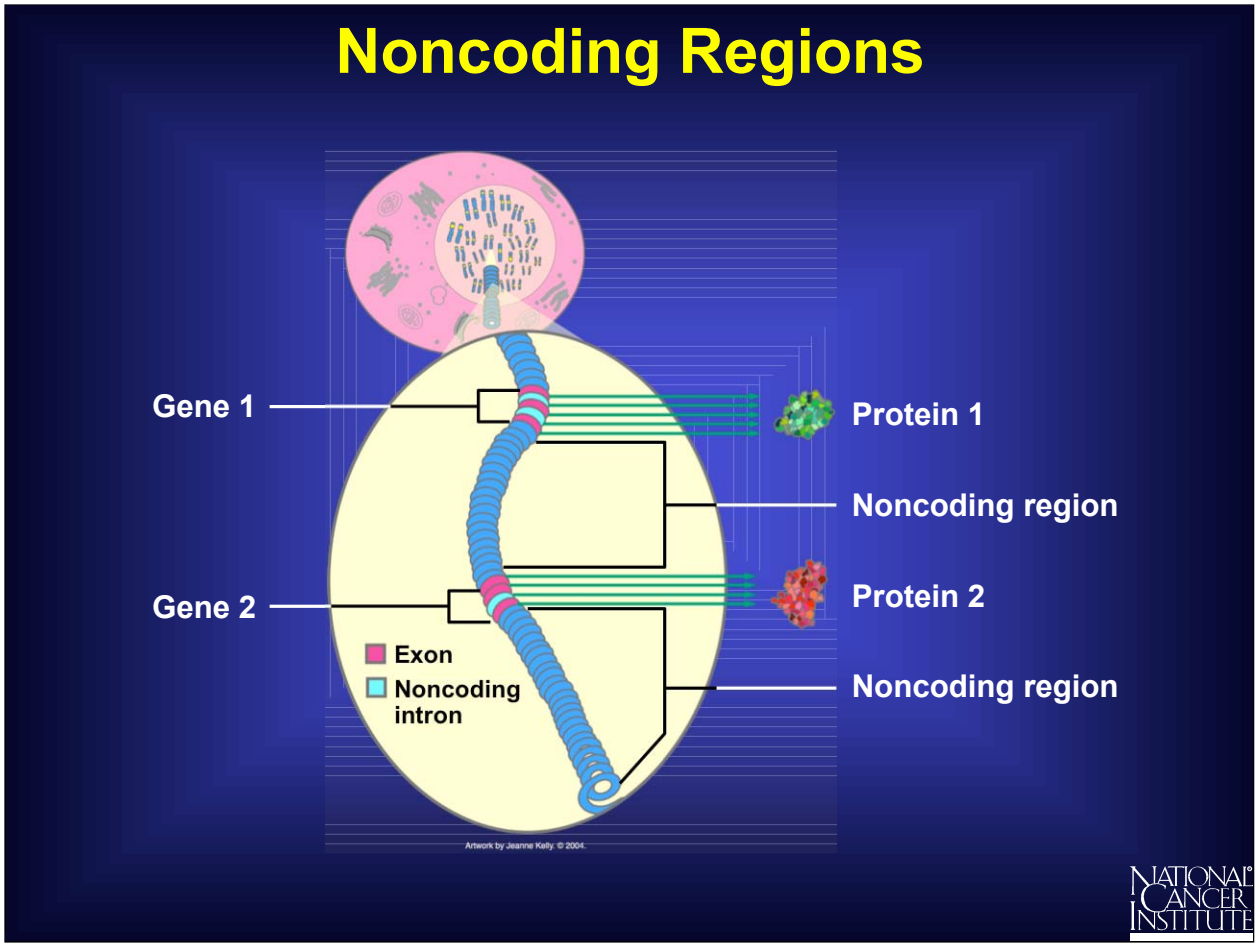
A human karyotype is a display of its genome. It shows all the chromosomes present in an individual after they have been stained and arranged in pairs called homologs. This is a male karyotype because there is an X and a Y chromosome present.

The centromere of a chromosome is the region that separates the two arms. The arm above the centromere, which is shorter, is called the p arm, while the longer arm is the q arm.

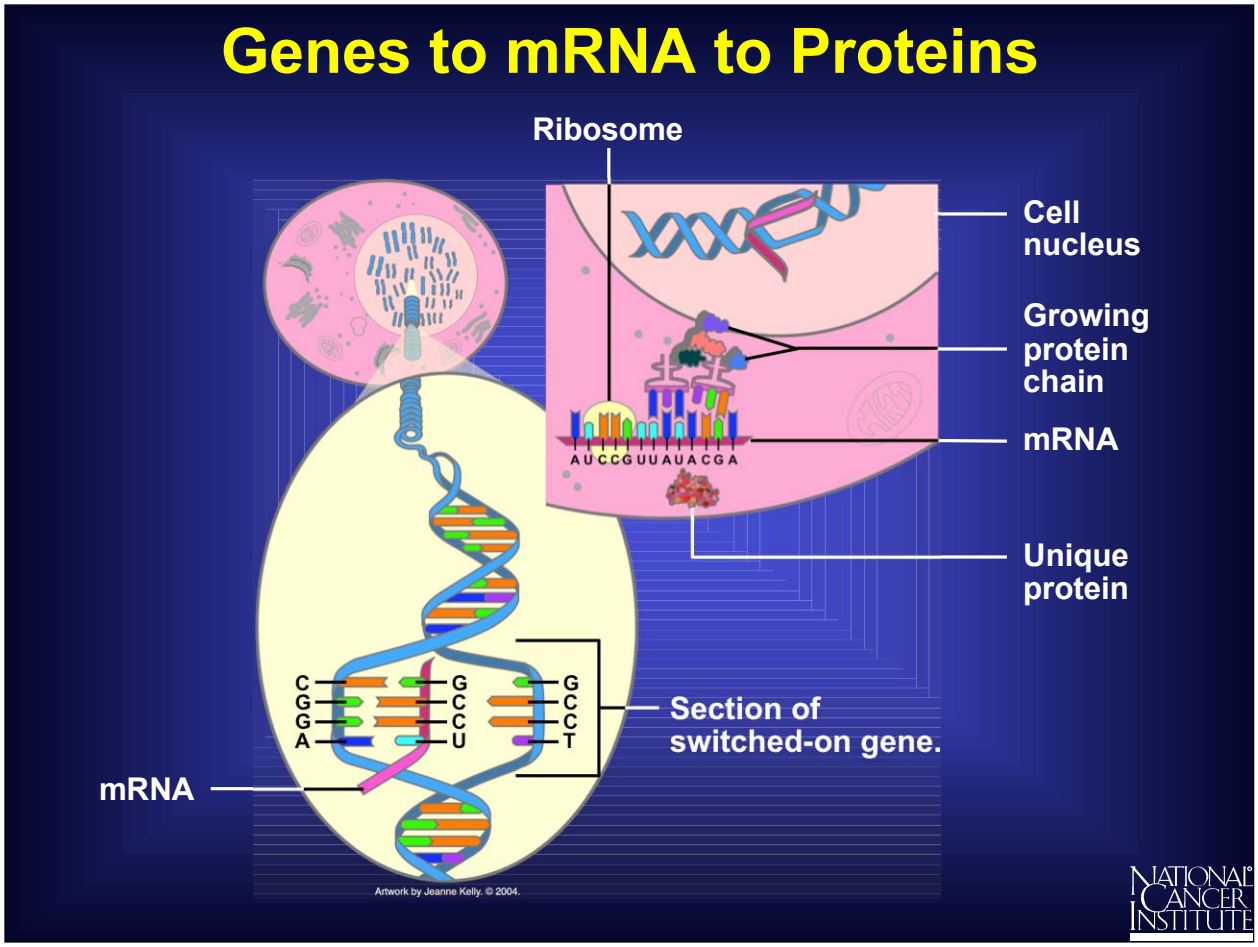


The 25,000 genes scattered throughout the human chromosomes comprise only about 3 percent of the total genome. These genes hold information critical to all human life. While all the component bases in a gene are copied as information leaves the nucleus, not all this information is kept. This is because within a gene there are both coding and noncoding stretches of bases. For example, in split genes, coding sections called exons supply the genetic instructions that are copied to direct protein building. These sections are preserved, but other noncoding sections within the gene, called introns, are rapidly removed and degraded.

Close to each gene is a "regulatory" sequence of DNA, which is able to turn the gene "on" or "off." Farther away, there are enhancer regions, which can speed up a gene's activity.

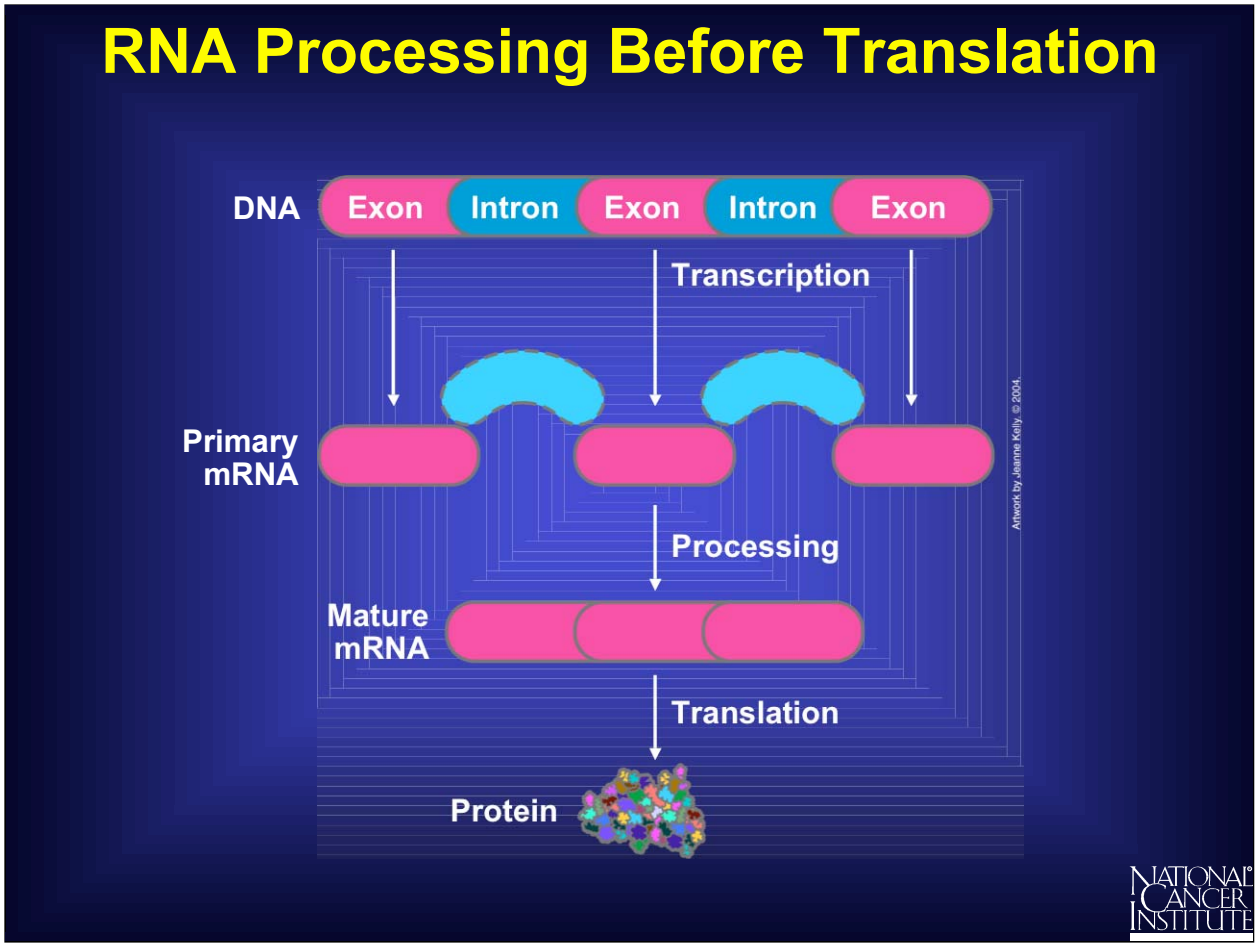


The massive DNA molecules known as chromosomes also have many noncoding regions located outside the genes. These contain large stretches of repetitive sequences. Some of the sequences in these locations are involved in the regulation of gene expression, and others simply act as spacers. Still other regions have functions as yet undiscovered.

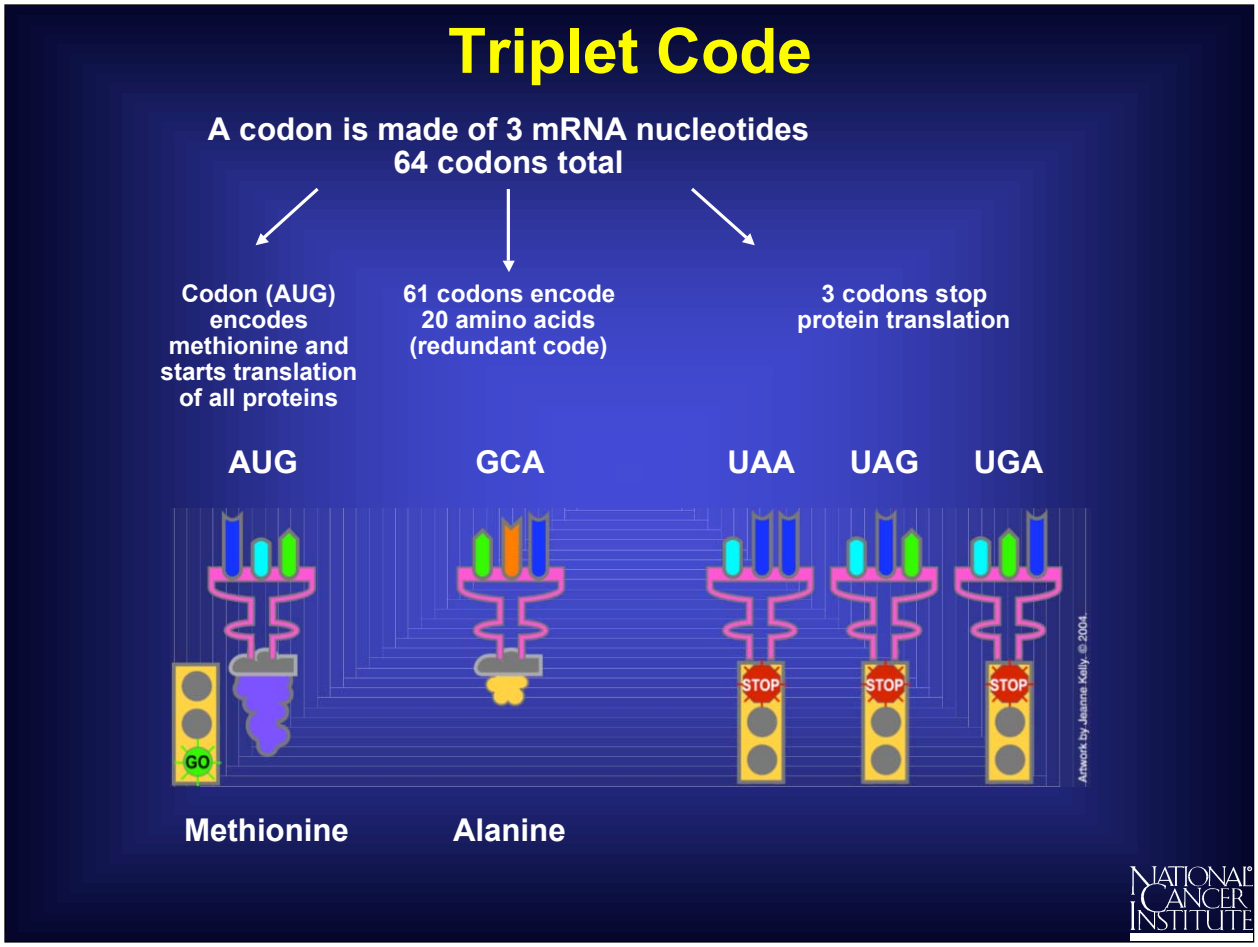


When a gene "switches on," it eventually makes a protein, but it does not do so directly. First, the gene codes an intermediary molecule called mRNA. To transfer a gene's information from DNA to mRNA, base pairing is used. However, there is one change: An adenine base (A) in the DNA matches with a new base called uracil (U) in the mRNA. This difference helps to distinguish mRNA from DNA.

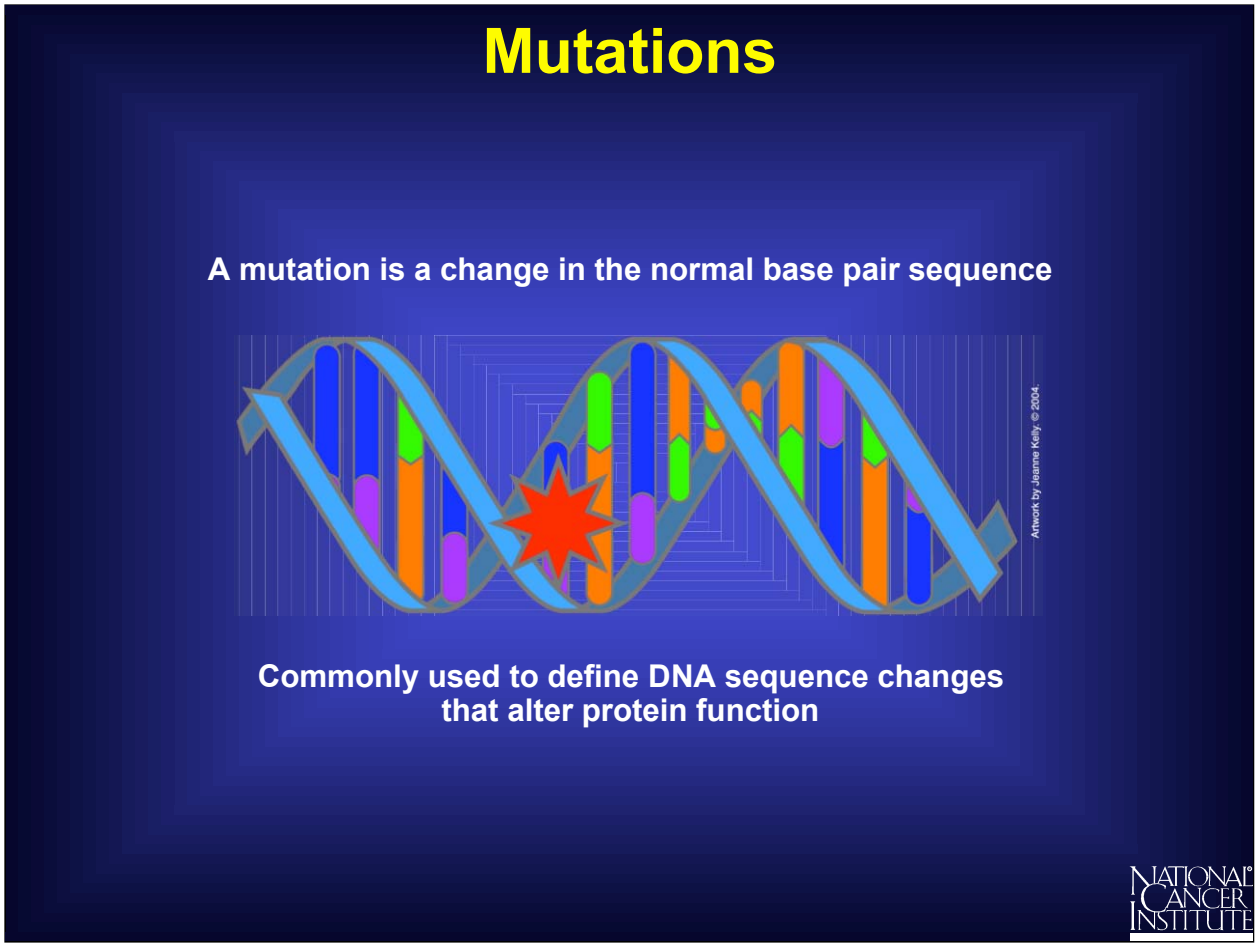
mRNA travels from the nucleus into the cytoplasm to cell organelles called ribosomes. There it directs the assembly of amino acids that fold into a unique protein.



Before mRNA leaves the nucleus, it undergoes further processing. The regions not involved in building proteins, called introns, are cut out of the message. The mature RNA that arrives at a ribosome contains only exons that will be used to build a protein in a process called translation.

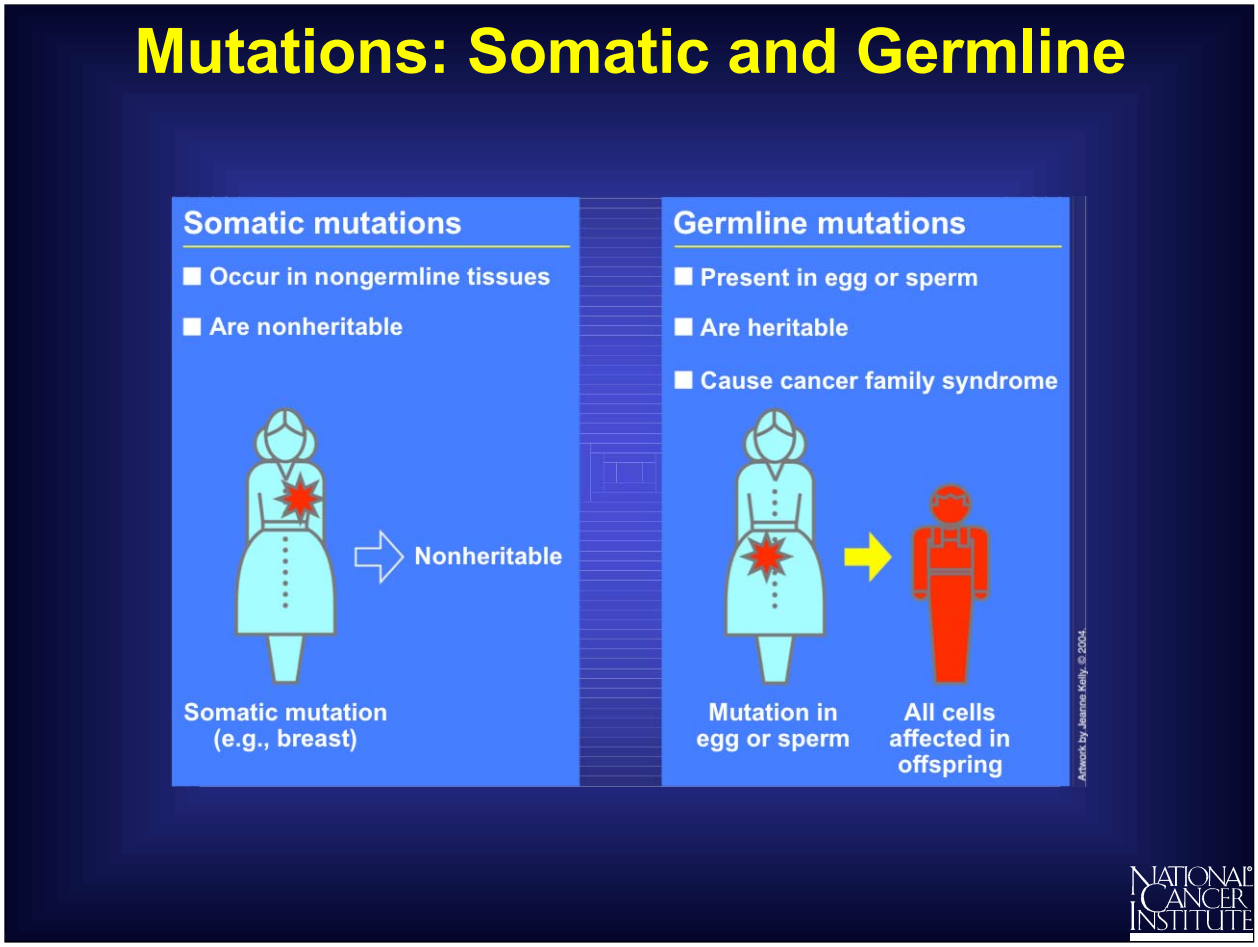


The translation of base sequences from DNA to protein is dependent on the nucleotide triplet in mRNA. Each mRNA triplet of nucleotides, called a codon, codes for a single amino acid, and, ultimately, a string of amino acids makes up a protein. Since the complementary DNA that specifies a particular mRNA has only four nucleotide bases in a gene, 64 (4X4X4) possible combinations of codons are available to code for 20 amino acids. So there is great redundancy. There are 60 mRNA triplets for 19 amino acids, 3 triplets for "stop," and 1 triplet to call for methionine, the 20th amino acid that signals "start." Most amino acids are coded for by more than one triplet codon. However, each triplet is linked to only one amino acid. (For more information on how genes build proteins, please see Genetic Variation.)

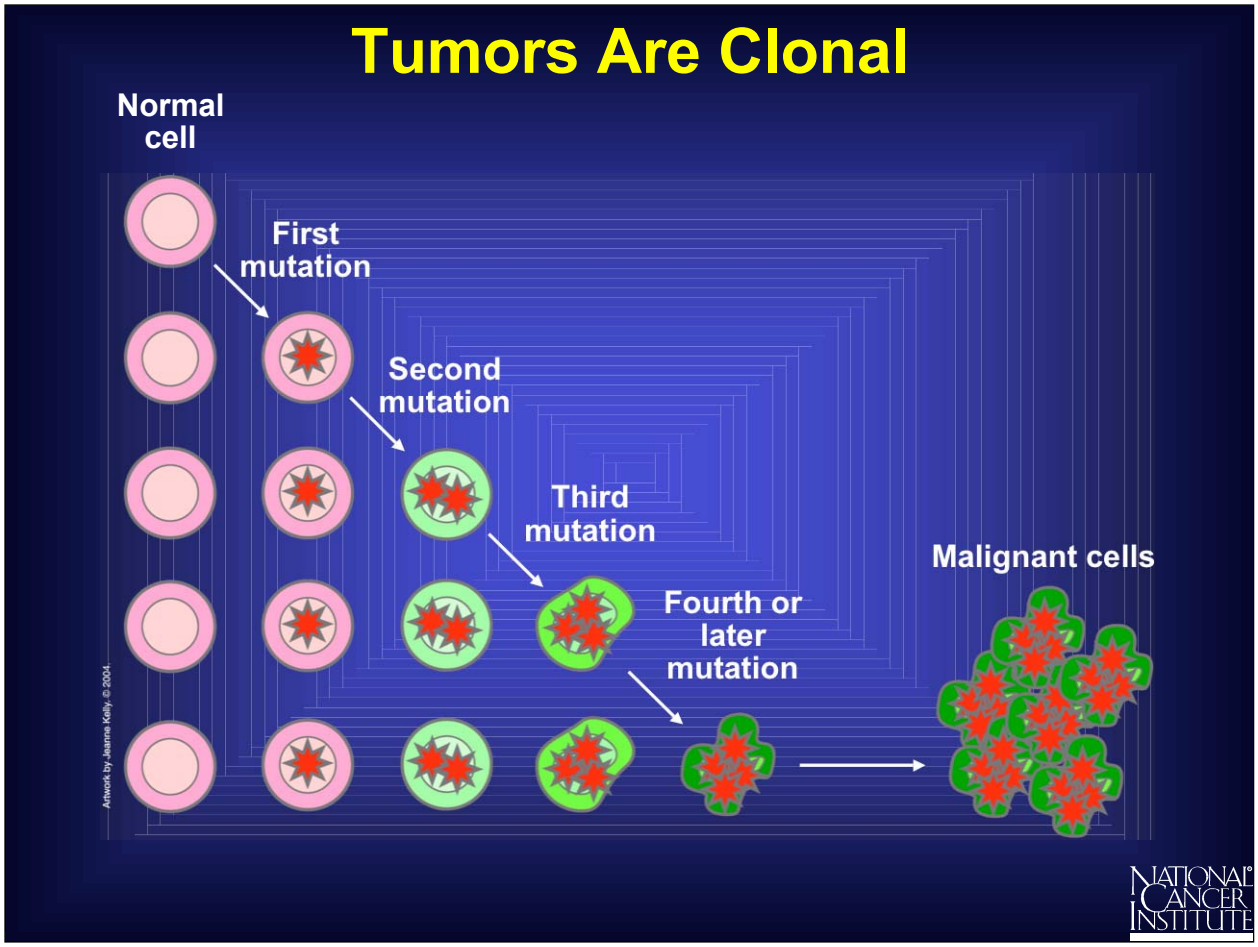


All mutations are changes in the normal base sequence of DNA. These changes may occur in either coding or noncoding regions. Mutations may be silent and have no effect on the resulting protein. This is especially true if they occur in noncoding regions of the DNA. But even base pair changes in the coding region may be silent because of the redundancy of the code. For example, a mutation within a codon may occur, yet still call for the same amino acid as was called for earlier.

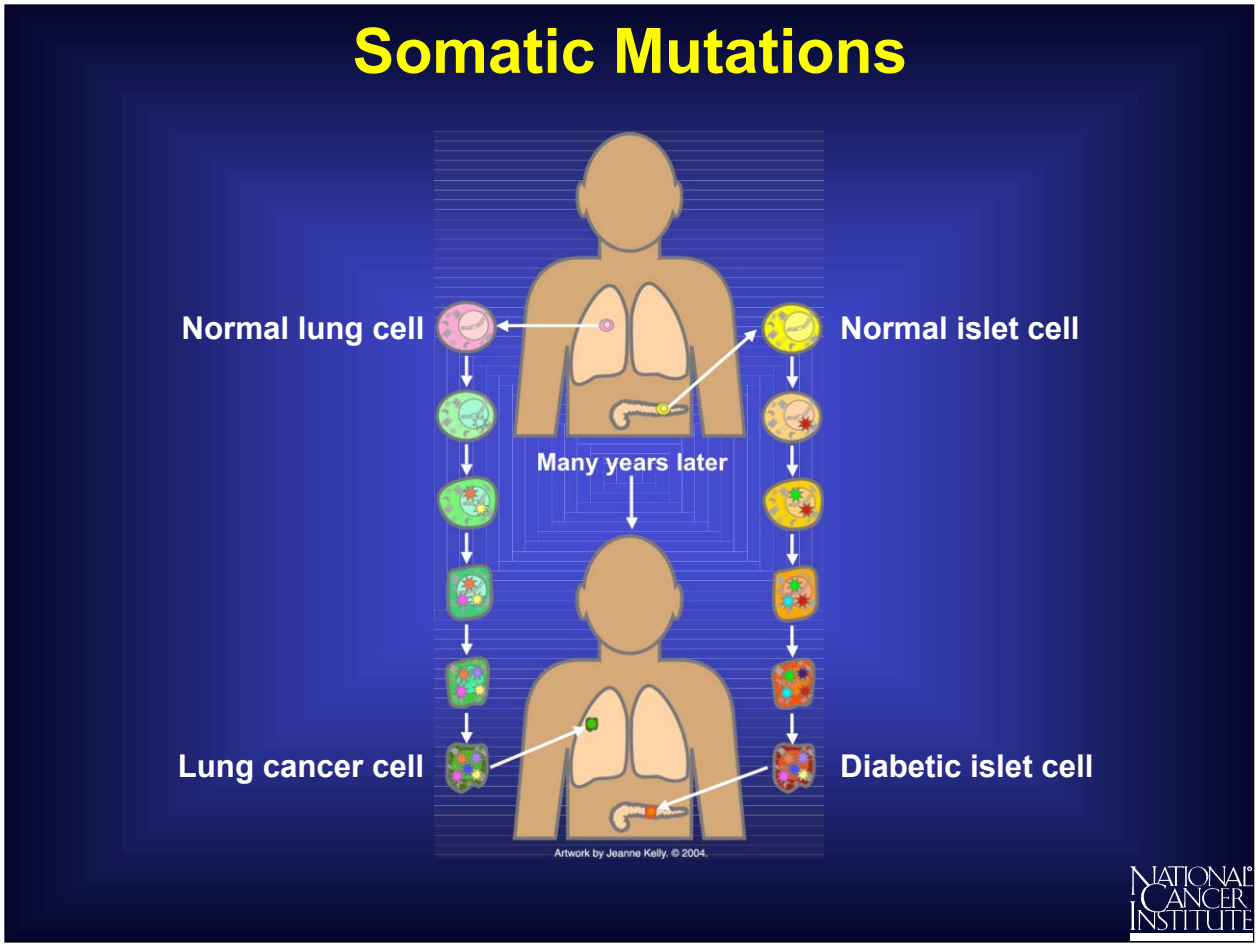
Mutations may involve a single base change--called a point mutation--or may involve larger sections of DNA through deletions, insertions, or translocations.



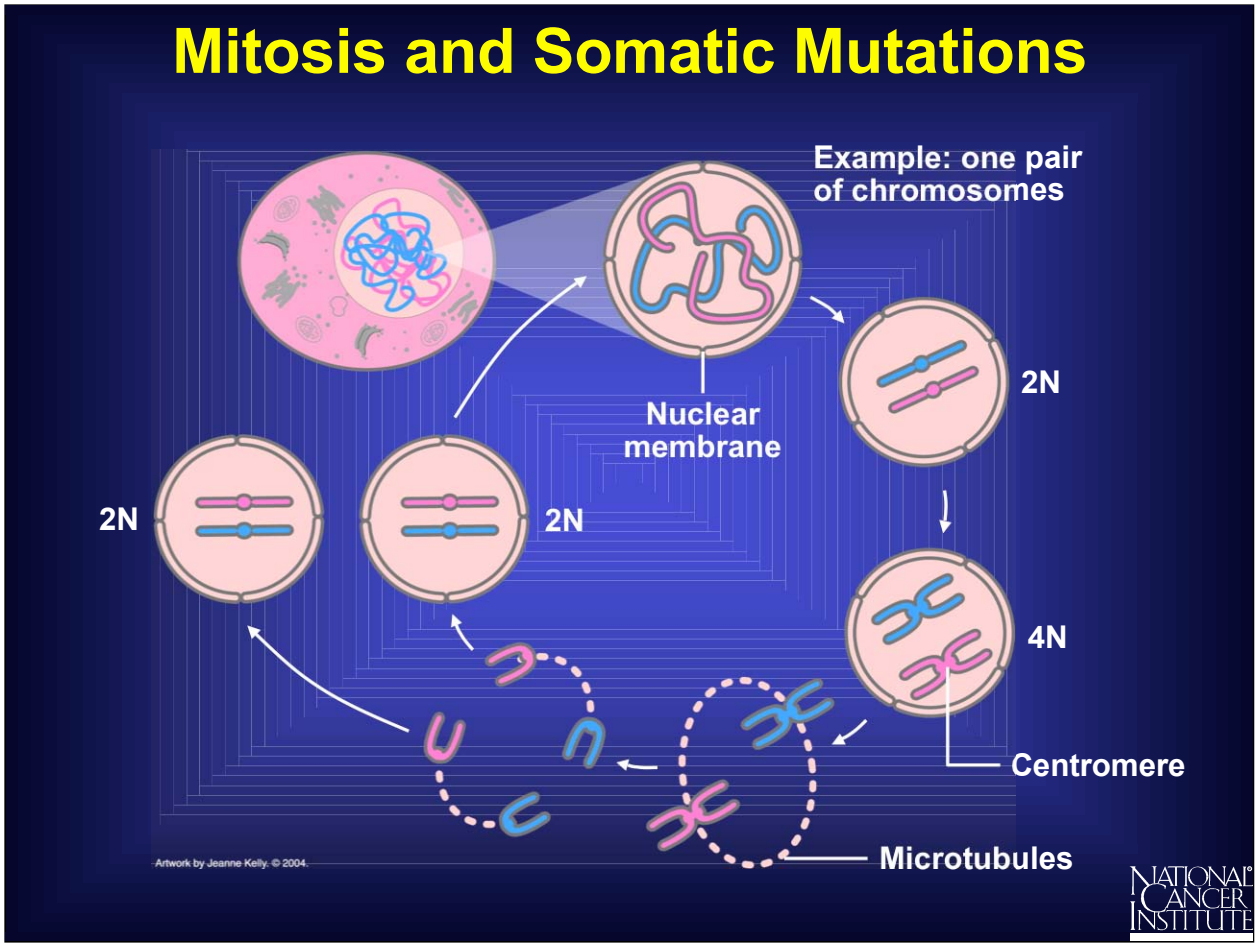
Most cancers arise from several genetic mutations that accumulate in cells of the body over a person's lifespan. These are called somatic mutations, and the genes involved are usually located on autosomes (non-sex chromosomes). Cancer may also have a germline mutation component, meaning that they occur in germ cells, better known as the ovum or sperm. Germline mutations may occur *de novo* (for the first time) or be inherited from parents' germ cells. An example of germline mutations linked to cancer are the ones that occur in cancer susceptibility genes, increasing a person's risk for the disease.



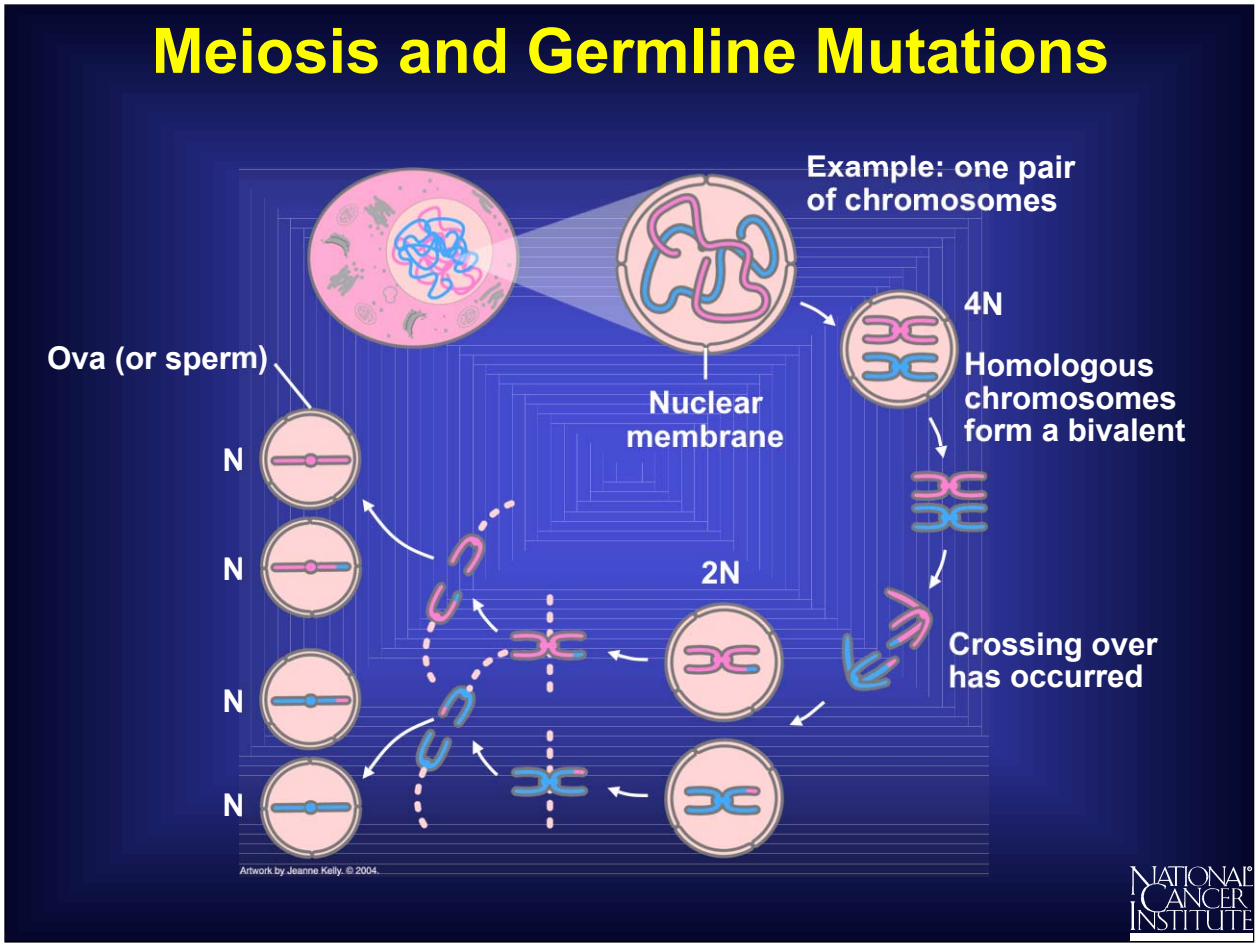
Each cell, when it divides, generates two identical new ones. So, when a cell acquires a mutation, it passes that mutation on to its progeny during cell growth and division. Because cells with cancer-linked mutations tend to proliferate more than normal cells, cellular candidates for additional mutations grow in number. Mutations continue to accumulate and are copied to descendant cells. If one cell finally acquires enough mutations to become cancerous, subsequent cancer cells will be derived from that one single transformed cell. So all tumors are clonal, which means that they originate from a single parent cell, whether that first mutant cell was of germline or somatic origin.



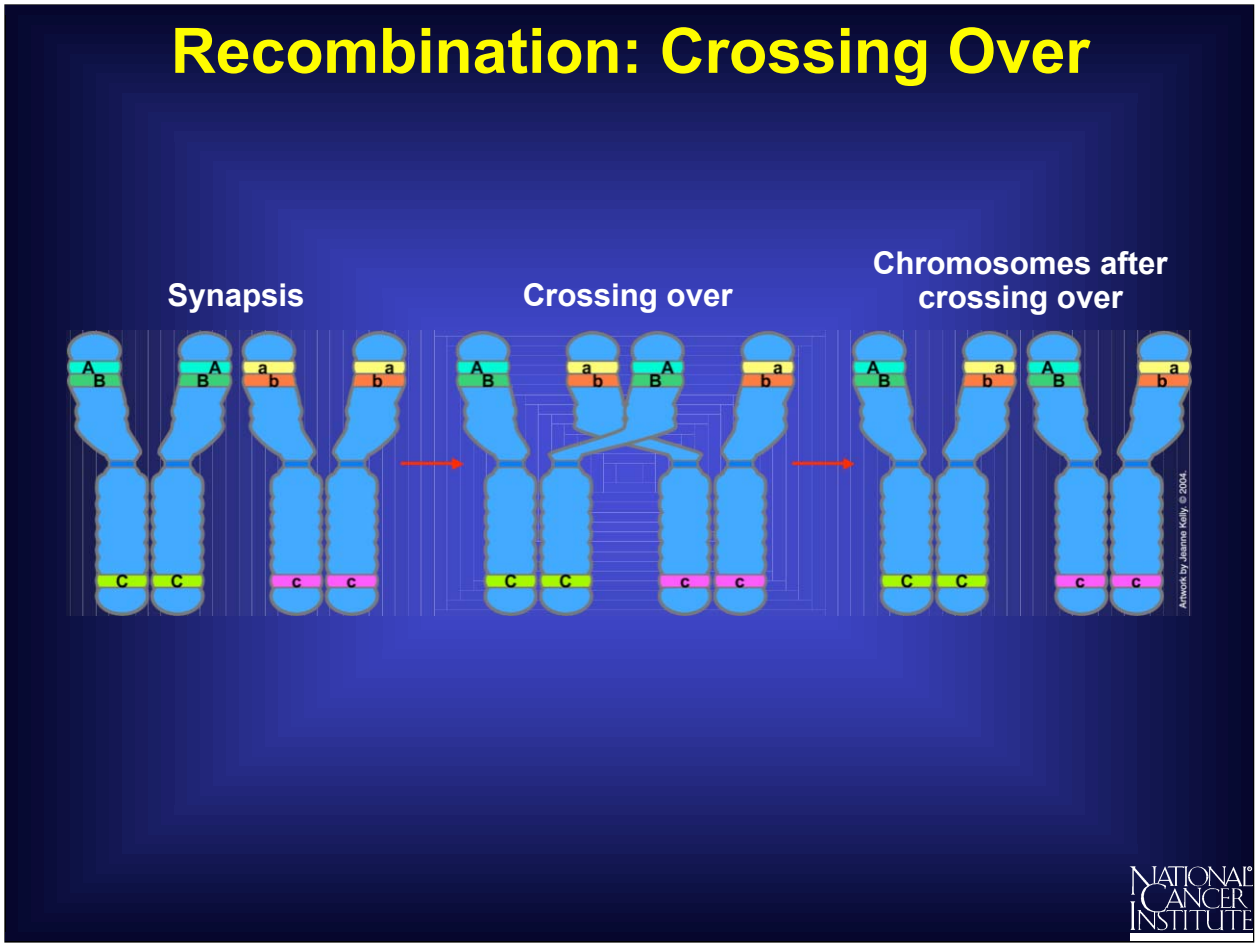
The majority of human cancers result from an accumulation of somatic mutations. Somatic mutations are not passed on to the next generation. An 80-year cancer-free lifespan is no small accomplishment. It requires as many as 10 million billion body cells to copy themselves correctly. It is easy to see how random errors can occur. These changes are acquired during a person's lifetime from exposures to carcinogens and other mutagens, or from random unrepaired errors that occur during routine cell growth and division. Occasionally, one of these somatic mutations alters the function of some critical genes, providing a growth advantage to the cell in which it has occurred. A clone then arises from that single cell.



Normal human cells with a nucleus having 23 pairs of chromosomes are called diploid or 2N to indicate these homolog pairs. During the cell growth cycle for body (somatic) cells, the DNA of all 23 pairs--46 chromosomes--copies itself (4N). When the cell next divides by a process called mitosis, each daughter cell ends up with 23 pairs or 2N, a complete set of chromosomes. If a mutation occurs during the process of mitosis, only the offspring of the mutated somatic cell will have the alteration present.

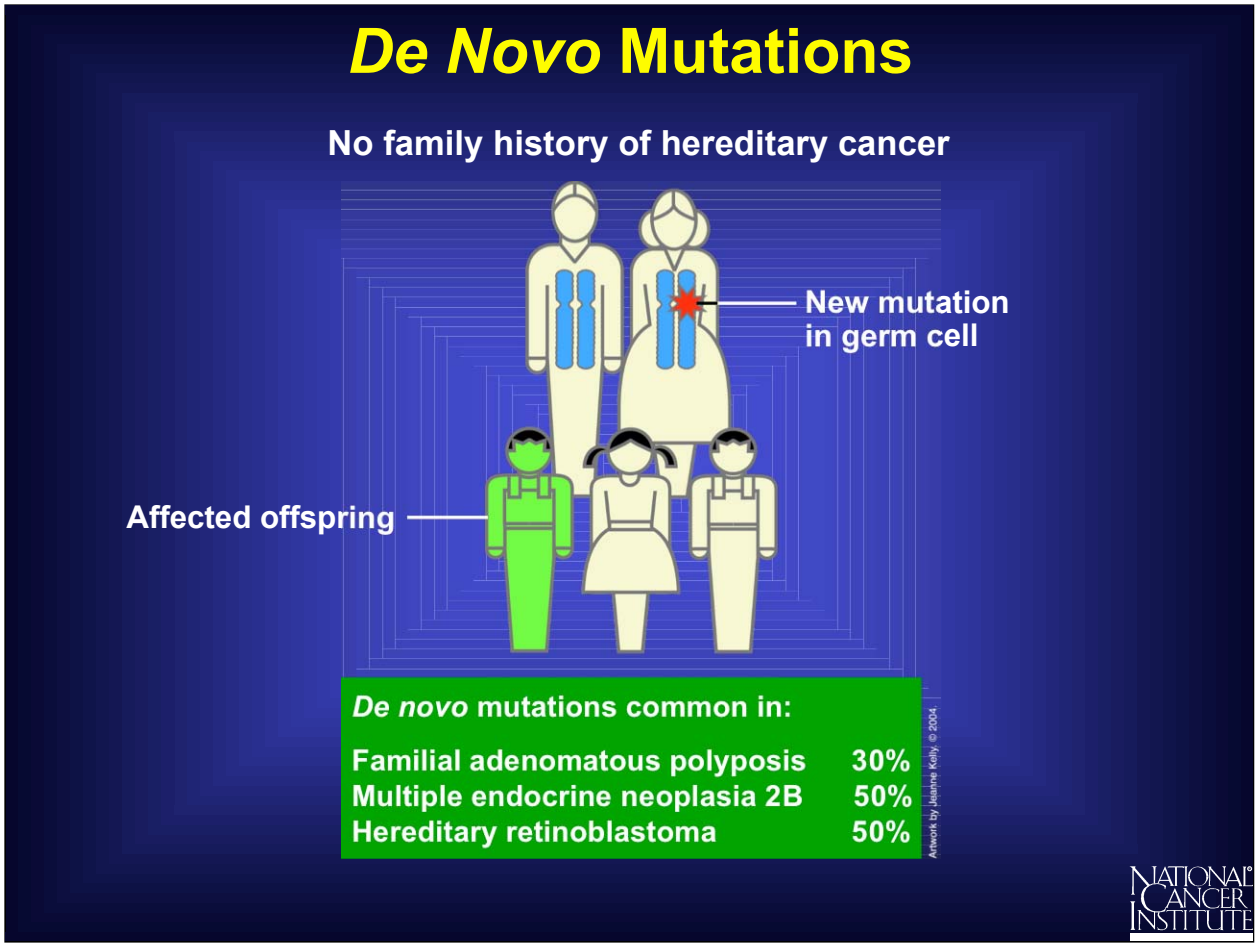


Unlike other human body cells, maturing germ cells, like ova or sperm, must cut their chromosome number from 46 to 23, from 2N to N. They do this through two specialized cell divisions in a process called meiosis. After meiosis is complete, each germ cell has only one-half of the 44 original body chromosomes (or autosomes) plus either an X or a Y sex chromosome.

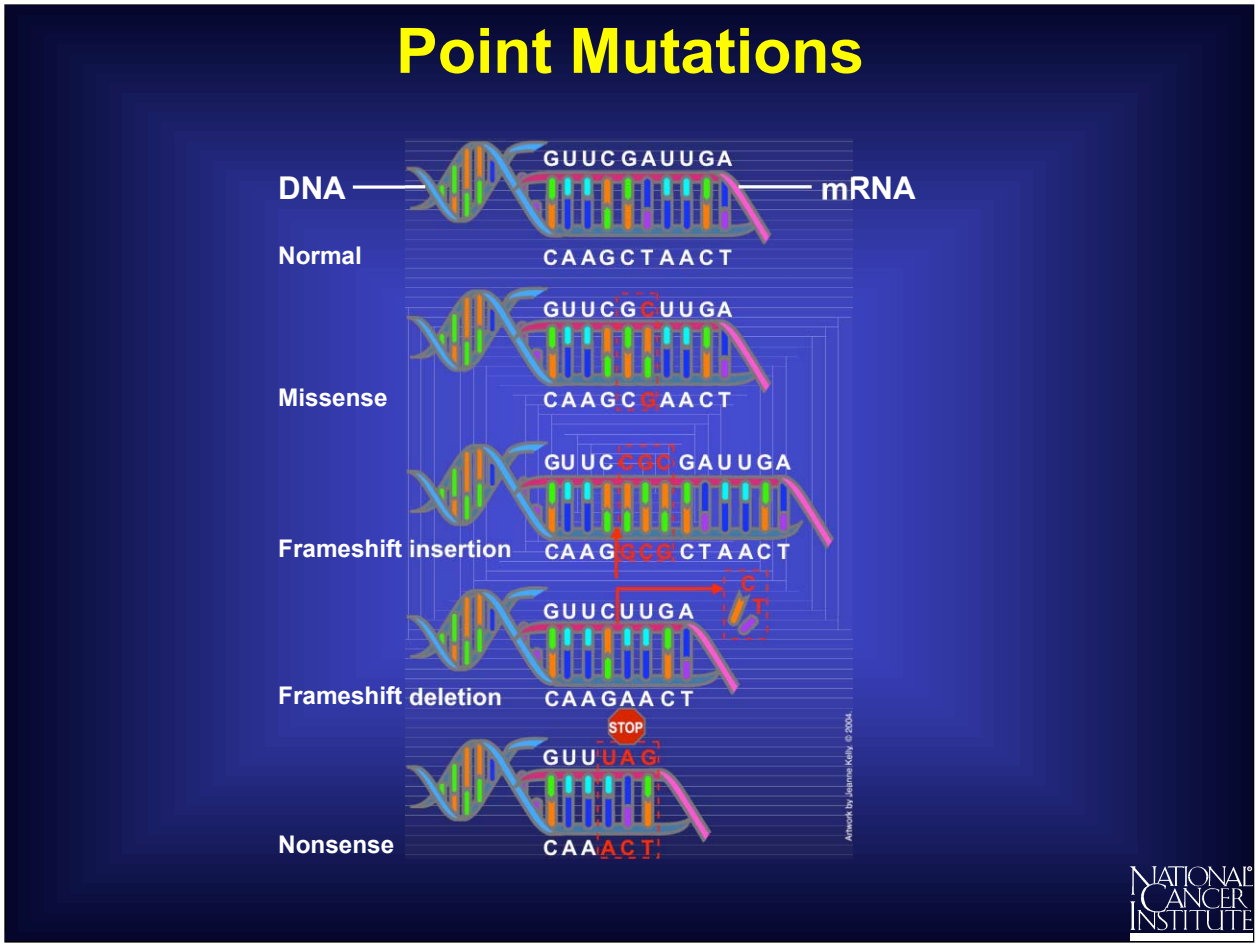


Early in meiosis, ***each*** chromosome ***pair*** copies itself. These homologs are all attached at the centromere and are wound very tightly around one another. Right before duplicate sets of homologs pull apart and move toward a different end of the cell to complete the first division, recombination can occur, as the intertwined genetic material separates. Then, later in meiosis, a second division occurs, and even the chromosomes within a homolog move apart, leaving only a haploid number (n) in each ovum or sperm. If mutations occur during meiosis, either in the ova or sperm, these will be germline mutations.

If mutated ova or sperm then go on to fertilization, their germline mutations will pass to every somatic cell in the new individual.



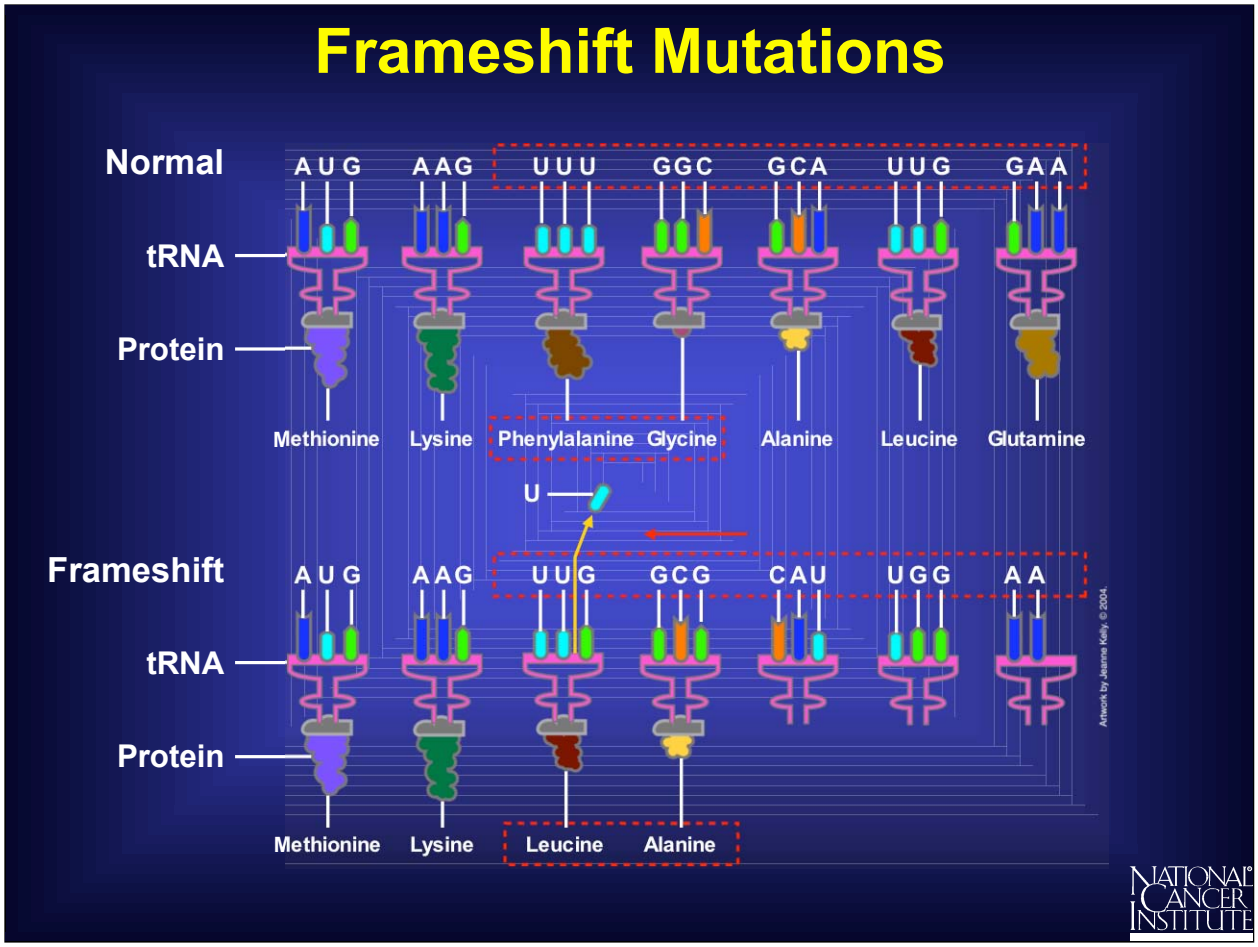
Inherited mutations had to start somewhere, and that somewhere is a *de novo* mutation. A *de novo* mutation is a new mutation that occurs in a germ cell and is then passed on to an offspring. All germline mutations started as a *de novo* mutation in some ancestor. *De novo* mutations are common in a few inherited cancer susceptibility syndromes.



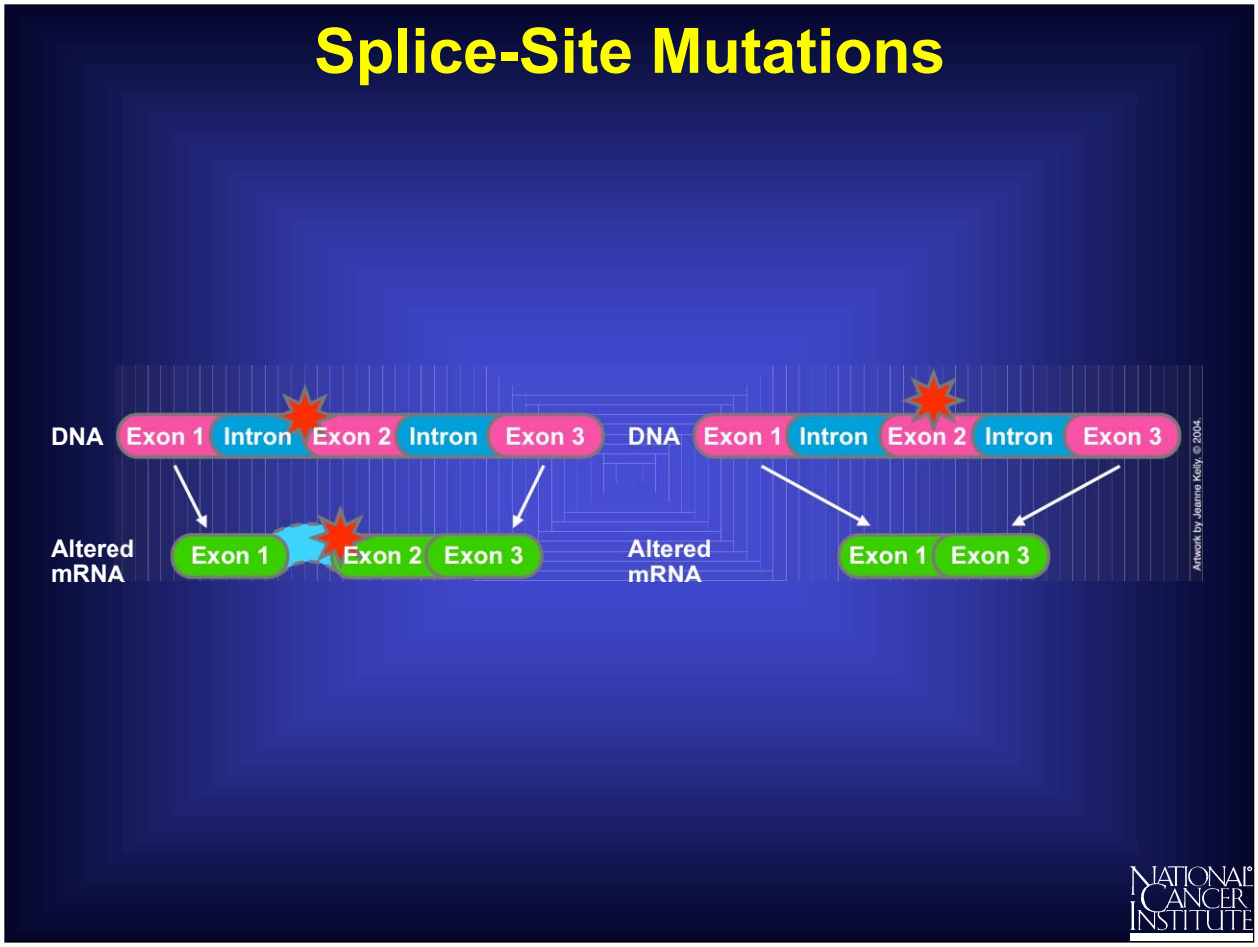
Point mutations, single base changes in DNA sequences, are the most common type of alteration in DNA. They can have varying effects on the resulting protein.

A missense point mutation substitutes one nucleotide for a different one, but leaves the rest of the code intact. The impact of these point mutations depends on the specific amino acid that is changed and the protein sequence that results. If the change is critical to the protein's catalytic site or to its folding, damage may be severe.

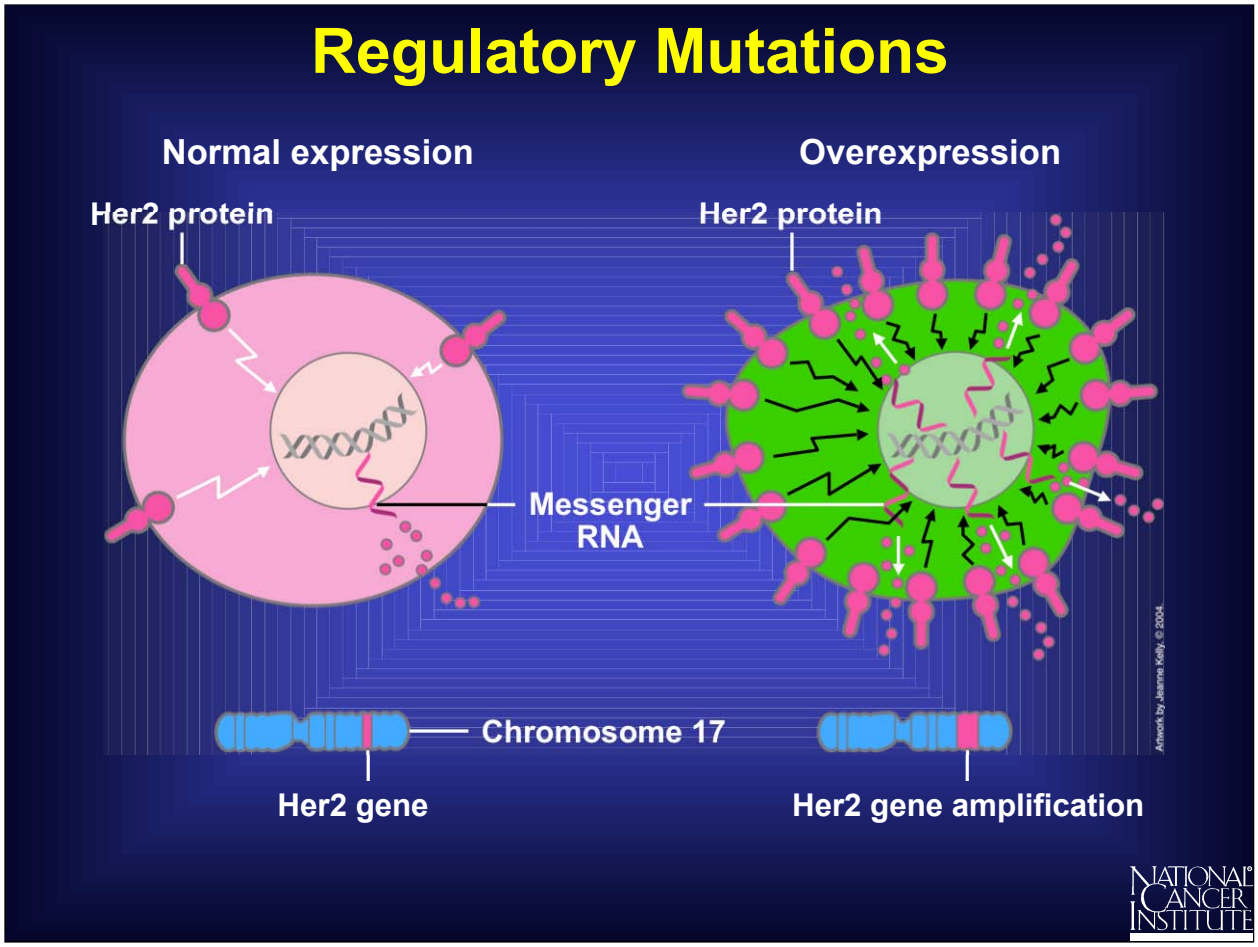
Nonsense mutations are point mutations that change an amino acid codon to one of the three stop codons, which results in premature termination of the protein. Nonsense mutations may be caused by single base pair substitutions or by frameshift mutations.



Another type of mutation that can occur is a frameshift mutation. When a gene is copied, the action begins in the nucleus. There an mRNA strand copies the DNA strand exactly. It codes for a protein precisely, leaving no gaps or spaces separating the triplets. This set of connected triplets is called the reading frame. A frameshift mutation is caused by the addition or loss of a nucleotide, or nucleotides. This alters the content of every triplet codon that follows in a reading frame. Frameshift mutations usually result in a shortened abnormal or nonfunctional protein, and they can create an early STOP codon downstream. If the number of added or missing base pairs is a multiple of three, the resulting protein may be drastically altered, and its function will depend on the extent of these alterations.

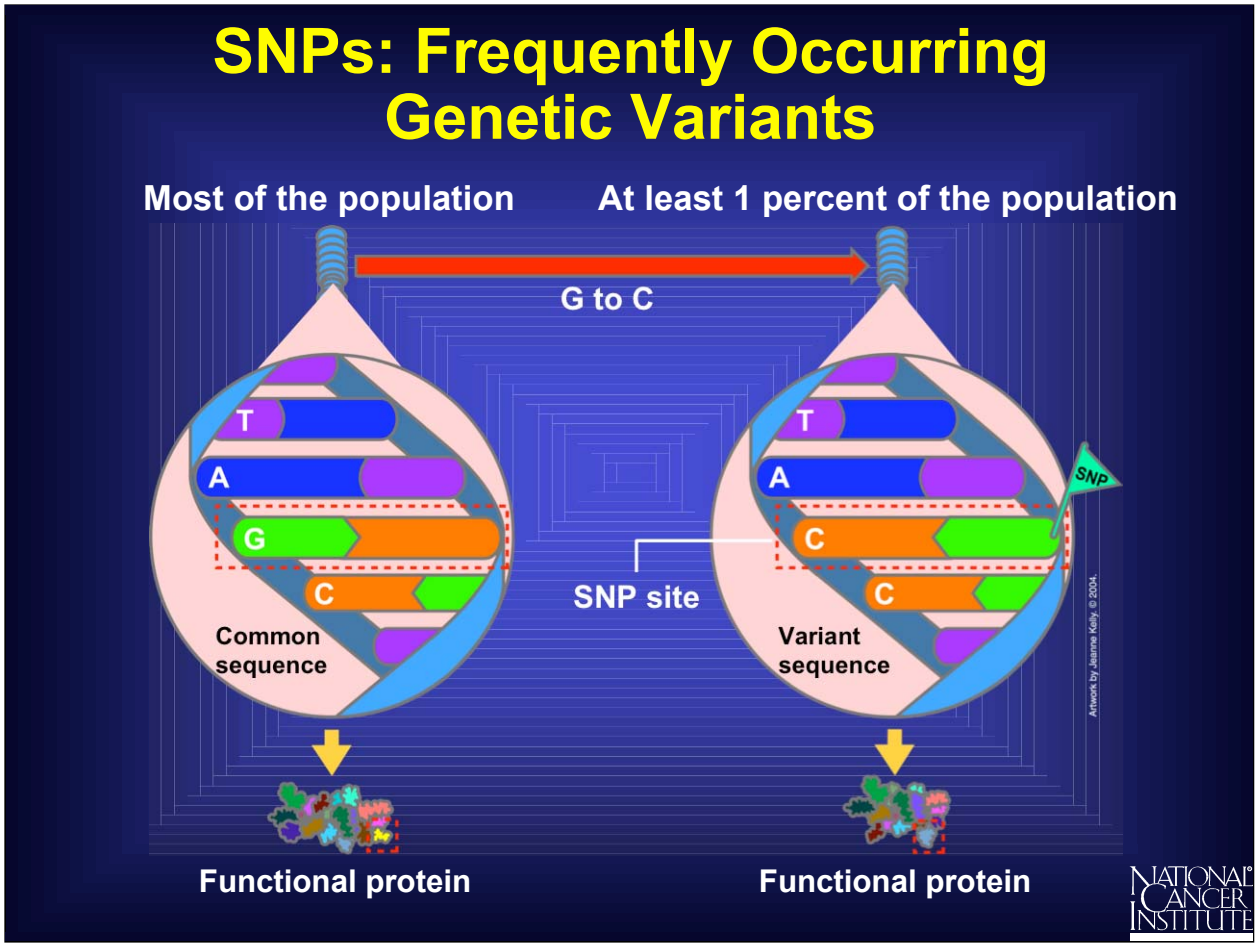


Splice-site mutations occur within genes in the noncoding regions (introns) just next to the coding regions (exons). They can have profound effects on the resulting protein, which may lead to disease. Before mRNA leaves the nucleus, the introns are removed and the exons are joined together. This process is called splicing. Splicing is controlled by specific intron sequences, called splice-donor and splice-acceptor sequences, which flank the exons. Mutations in these sequences may lead to retention of large segments of intronic DNA by the mRNA, or to entire exons being spliced out of the mRNA. These changes could result in production of a nonfunctional protein.

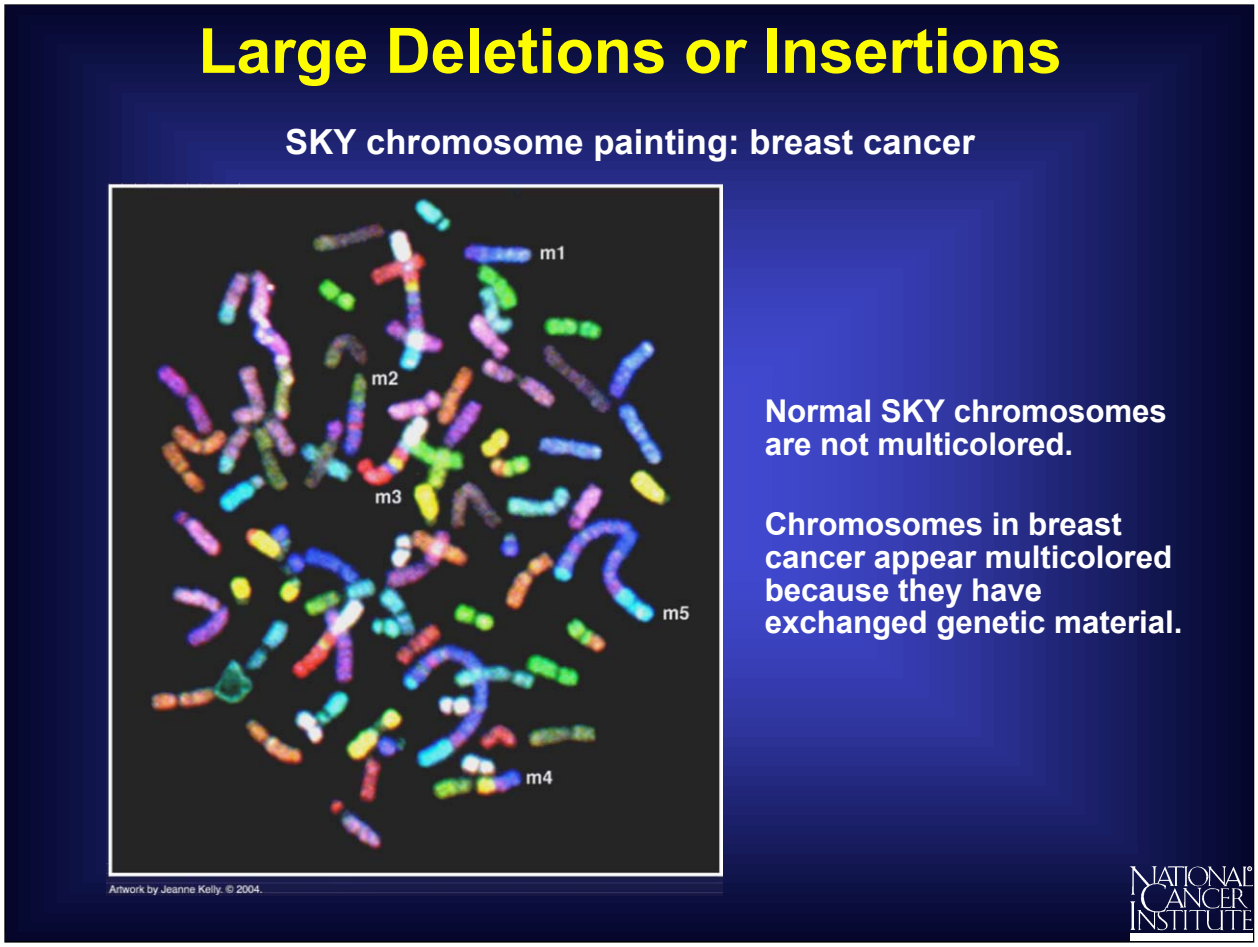


Although mutations in the noncoding region are generally silent, that is not always the case. Some of the most important regulatory regions are in the 5′ noncoding flanking region of the gene. Promoter sequences that regulate the gene are located there. Also, enhancer sequences that regulate the rate of gene activity are in noncoding regions a considerable distance from the gene. And gene repressor regions, which negatively regulate gene activity, also exist. Mutations in any of these regions can change the rate of protein production.

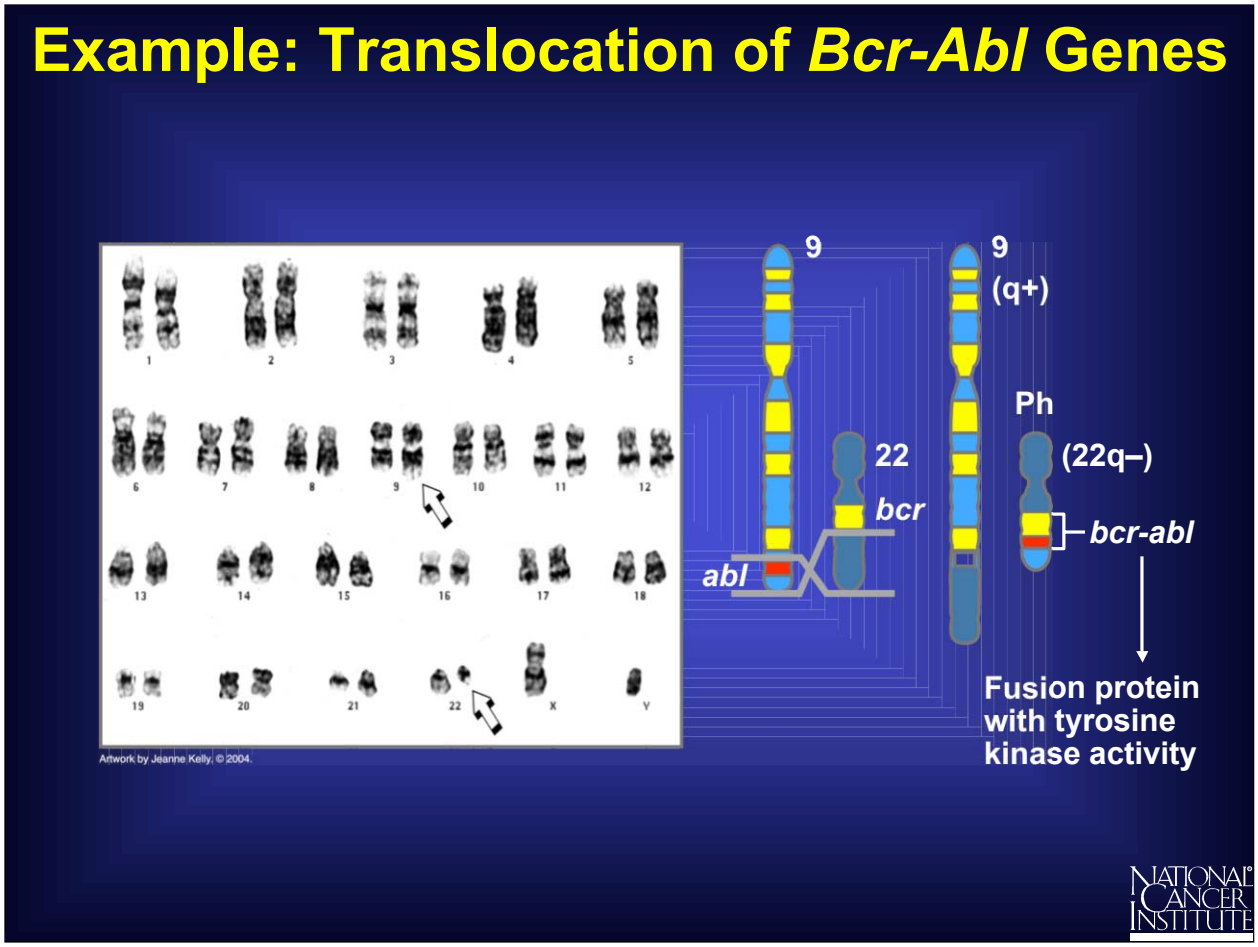
Her2 protein expression is a good example of how gene amplification can have a regulatory impact upon a tumor's growth. In breast cancer, overexpression of Her2 protein results from gene amplification in chromosome 17. This increase in production of growth-signaling molecules speeds up the rate of the cancer's progress.



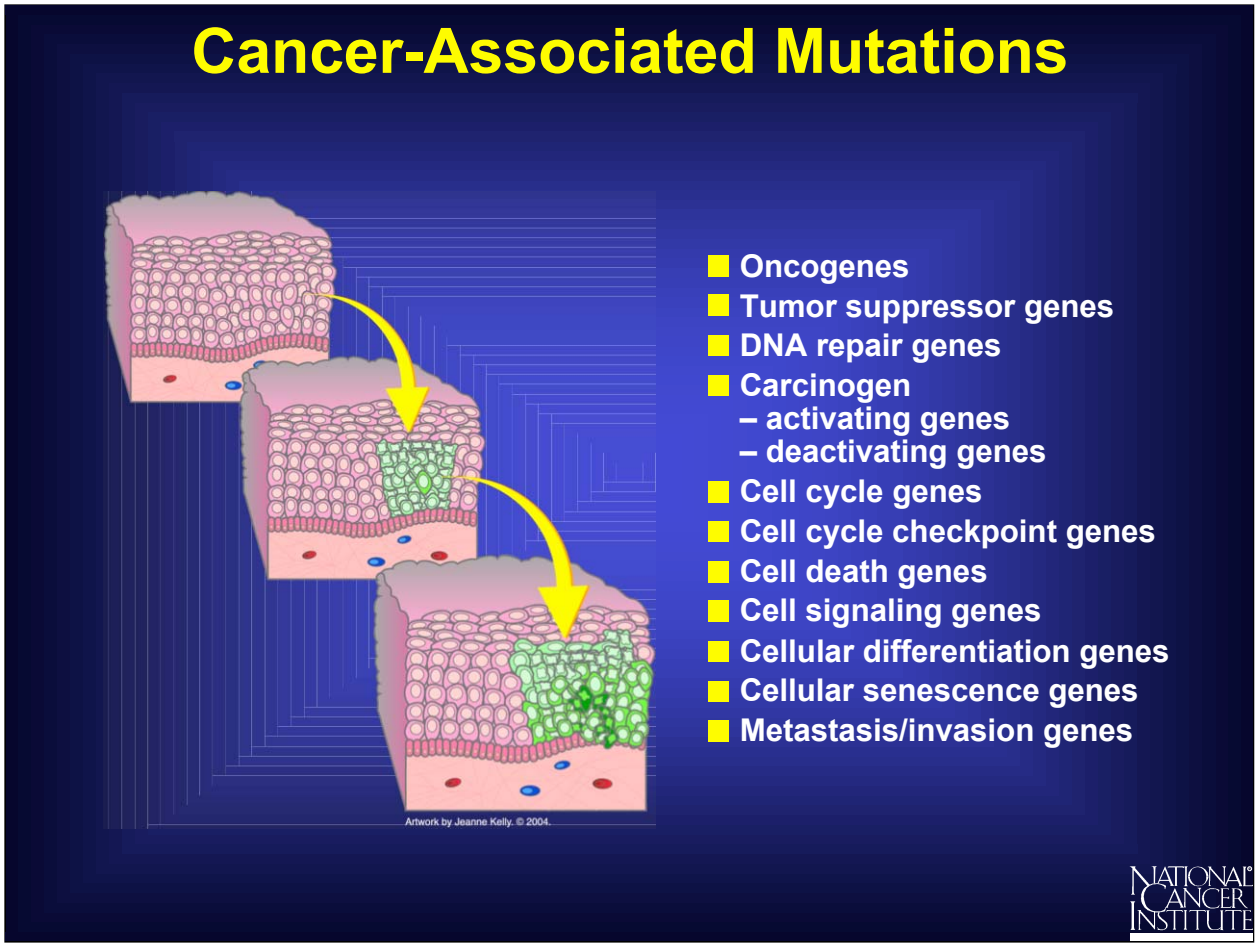
There are over a million single nucleotide polymorphisms (SNPs) in the human genome. SNPs are specific sites within a human genome at which some individuals will have one nucleotide present while other individuals will have a different one. SNPs begin their existence as point mutations, and they eventually become established in a population. This substitution must occur in a significant proportion (more than 1 percent) of a large population for it to be called a SNP. Here is an example: In the DNA sequence TAGC, a SNP occurs when the G base changes to a C, and the sequence becomes TACC. When SNPs occur within a gene, the protein that results usually remains somewhat functional.



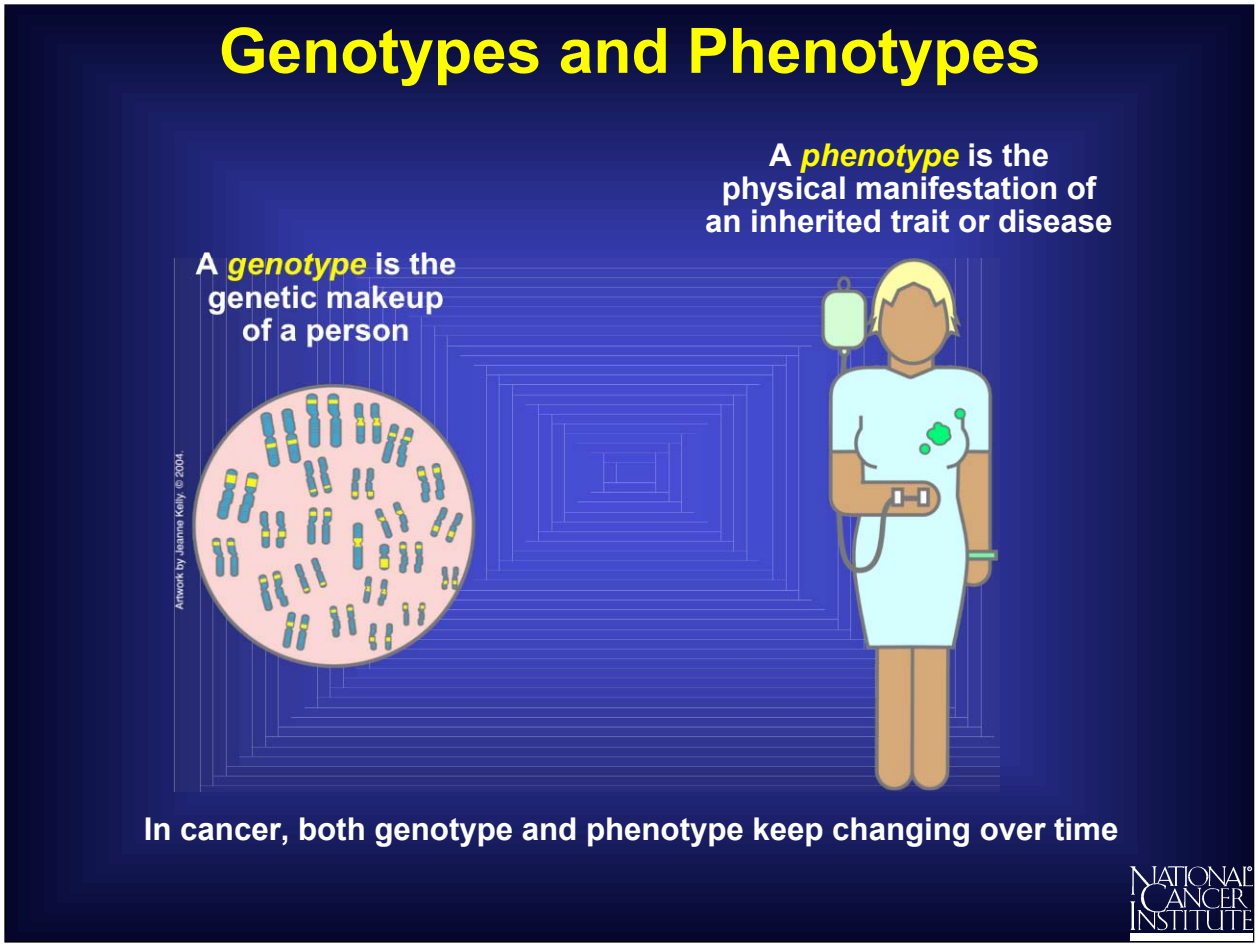
Large deletions or insertions in a chromosome also may lead to cancer. These may occur during mitosis or during recombination in meiosis. Translocations occur when segments of one chromosome break off and fuse to a different chromosome, without any loss of genetic material. Many of these have been found to enable tumor development. Inversions are mutations that arise when two breaks occur in a chromosome and the piece is reinserted in reversed order. Other chromosomal abnormalities include nondisjunction, the failure of the homologs (chromosome pairs) to separate as new cells divide.



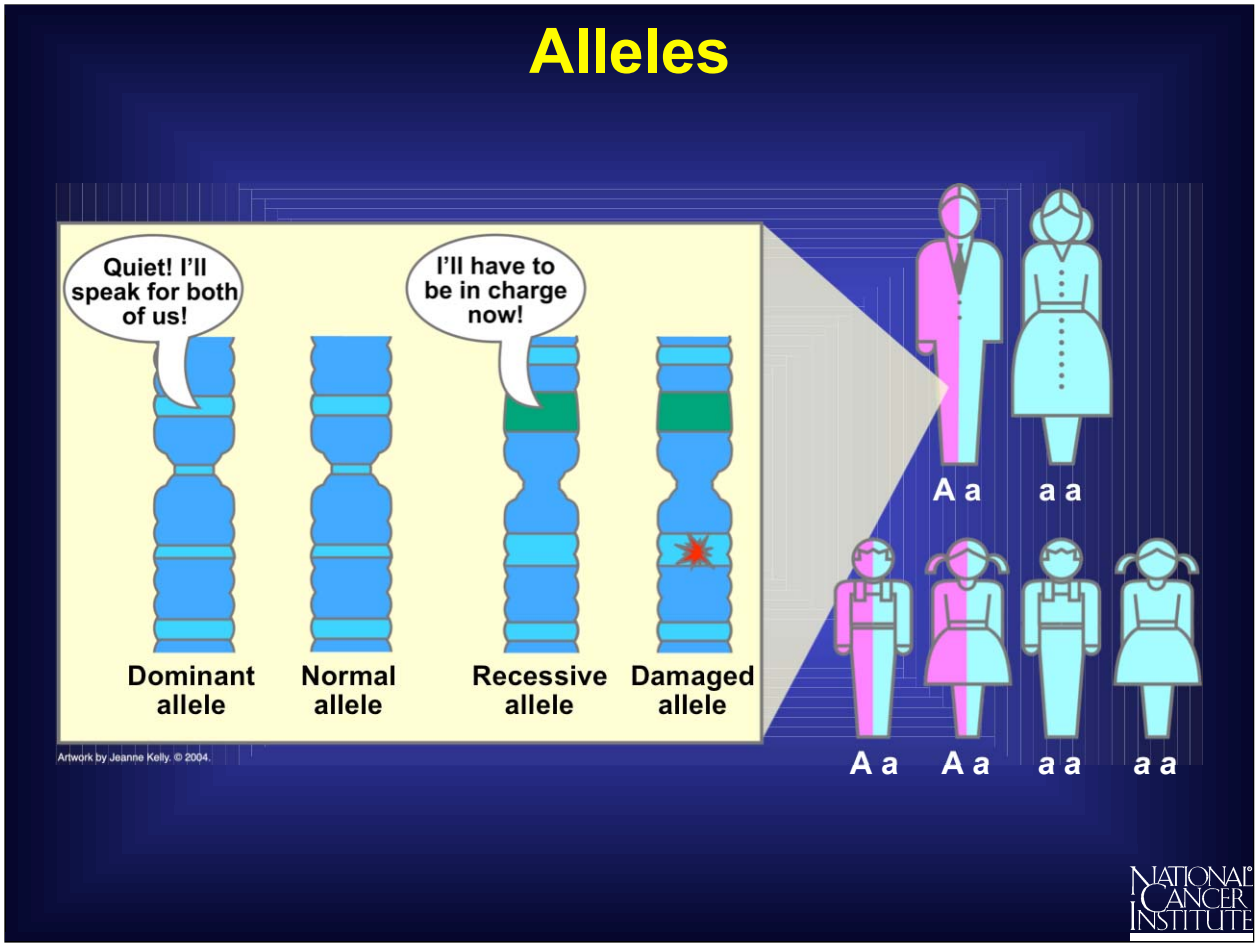
In chronic myelogenous leukemia, a translocation occurs between chromosomes 9 and 22. This rearrangement of genomic material creates a fusion gene call *Bcr-Abl* that produces a protein (tyrosine kinase) thought to promote the development of leukemia. The drug Gleevec blocks the activation of the Bcr-Abl protein.



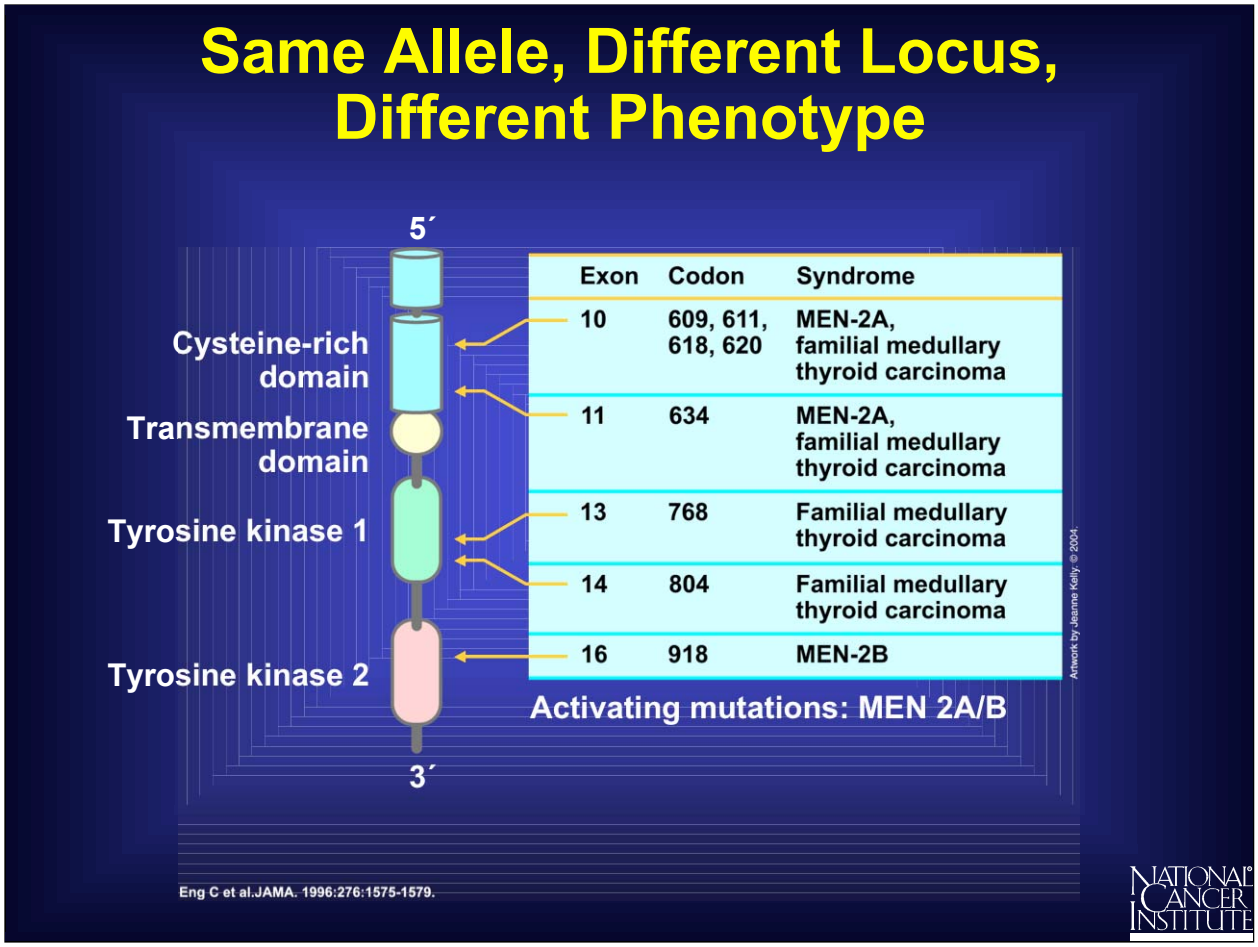
Cancer-associated mutations, whether somatic or germline, whether point mutations or large deletions, alter key proteins and their functions in the human biosystem. A wide variety of mutations seems to be involved. Even mutations in noncoding regions, such as in promoters, enhancers, or negative regulatory regions, can result in under- or overexpression of proteins needed for normalcy. Other mutations may cause production of important checkpoint proteins to malfunction. Collectively, these mutations conspire to change a genome from normal to cancerous.



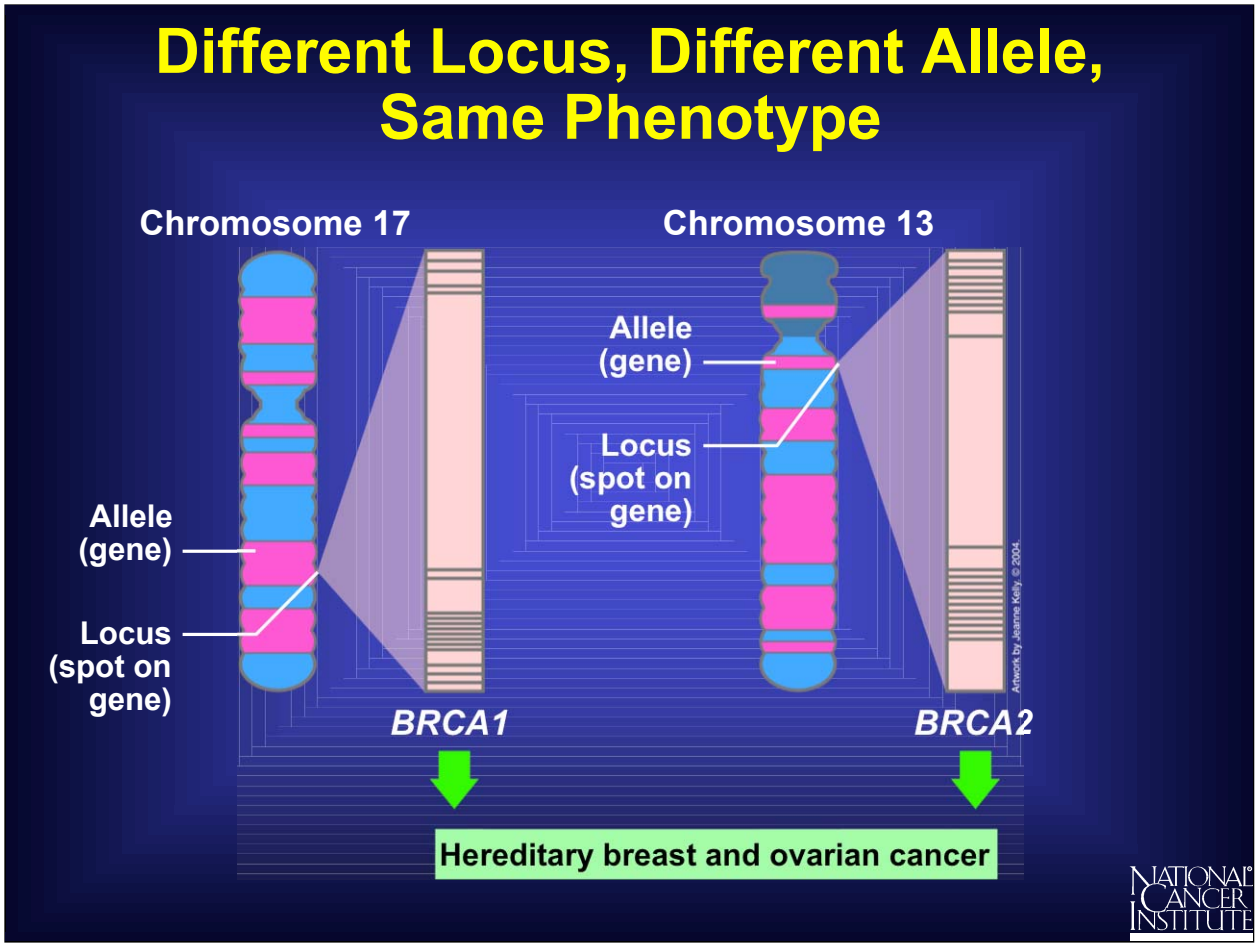
Cancer may start as a new genotype, that is, as a change in the genetic makeup of a person, but it ultimately produces a new phenotype as well. A phenotype is the physical manifestation of a genotype in the form of a trait or disease. Cancer is known for its ever-changing genotypes and phenotypes.



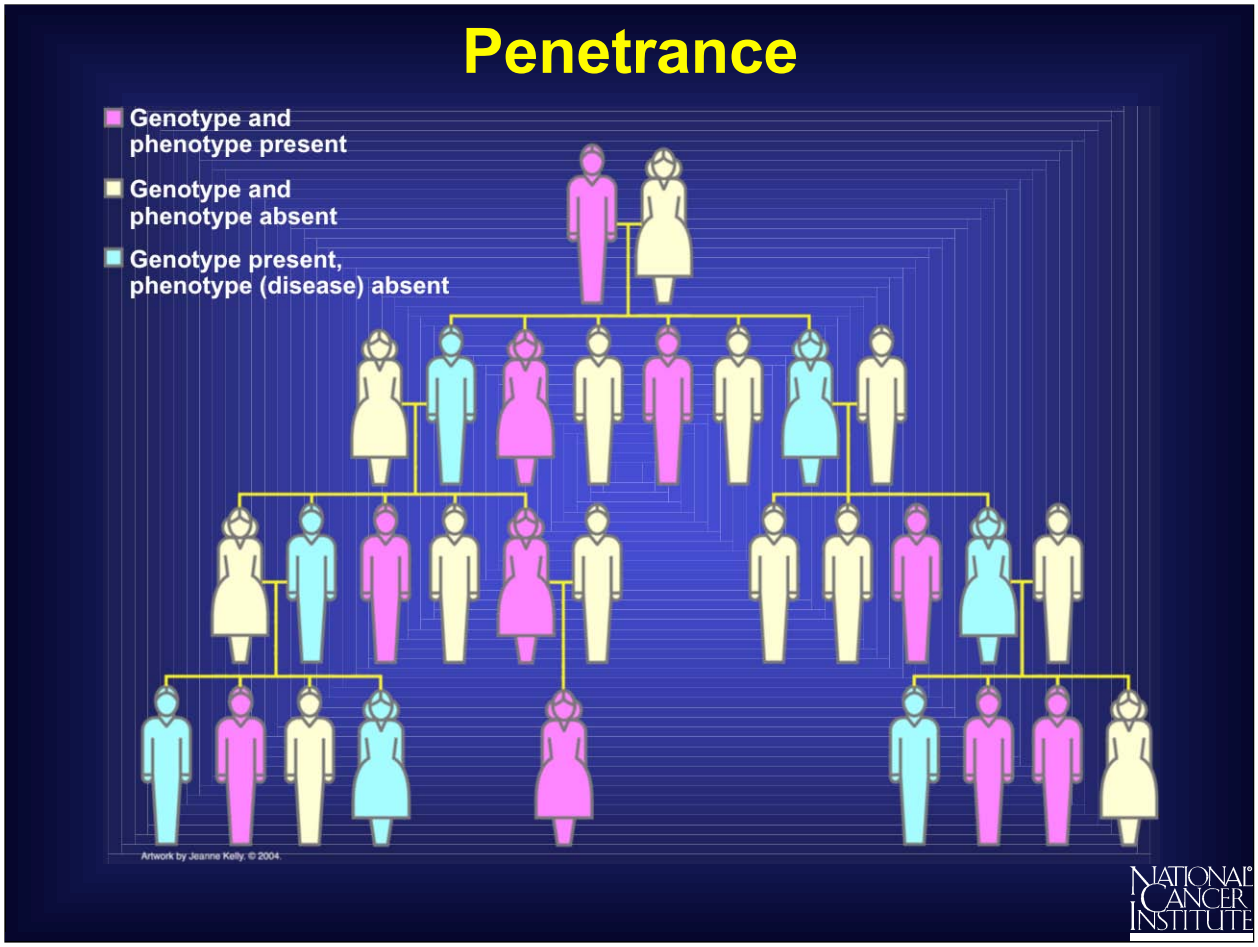
All genotypes are not created equal in their influence on phenotype. Genes come in many varieties called alleles, and some are more dominant than others. In a pair of alleles, the effect of a dominant allele prevails over the effect of a recessive allele. And the effects of a recessive allele become apparent only if the dominant allele becomes inactivated or lost.



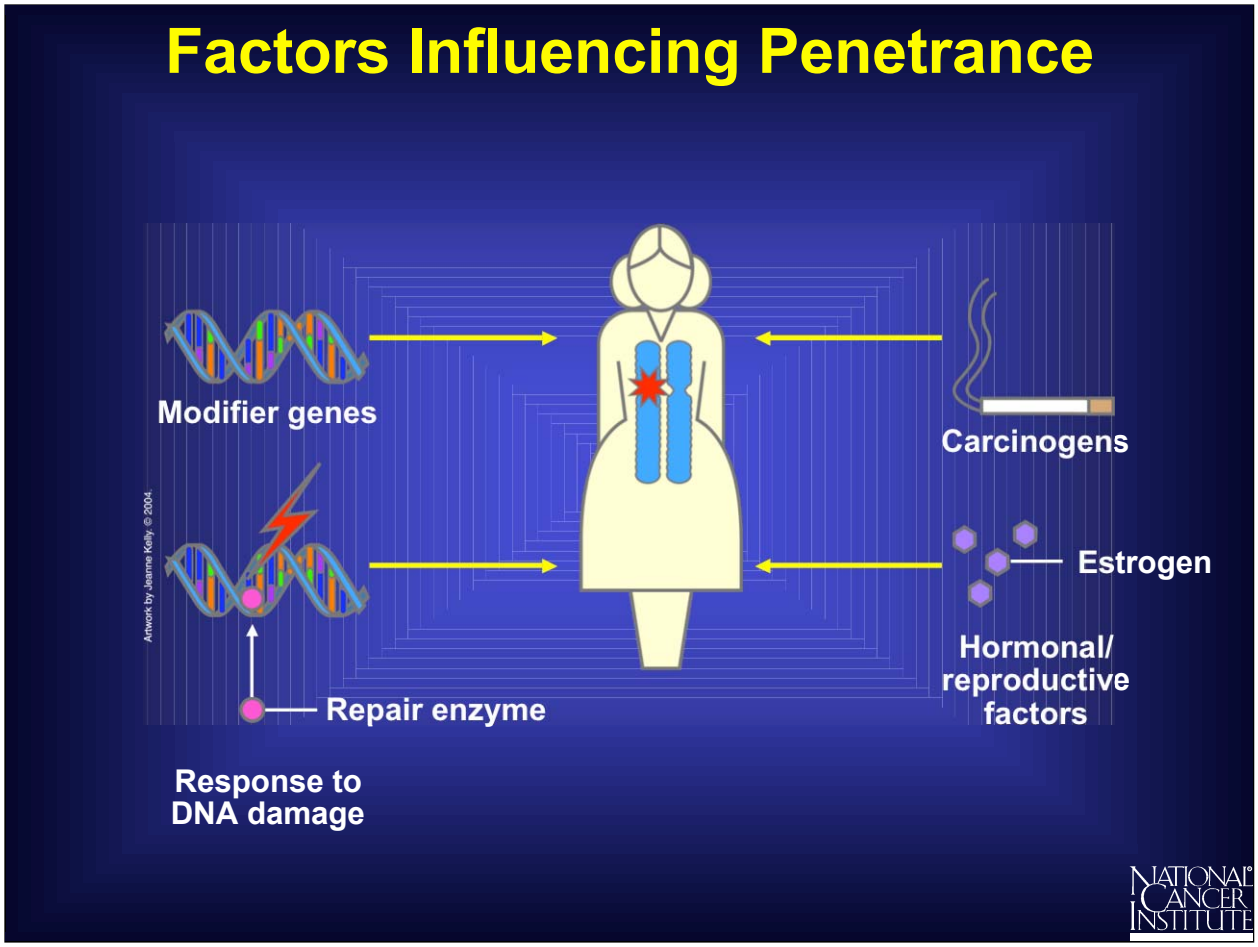
Different mutations in the same gene can result in different phenotypes. A good example is the *RET* proto-oncogene. Germline mutations of *RET* lead to multiple endocrine neoplasia (MEN) type 2. The disease produced varies depending on where in the *RET* gene the germline mutation sits, so the phenotype may be MEN-2A, MEN-2B, or familial medullary thyroid cancer.



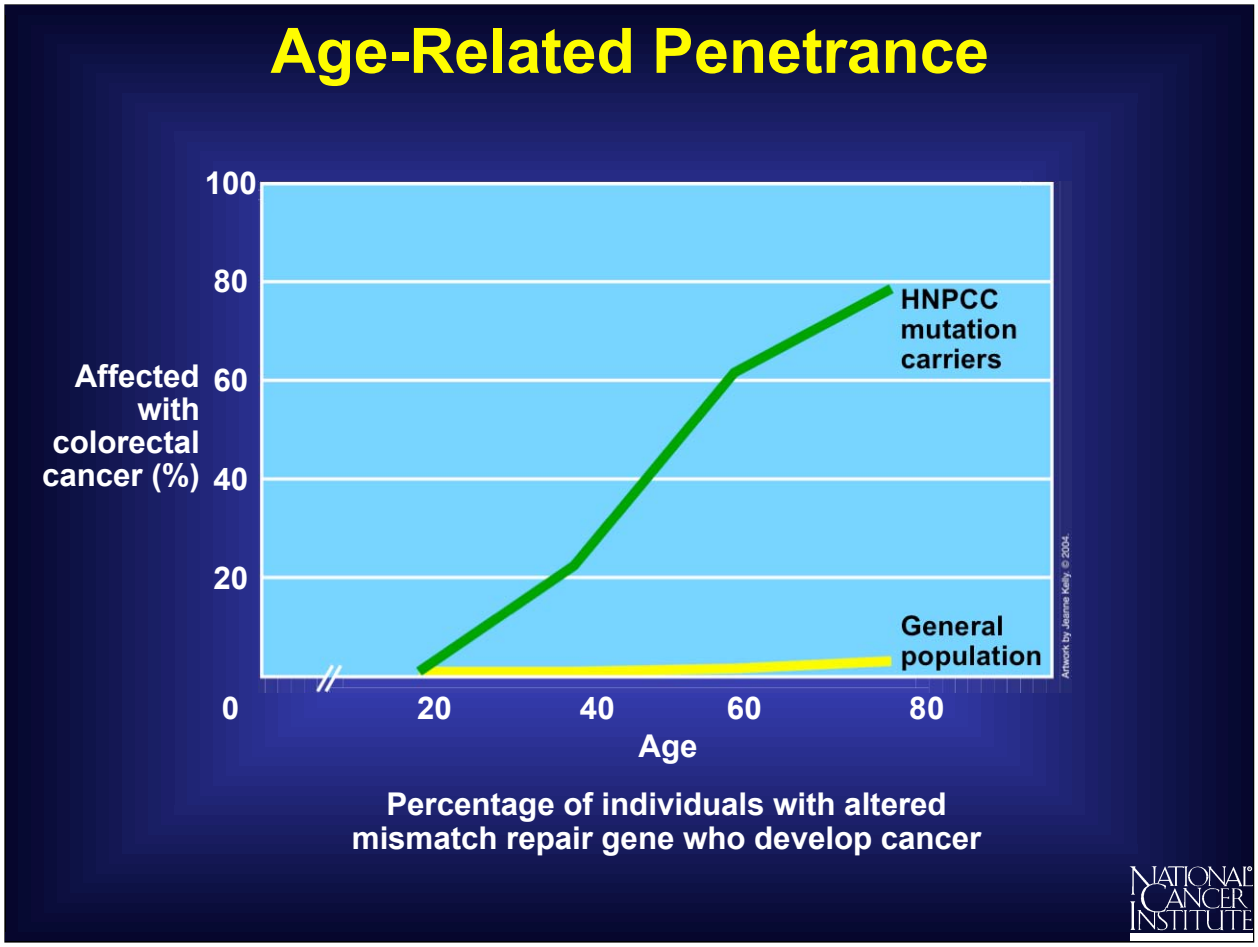
Many cancer susceptibility syndromes are genetically heterogeneous (a mixture), which means that different mutations (genotypes) can be expressed as the same phenotype (e.g., cancer). These different mutations may be located within the same gene but at different locations (locus heterogeneity) or on different genes altogether (allelic heterogeneity). For example, hereditary breast and ovarian cancer susceptibility has both locus and allelic heterogeneity. More than 500 different mutations have been identified that can occur in the *BRCA1* gene on chromosome 17 and increase a woman's risk for breast cancer. And more than 300 mutations scattered throughout the *BRCA2* gene on chromosome 13 are associated with hereditary breast and ovarian cancer susceptibility.



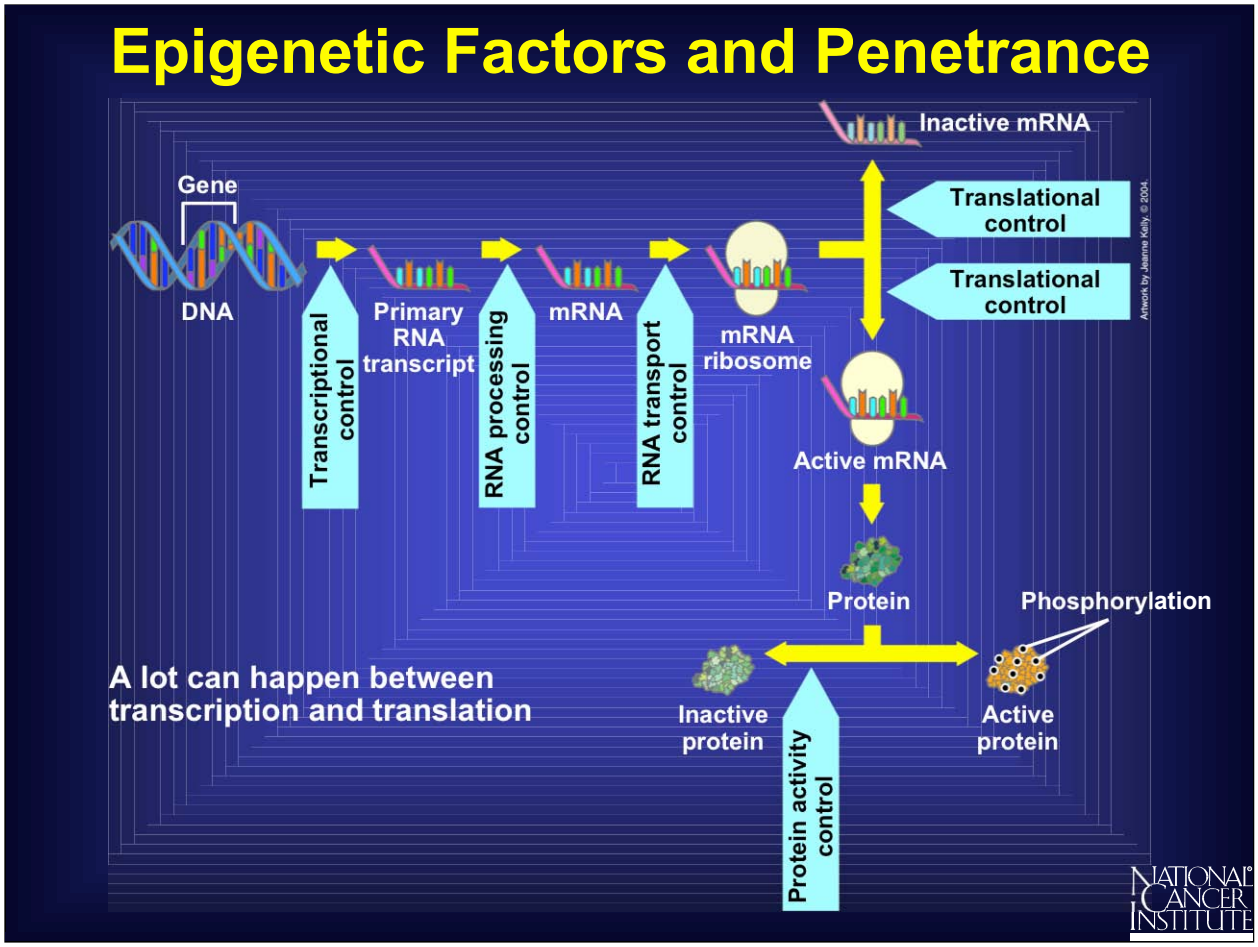
Sometimes one person with a dominant allele will express a trait, yet that same genotype in another person will remain silent. This is an example of differences in penetrance. In classic Mendelian genetics, if an individual carries a dominant allele, the trait will be expressed (genotype = phenotype). However, if all carriers of a certain dominant allele in a population do not express the trait (same genotypes/different phenotypes), the gene is said to have incomplete penetrance.



Modifier genes affect the expression of some alleles, which may increase or decrease the penetrance of a germline mutation such as an altered cancer susceptibility allele. Penetrance may also be affected by mutations in DNA damage response genes, whose normal function is to recognize and repair genetic damage. If repair malfunctions, mutations may accumulate in other genes, increasing the likelihood that a given cell will progress to cancer.

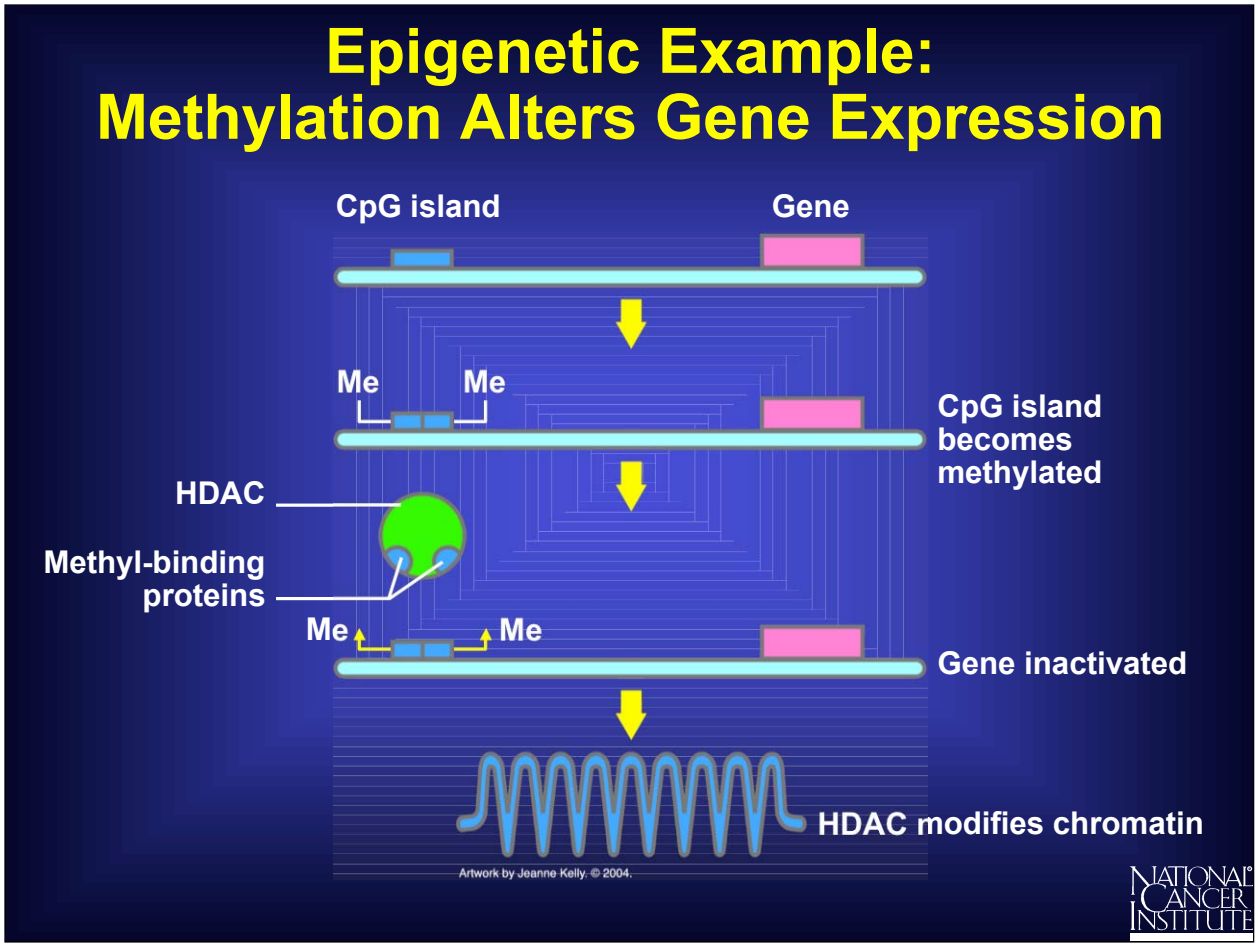


Penetrance is usually age related, meaning that the trait is not expressed in most carriers at birth but occurs with increased frequency as the carriers get older. For example, germline mutations in mismatch repair genes associated with hereditary nonpolyposis colorectal cancer (HNPCC) are incompletely penetrant. So not all individuals who carry these mutations will get colorectal cancer, but the risk increases as individuals age. About 20 percent of carriers will never develop colorectal cancer.



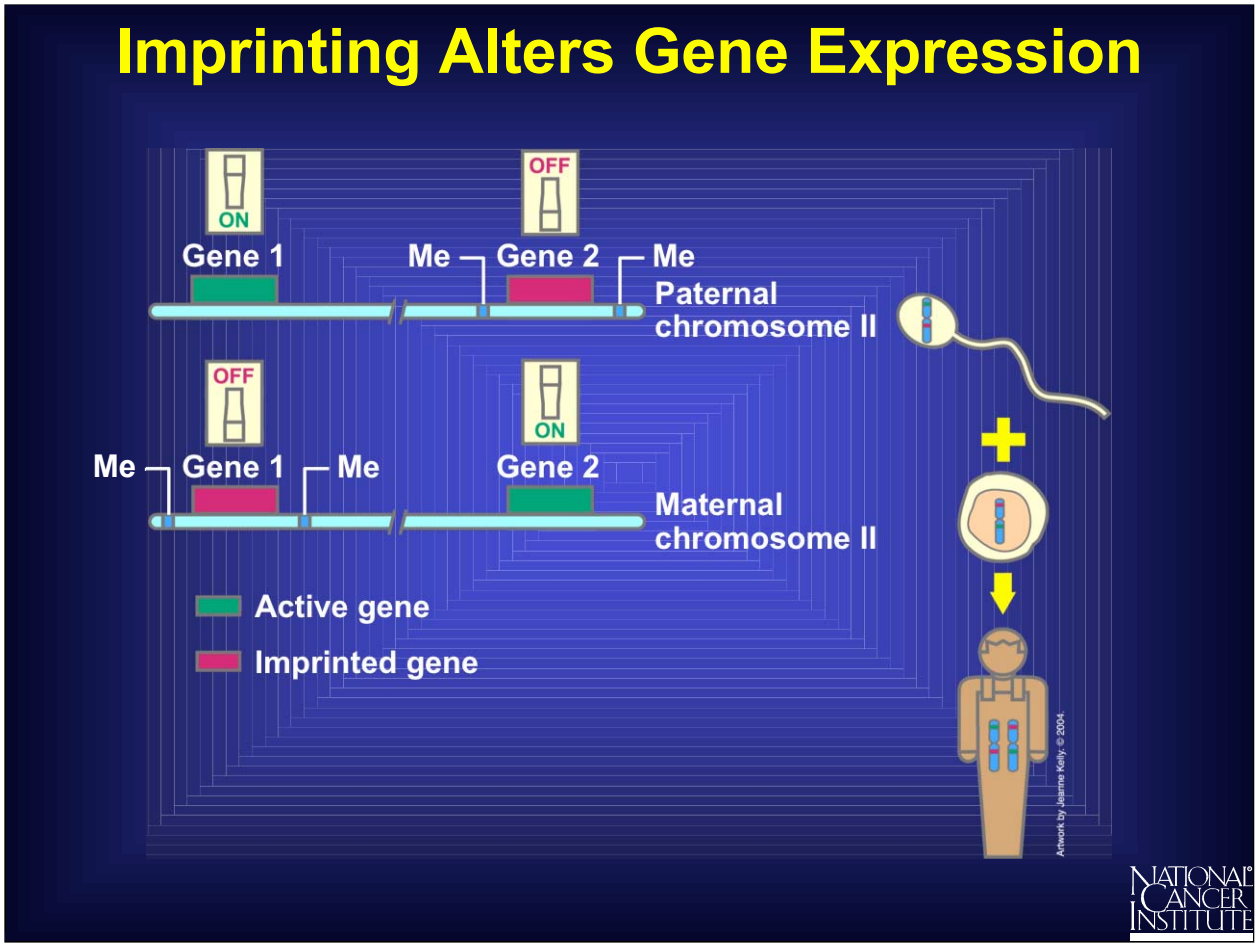
Epigenetic factors are mechanisms outside the gene such as a cell's exposure to carcinogens or hormones, or genetic variations that modify a gene or its protein by methylation, demethylation, phosphorylation, or dephosphorylation. These factors can alter what is ultimately expressed; they can change a phenotype. For example, hormone and reproductive factors may influence the penetrance of certain cancer-linked mutations. Breast and ovarian cancer are more likely to occur in women with early menarche, late menopause, and a first child after age 30 (or no children at all). These factors are believed to be linked to a woman's exposure to estrogen and progesterone and their effects on cell differentiation in the breast that occur during pregnancy.

In cancer, both the genotype and the phenotype change over time. Epigenetic factors play a key role in these changes.

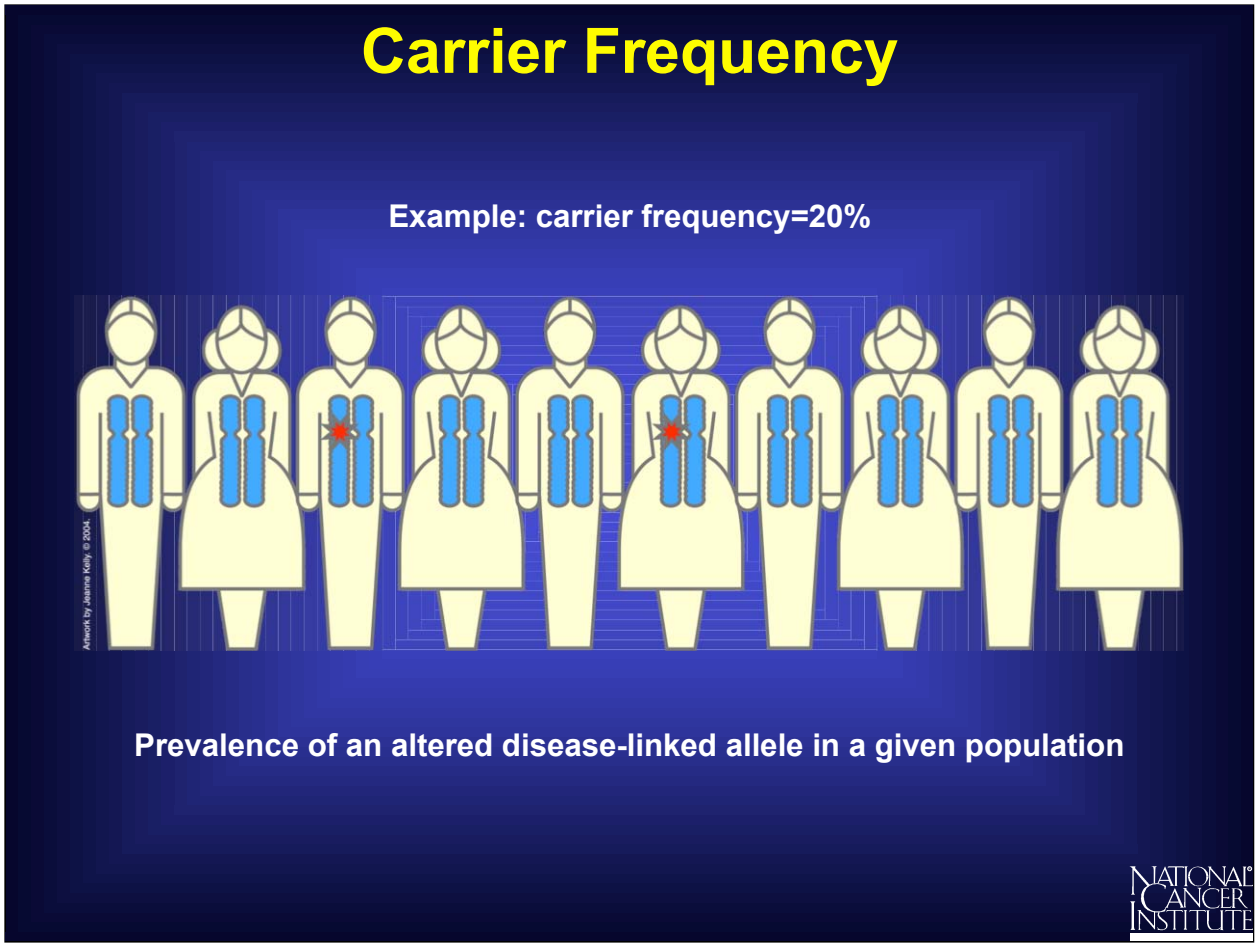


Methylation of the genome can render areas silent. There are two types of methylation that occur. Maintenance methylation adds methyl groups to newly synthesized strands of DNA at spots *opposite* methylated sites on the parent strand. This activity makes sure that daughter molecules of DNA maintain a methylation pattern after cell division. There is also *de novo* methylation, which can add methyl groups to totally new positions and change the pattern in a localized region of the genome.

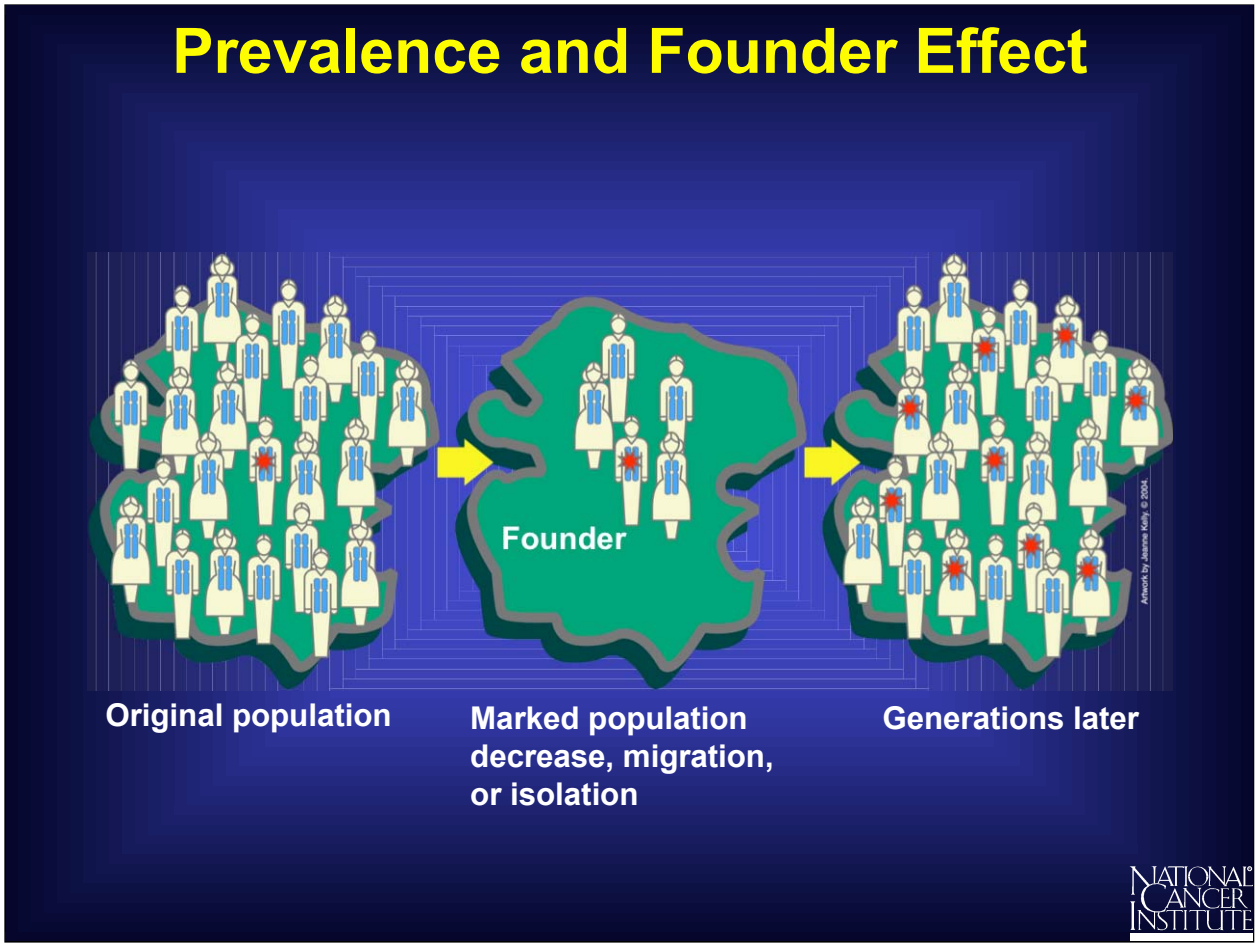
Genes that must be expressed in all tissues have unmethylated regions, called CpG islands, located upstream. On the other hand, genes that must be turned off in differentiated tissues have these islands methylated. This allows a histone deacetylase complex nicknamed HDAC to bind, compress the shape of the genomic material, and inactivate the gene.



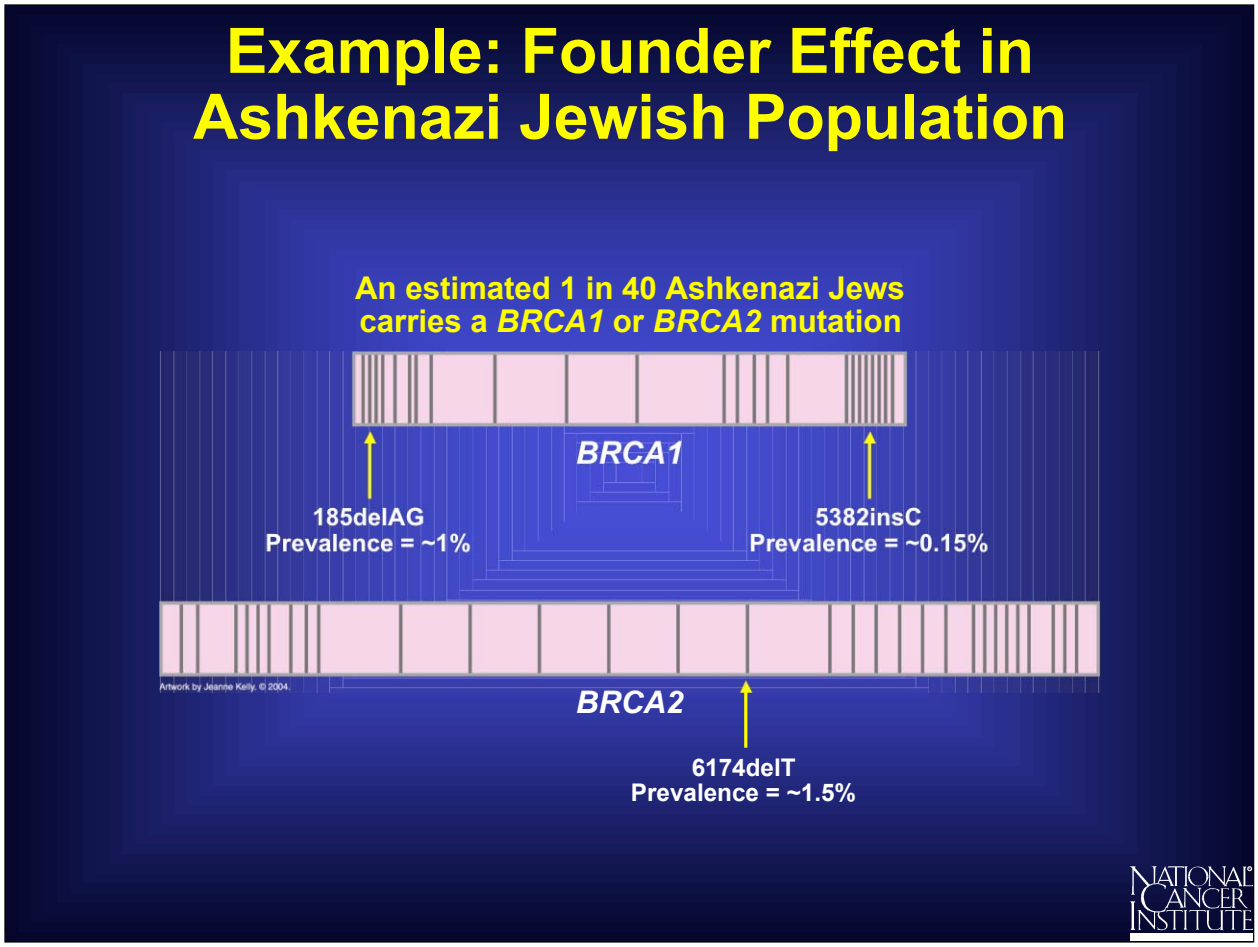
Genomic imprinting is an uncommon event in human genomes that occurs when only one of a pair of genes present on homologous chromosomes is expressed because the other has been silenced by methylation. Thirty genes in humans display such imprinting. Curiously, for specific genes, the maternal copy is the one chosen to be silenced; for others, the paternal copy is selected.



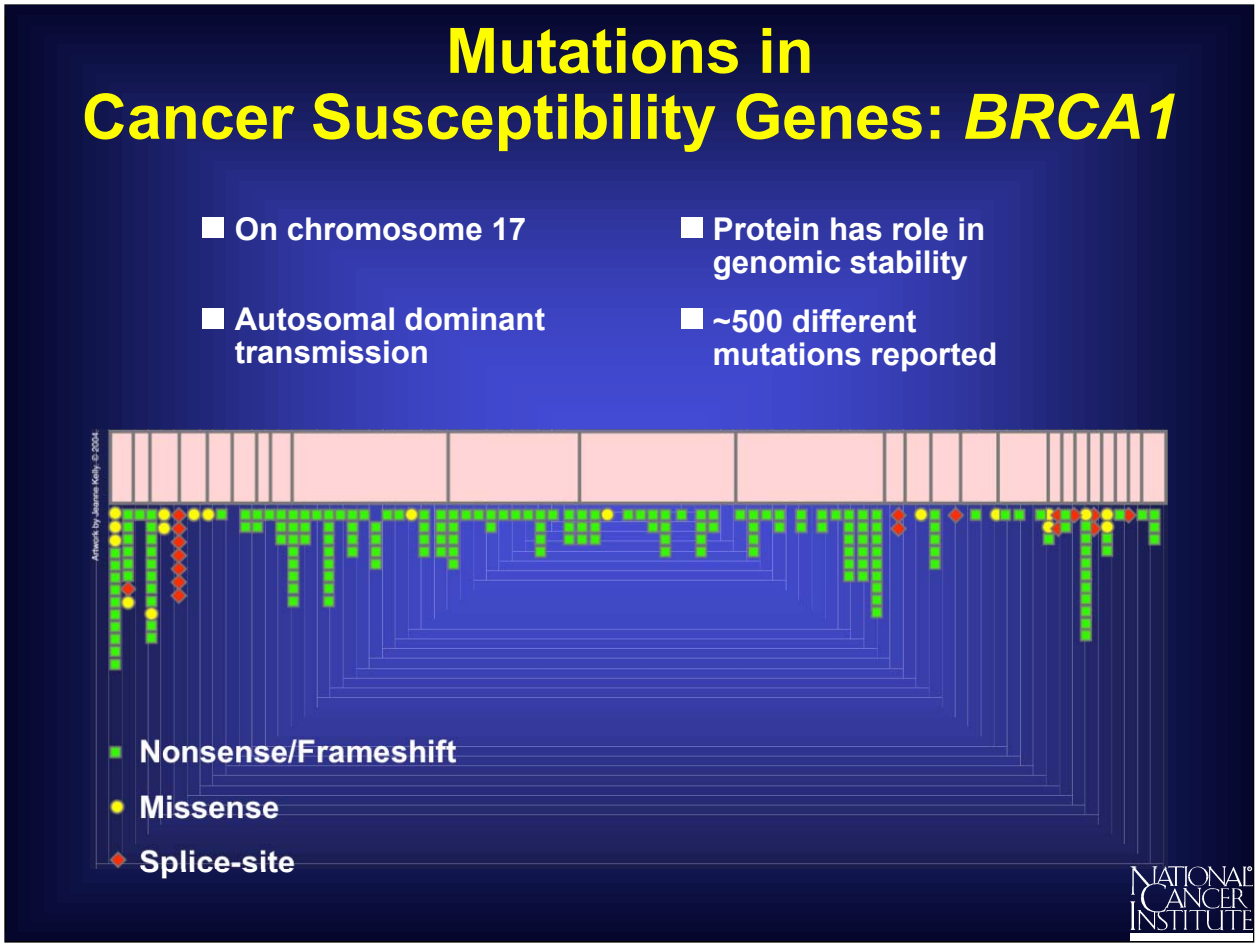
Carrier frequency describes the prevalence in a given population of germline mutations in a specific gene. A mutation carrier is sometimes called a heterozygote because two different alleles are present at a given locus--one with a germline mutation and one normal allele. Here, 2 out of 10 individuals carry a mutated allele at a particular gene locus, so the carrier frequency is 20 percent.



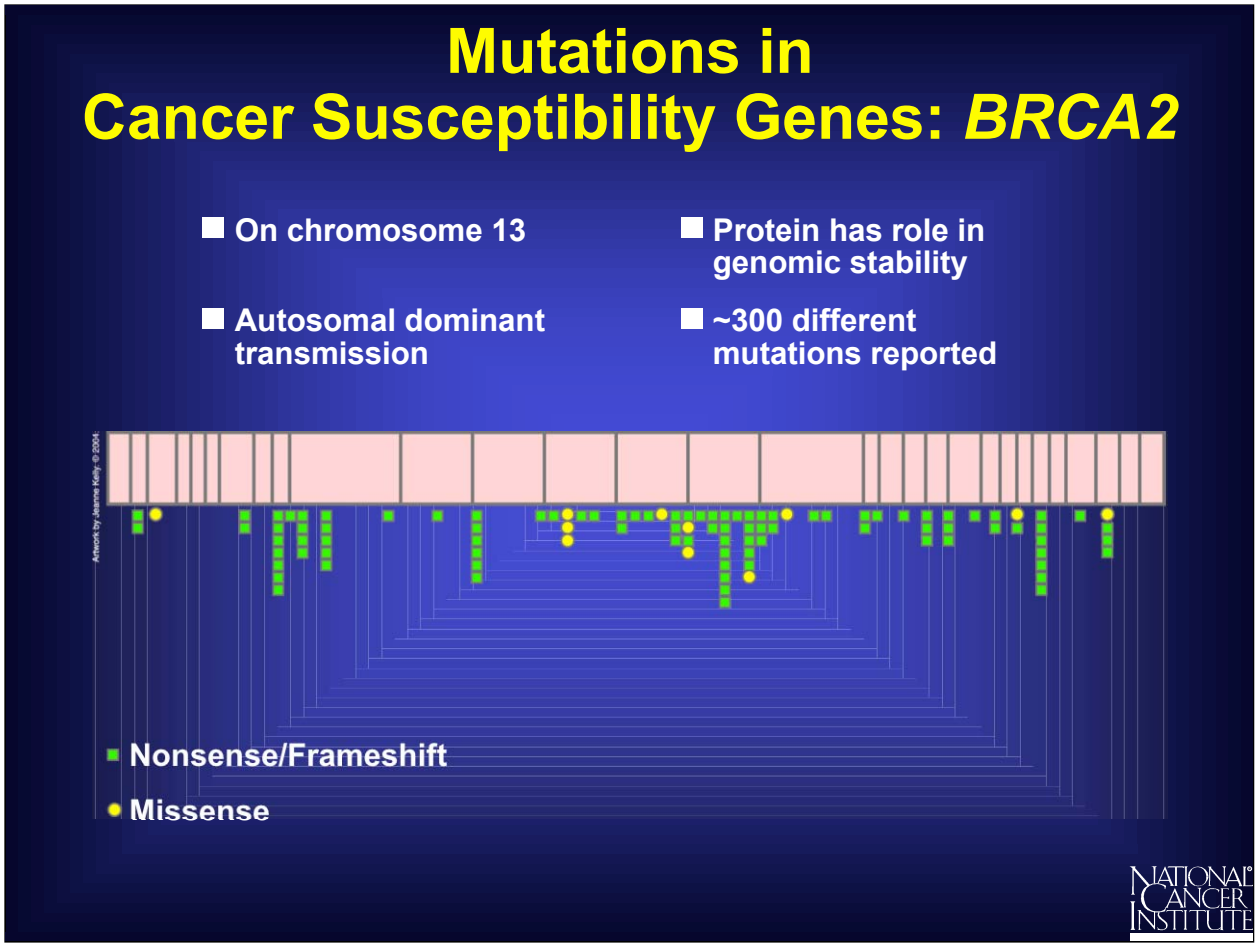
Some populations have a higher prevalence of specific cancer-associated alleles than others. This may result from a founder effect, which occurs when a population undergoes rapid shrinkage and then expansion in an isolated setting. In a population that is geographically or reproductively isolated, an individual called a founder carries or develops a germline mutation that is rare in the general population.



Because of reproductive isolation, later generations of an isolated population will have a higher frequency of a mutation than the original population. For example, Ashkenazi Jews were segregated from the rest of the population and lived in separate communities for hundreds of years. Today, one percent of the Ashkenazi Jewish population--one person in 40--carries a 185delAG mutation in *BRCA1*, which places them at higher than the average risk for breast and ovarian cancer.

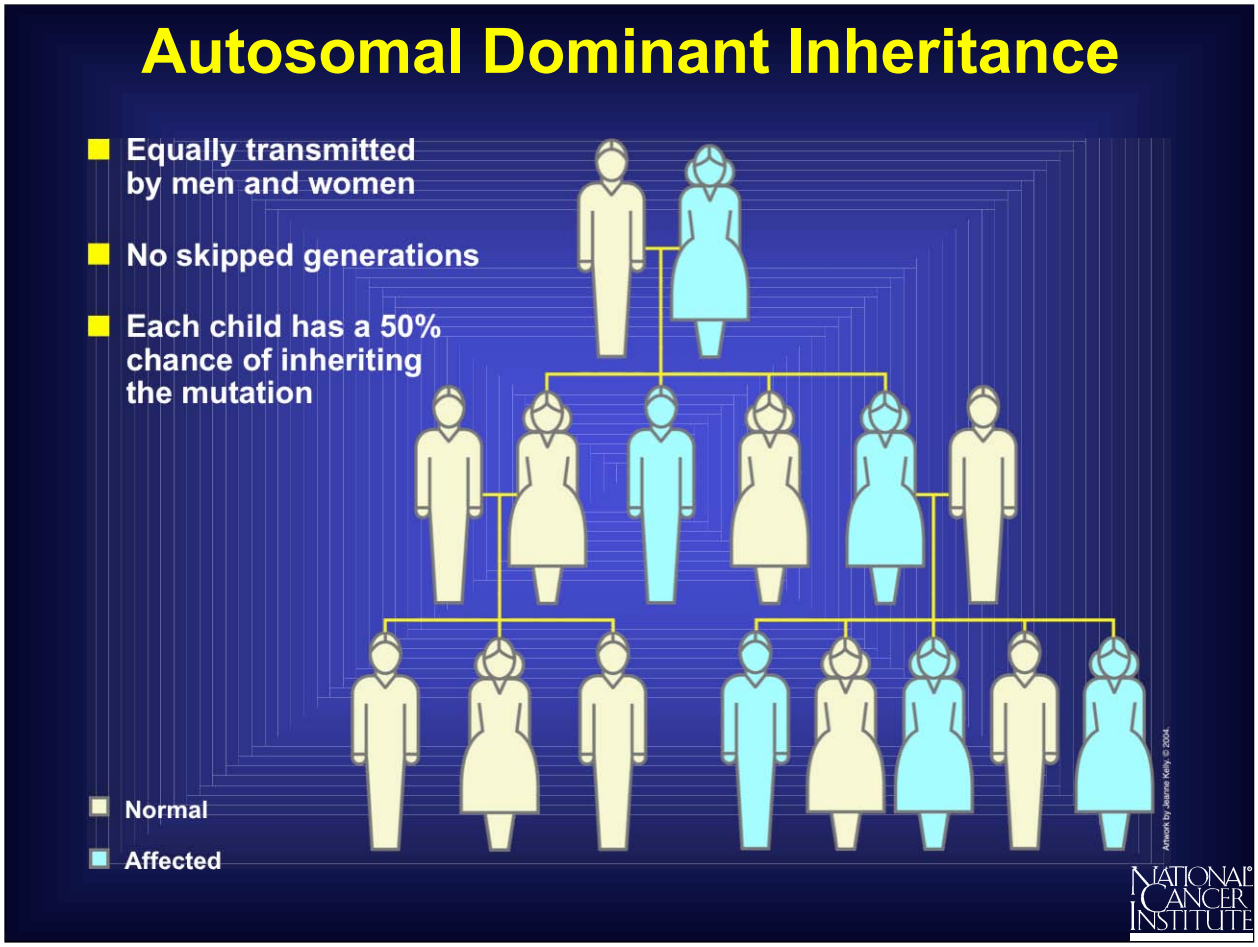


*1*Here is an example of the mutations seen in the *BRCA1* breast cancer susceptibility gene. Individuals who inherit these cancer-predisposing germline mutations carry their mutated alleles in every cell in their bodies.



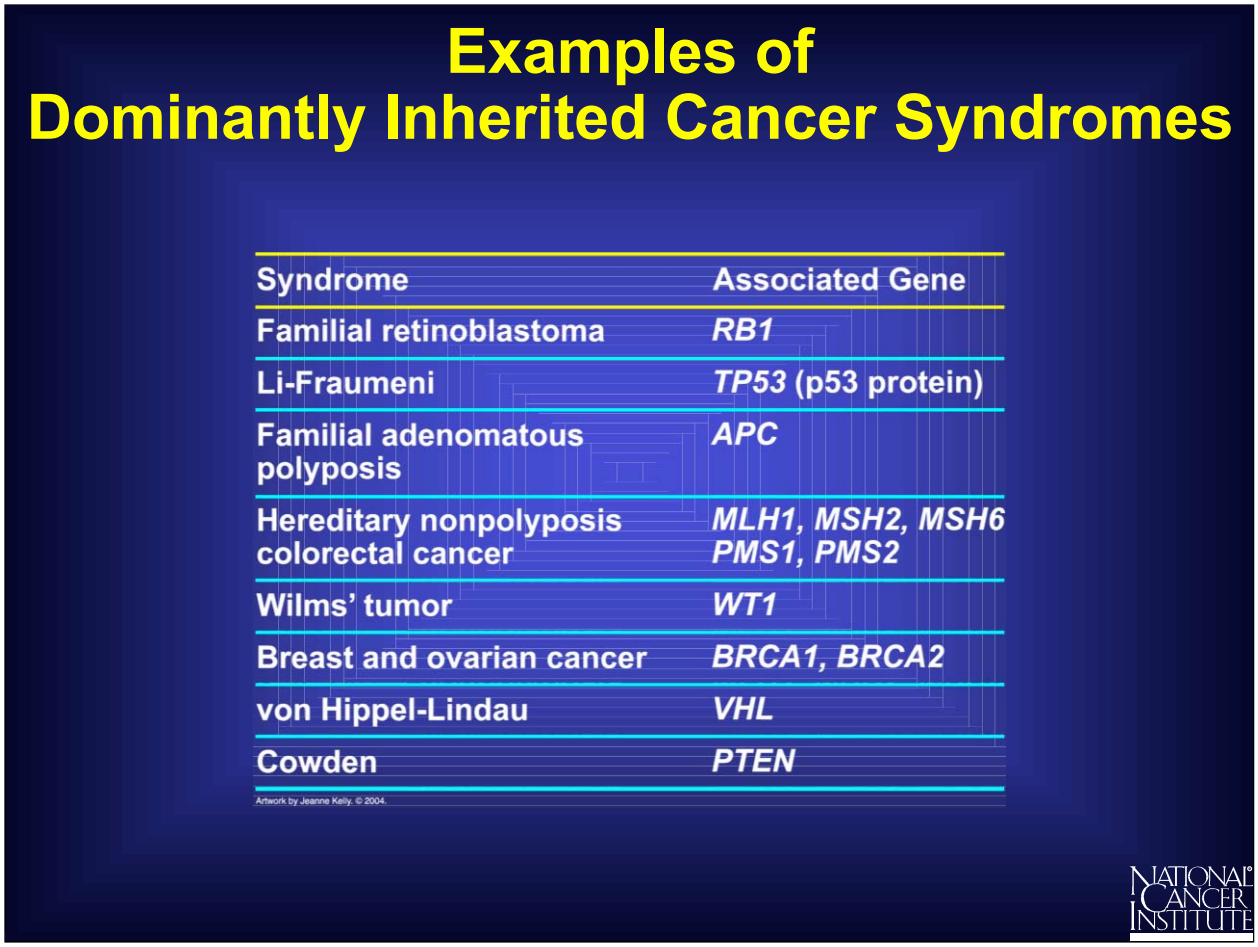
Here is an example of the mutations seen in the *BRCA2* breast cancer susceptibility gene.

Inheriting these mutated alleles greatly increases a person's lifetime risk for developing cancer. This may explain why cancers linked to germline mutations in susceptibility genes often occur at an earlier age and in multiple sites.

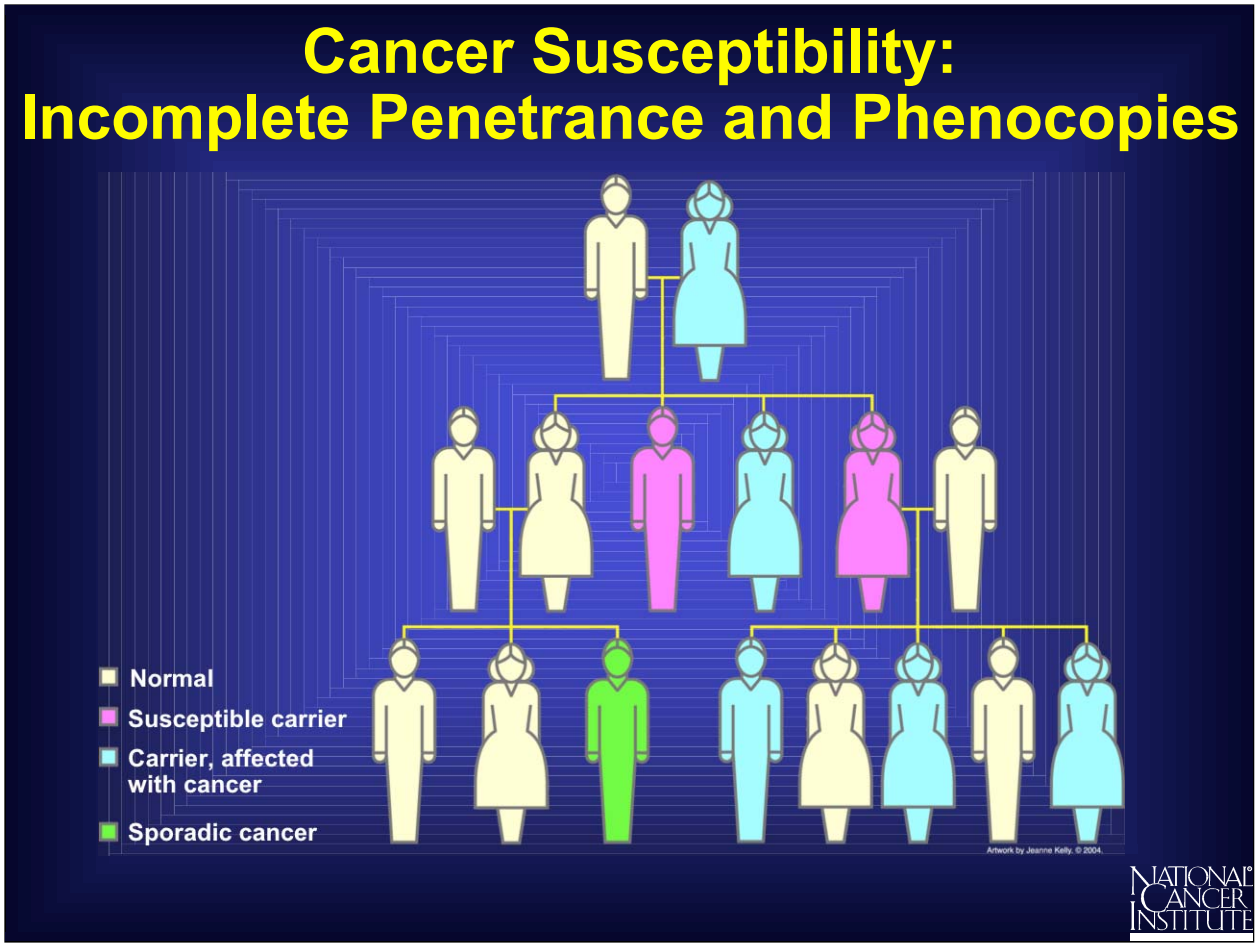


Most hereditary cancer syndromes are inherited in autosomal dominant fashion.

Dominant inheritance occurs when only ***one copy*** of an allele is required for a particular trait to be expressed (phenotype). In autosomal dominant inheritance, multiple generations express the traits, with no skipped generations (assuming complete penetrance).

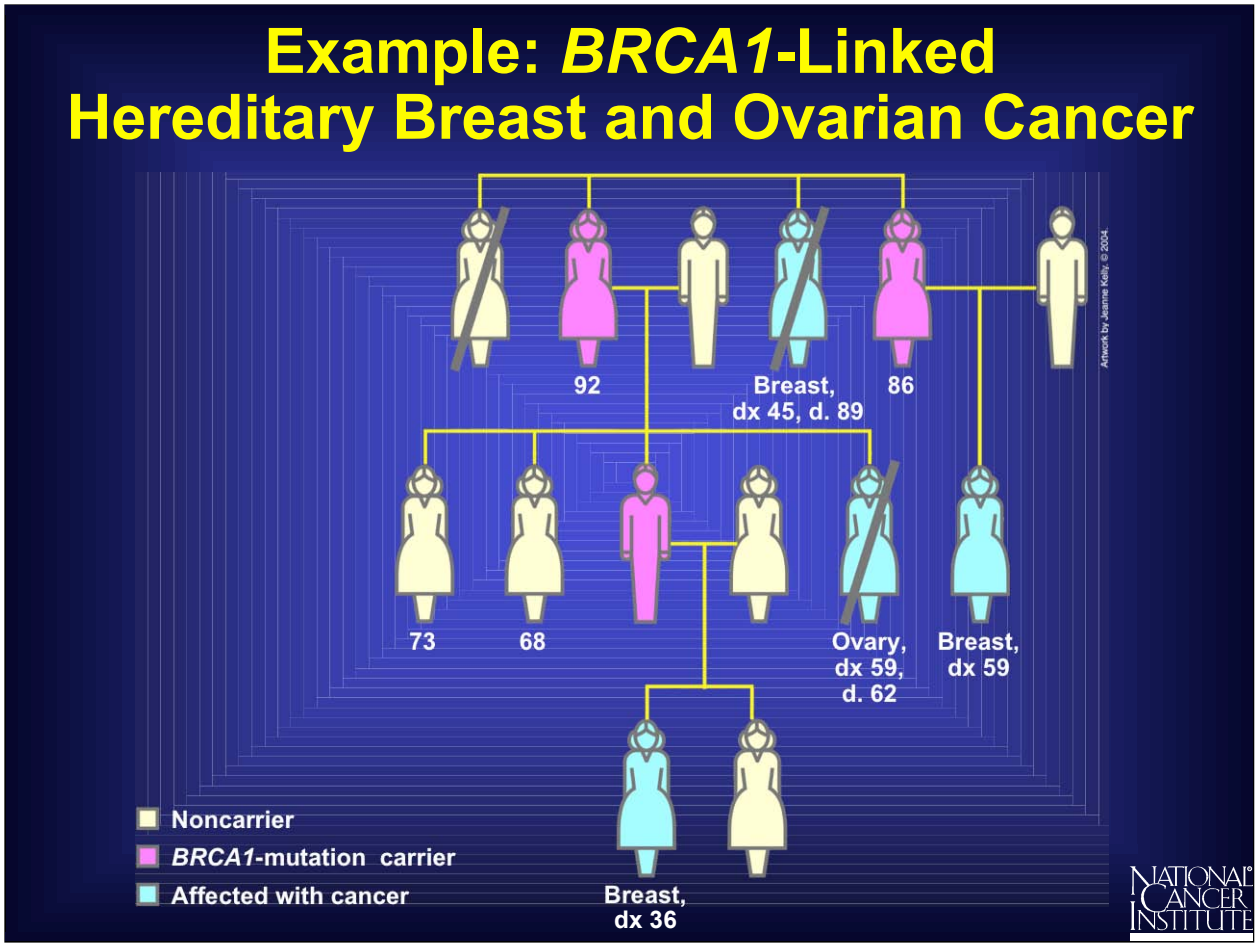


Hereditary cancer syndromes are relatively uncommon, accounting for only about 5 to 10 percent of all cancers. Nevetheless, as many as 50,000 cancers newly diagnosed in the U.S. each year are associated with a hereditary syndrome.

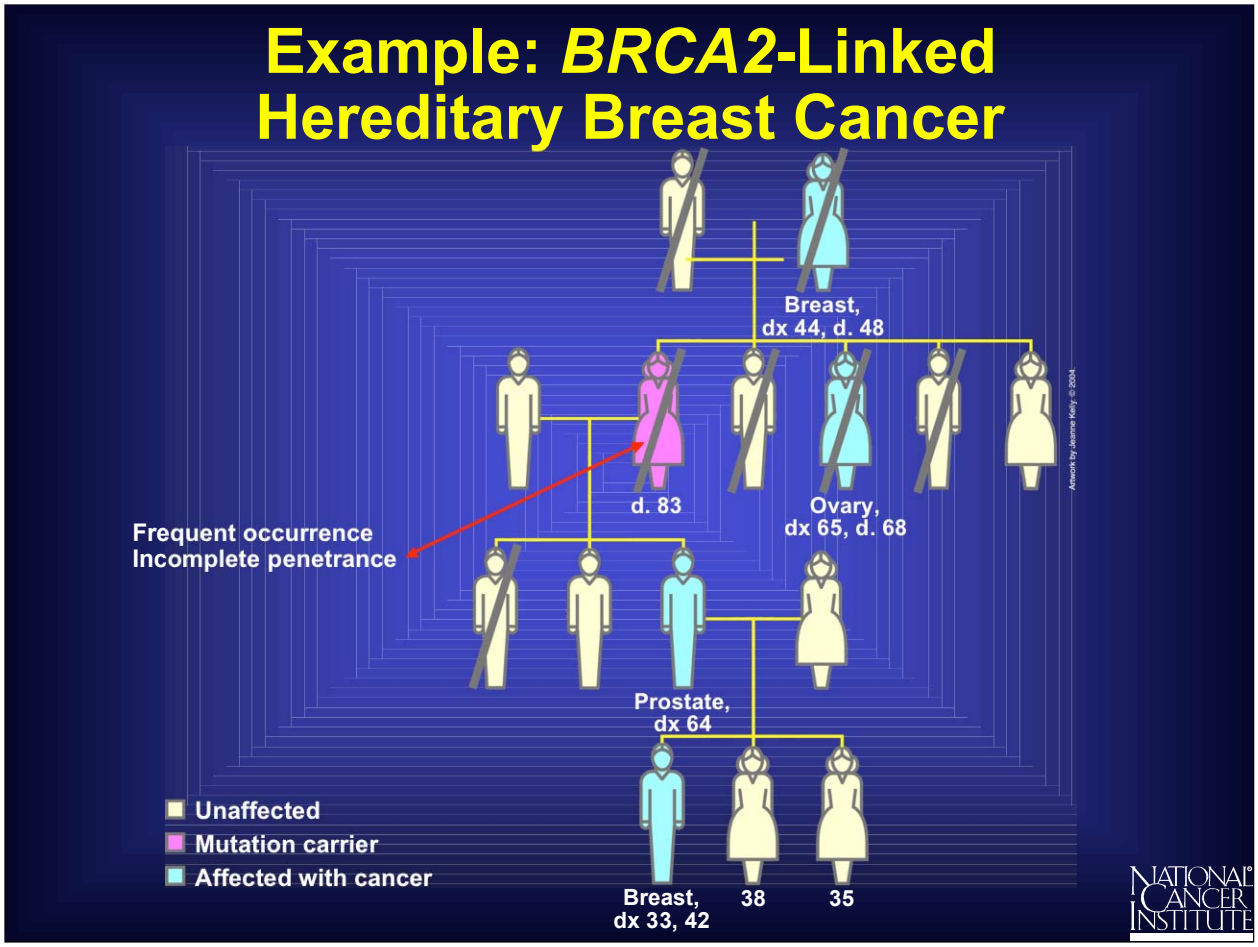


Individuals who inherit cancer susceptibility mutations inherit a predisposition to cancer, not cancer itself. Some mutation carriers inherit their predisposing genotypes in an autosomal dominant fashion, yet they do not develop cancer, indicating that their altered genes are incompletely penetrant. A somatic mutation in a second allele is required for cancer to develop.

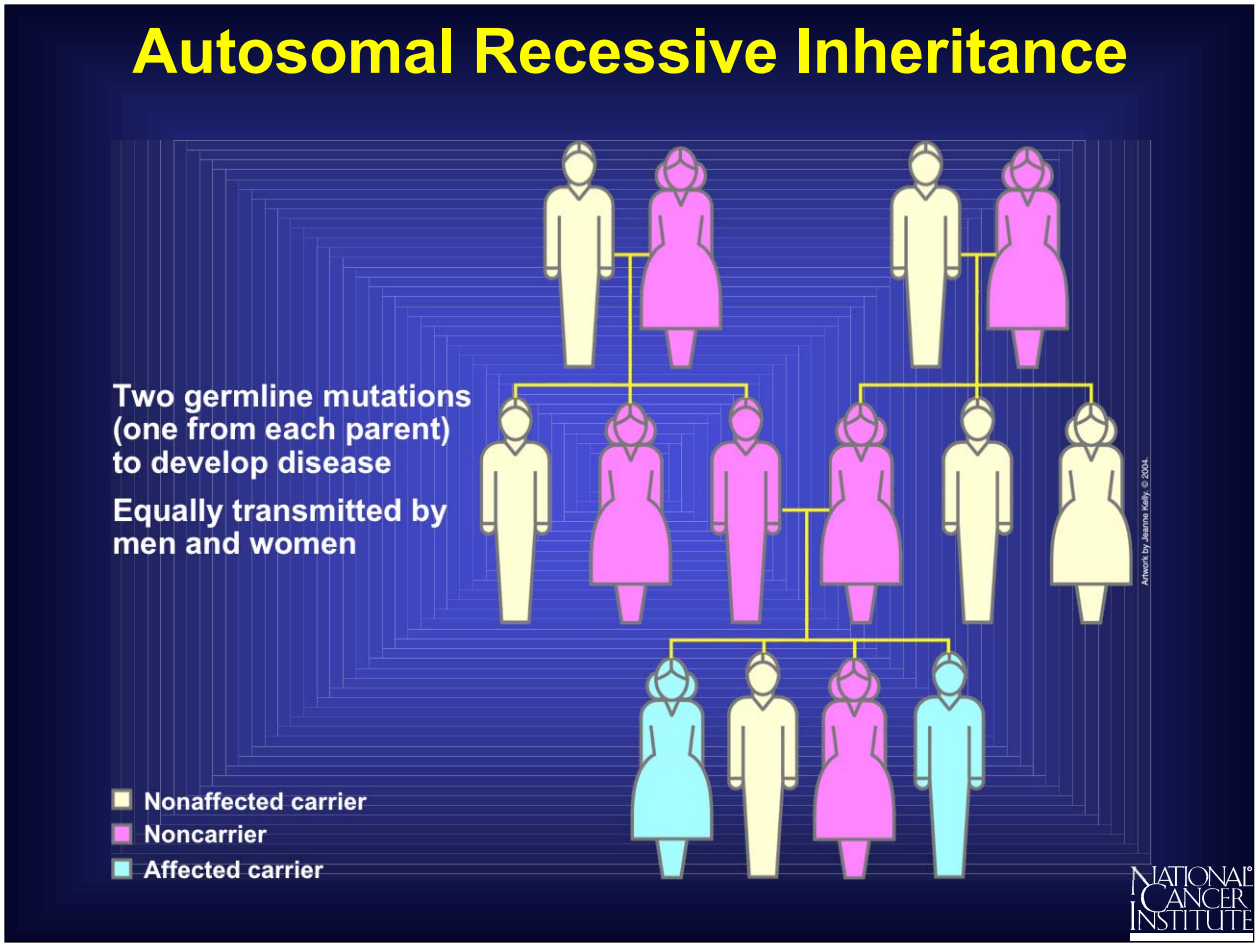
Further confusing the situation is the fact that sporadic forms of cancer may also occur in families along with a hereditary cancer syndrome. These cases of sporadic cancer are called phenocopies because their phenotype is similar to that of the affected mutation carriers, but their genotype is different. Genetic testing may determine if the cancer is hereditary or sporadic in nature.



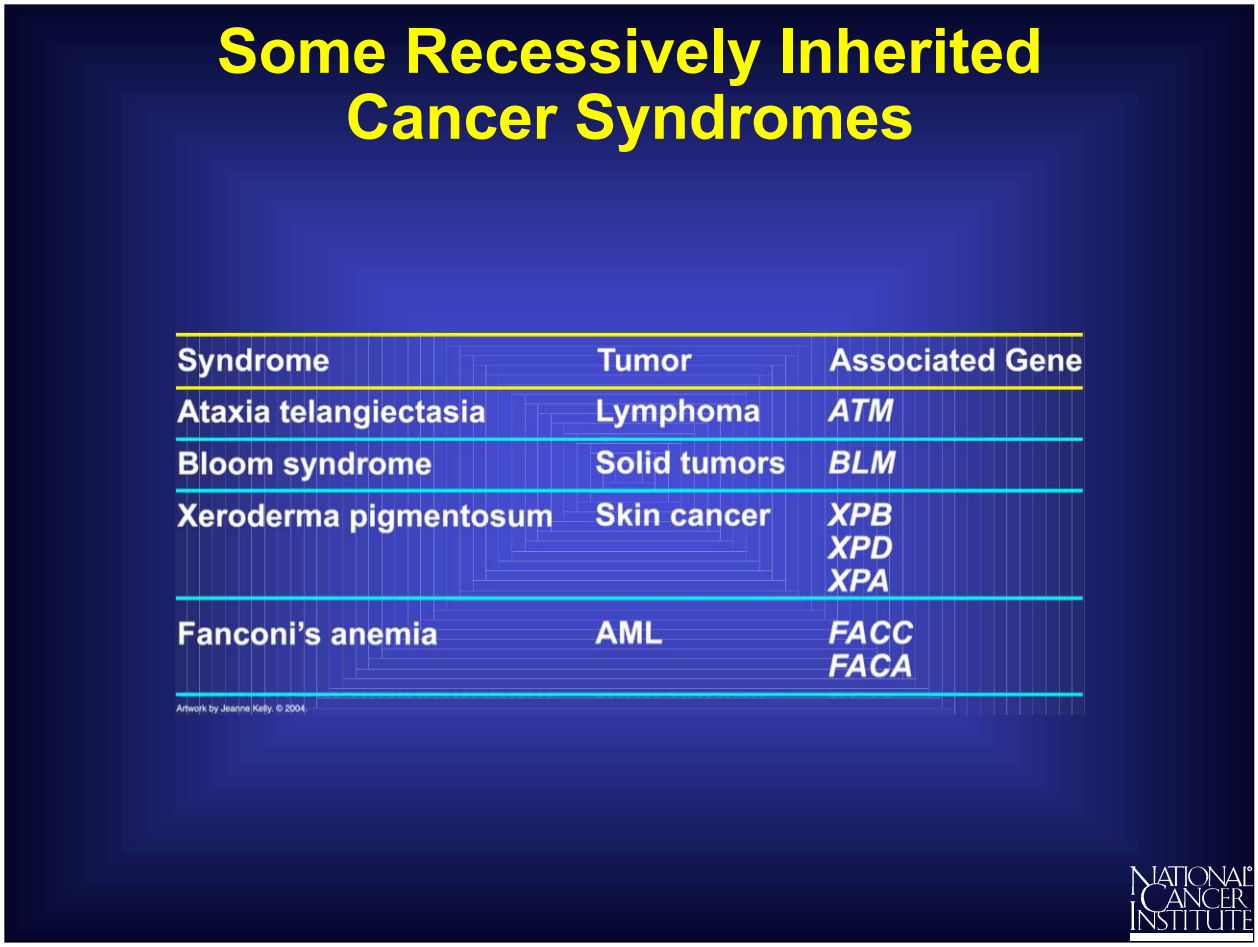
In this pedigree of a family with a *BRCA1* mutation, numbers below each person indicate age at first cancer diagnosis, if affected; age at death, if deceased; and age at interview, if alive. This family exemplifies several hallmarks of hereditary breast and ovarian cancer. The fact that the mutation is passed on by autosomal dominant transmission is evident in that approximately 50 percent of family members in each generation carry the mutation. Notice that an unaffected father passes the mutation to his affected daughter, showing that transmission of the *BRCA1* mutation can occur through either parent. Note the high penetrance of the disease and early age at onset. The penetration is incomplete, though high, as shown by one female carrier who lives to age 86 and another who lives to age 92 without a diagnosis of breast or ovarian cancer.



In this pedigree, it again becomes clear that most mutations in cancer susceptibility genes are germline and pass as dominant traits with incomplete penetrance. Note the female carrier who lives to age 83 and dies of natural causes even though her mother was affected by breast cancer and died at age 48. Also note two males: one diagnosed with breast cancer and the other with prostate cancer. Men who inherit an abnormal *BRCA2* gene have an increased risk (80 times the lifetime risk of men without the mutation) for male breast cancer. They also are three to seven times more likely than men without the mutation to develop prostate cancer.



In autosomal recessive inheritance, two copies of the allele are required for the trait to be expressed. Carriers of one disease allele will not develop the illness, and several generations may be unaffected, leading to the appearance of skipped generations. Males and females are equally affected. If both parents carry one copy of the recessive allele, one in four offspring, on average, will express the trait.


Some Recessively Inherited Cancer Syndromes
Syndrome
Tumor
Associated Gene
Ataxia telangiectasia
Lymphoma
ATM
Bloom syndrome
Solid tumors
BLM
Xeroderma pigmentosum
Skin cancer
XPB
XPD
XPA
Fanconi's anemia
AML
FACC
FACA
Artwork by Jeanne Kelly. © 2004.
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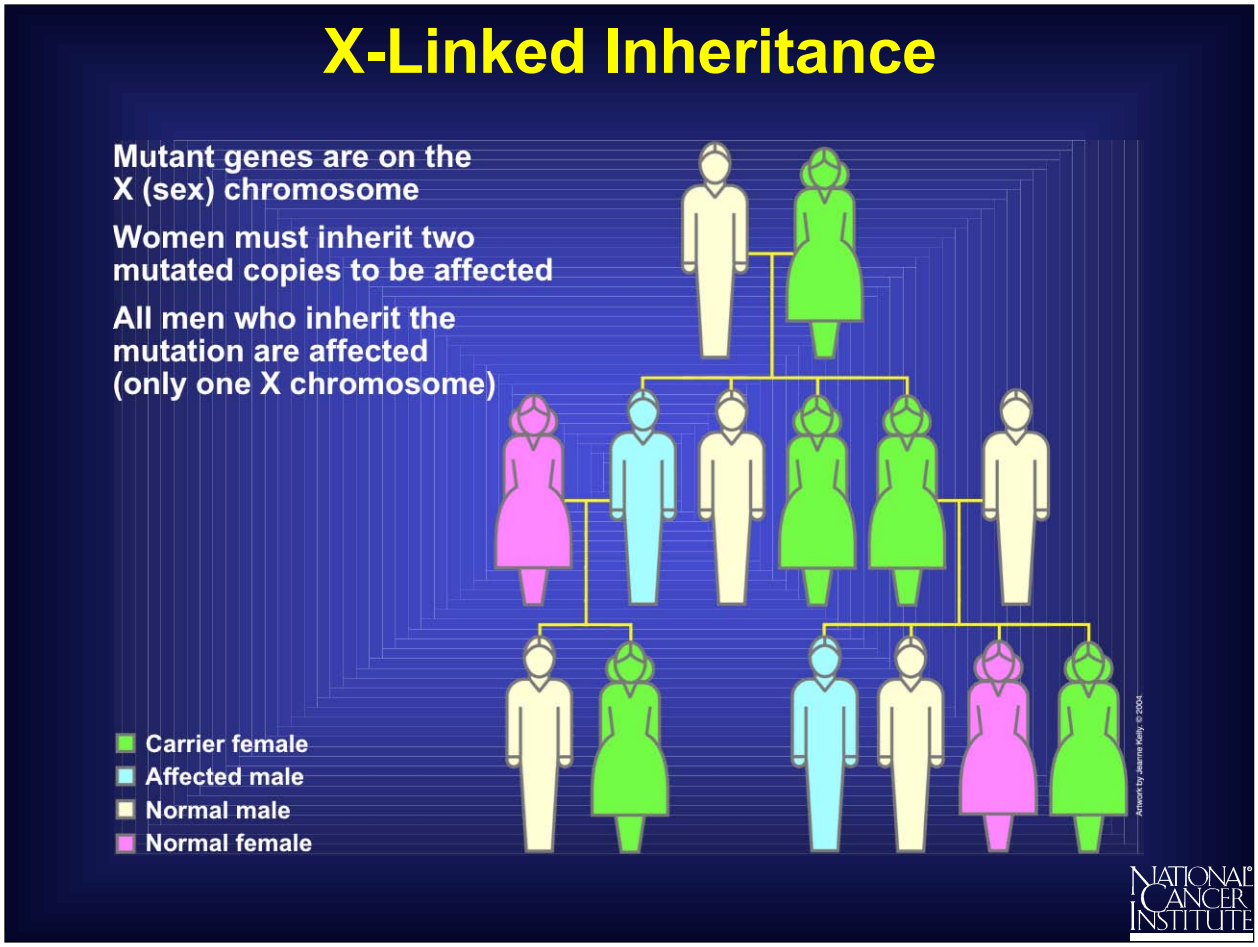
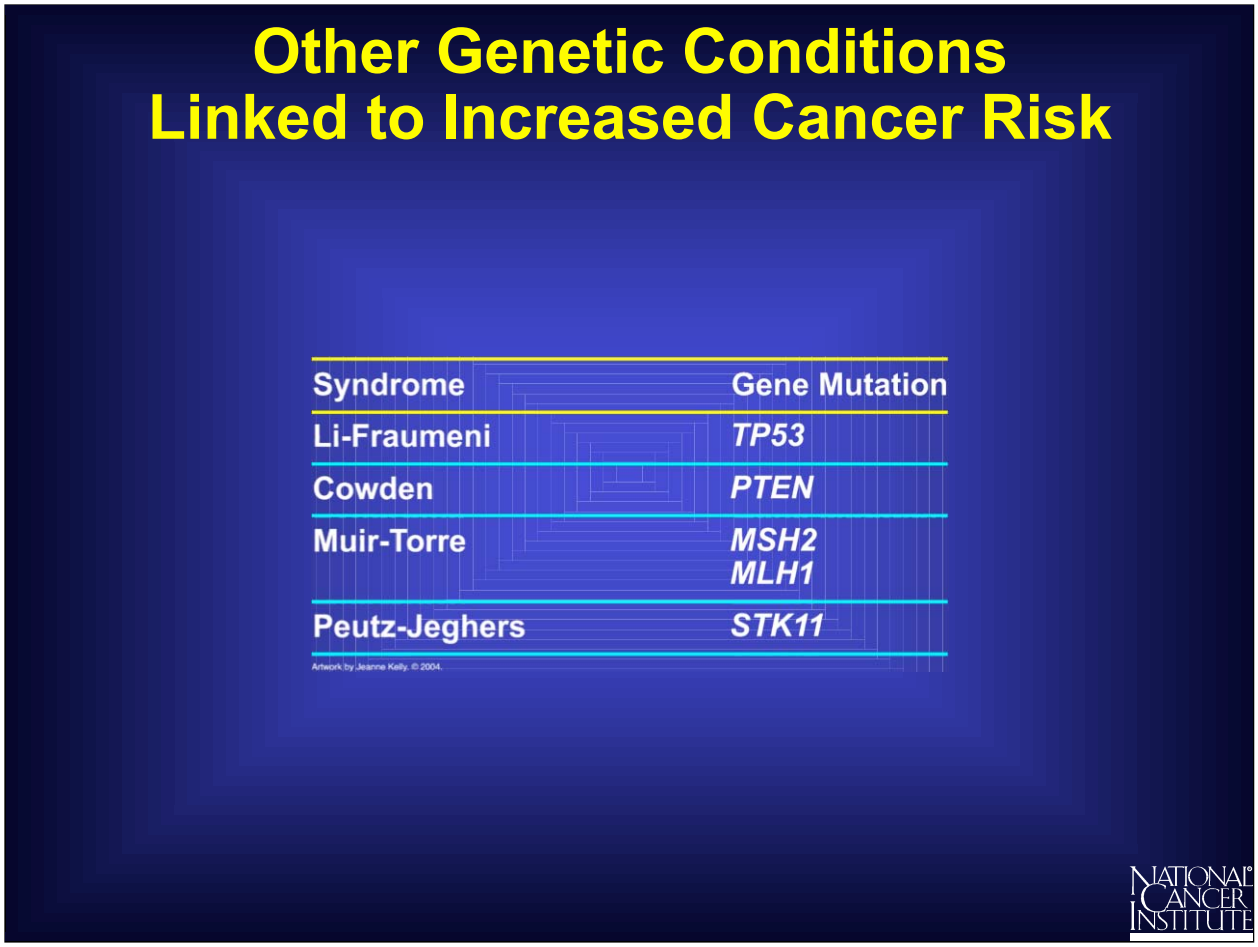
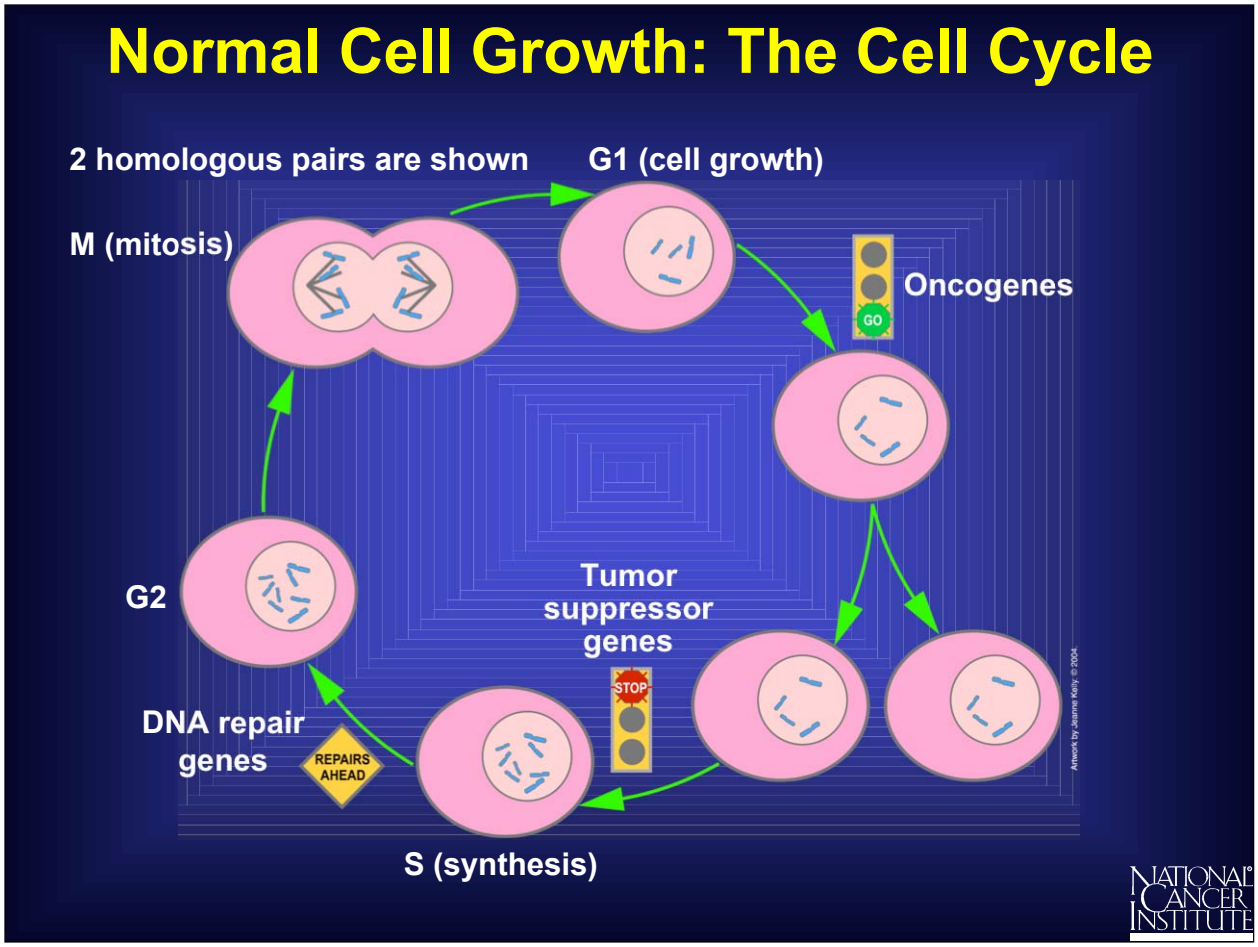


In X-linked inheritance, the gene of interest is on the X chromosome, not on an autosome. Because females have 2 X chromosomes, they must inherit two copies of the disease allele to express the disease phenotype. Females with only one mutated allele are carriers.

Males are more frequently affected because they only have one X chromosome and need only one allele mutated to express a disease phenotype. All males who inherit a copy of the abnormal X chromosome are affected by the disease (assuming 100 percent penetrance).



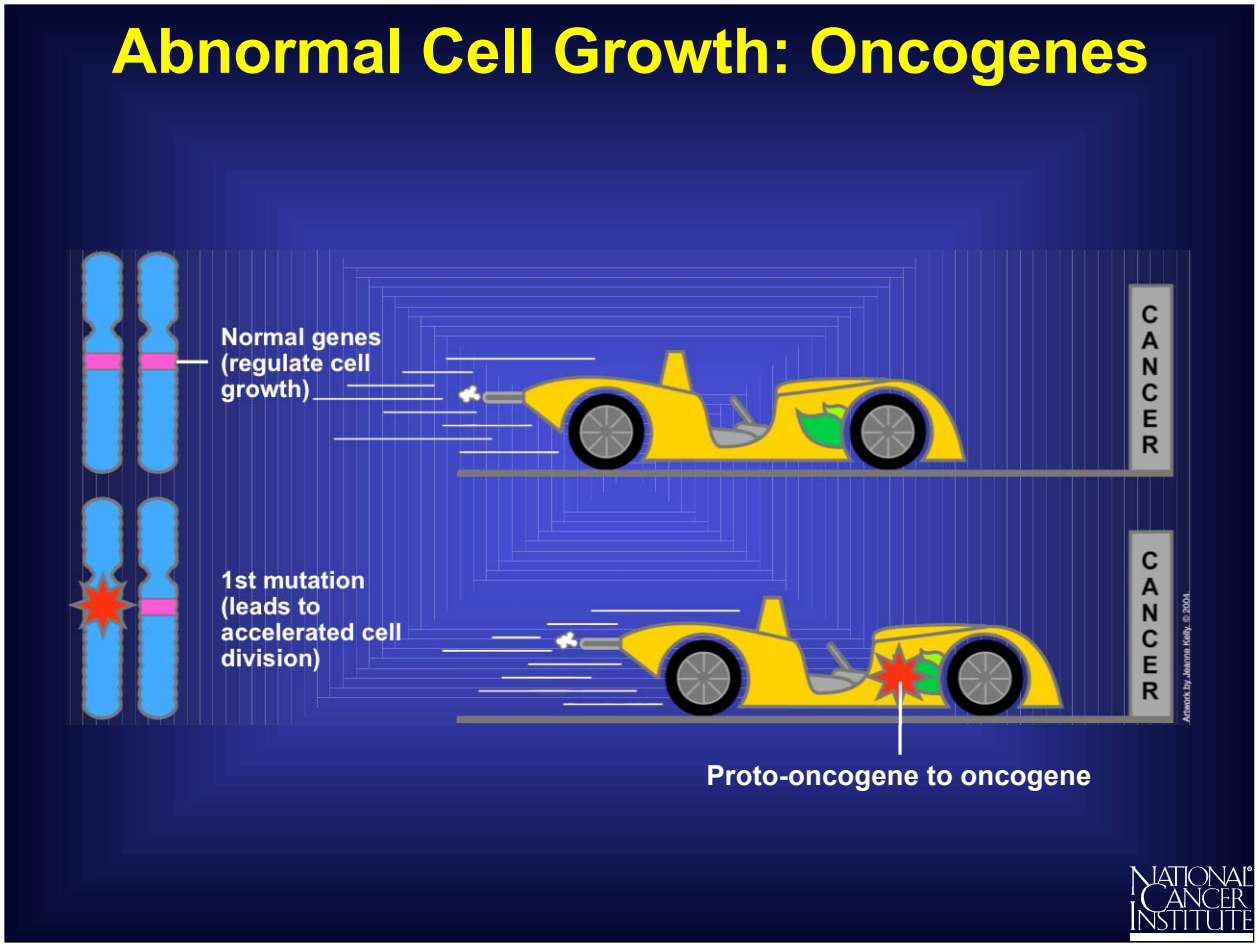
Hereditary susceptibility to breast cancer occurs in several other rare genetic conditions. Breast cancer is the most common adult manifestation of Li-Fraumeni syndrome, a multiple cancer syndrome caused by germline mutations in the *TP53* gene. Breast cancer also is the most frequent malignancy diagnosed in Cowden syndrome, a condition with germline mutations in the *PTEN* gene. Both benign and malignant breast tumors occur in Muir-Torre syndrome, a condition related to hereditary nonpolyposis colon cancer (HNPCC), characterized by germline mutations in the DNA mismatch repair genes *MSH2* and *MLH1*. Patients with Peutz-Jeghers syndrome display abnormal pigmentation, gastrointestinal polyps, and, if they are women, they are at increased risk for breast cancer and they experience early onset bilateral disease.



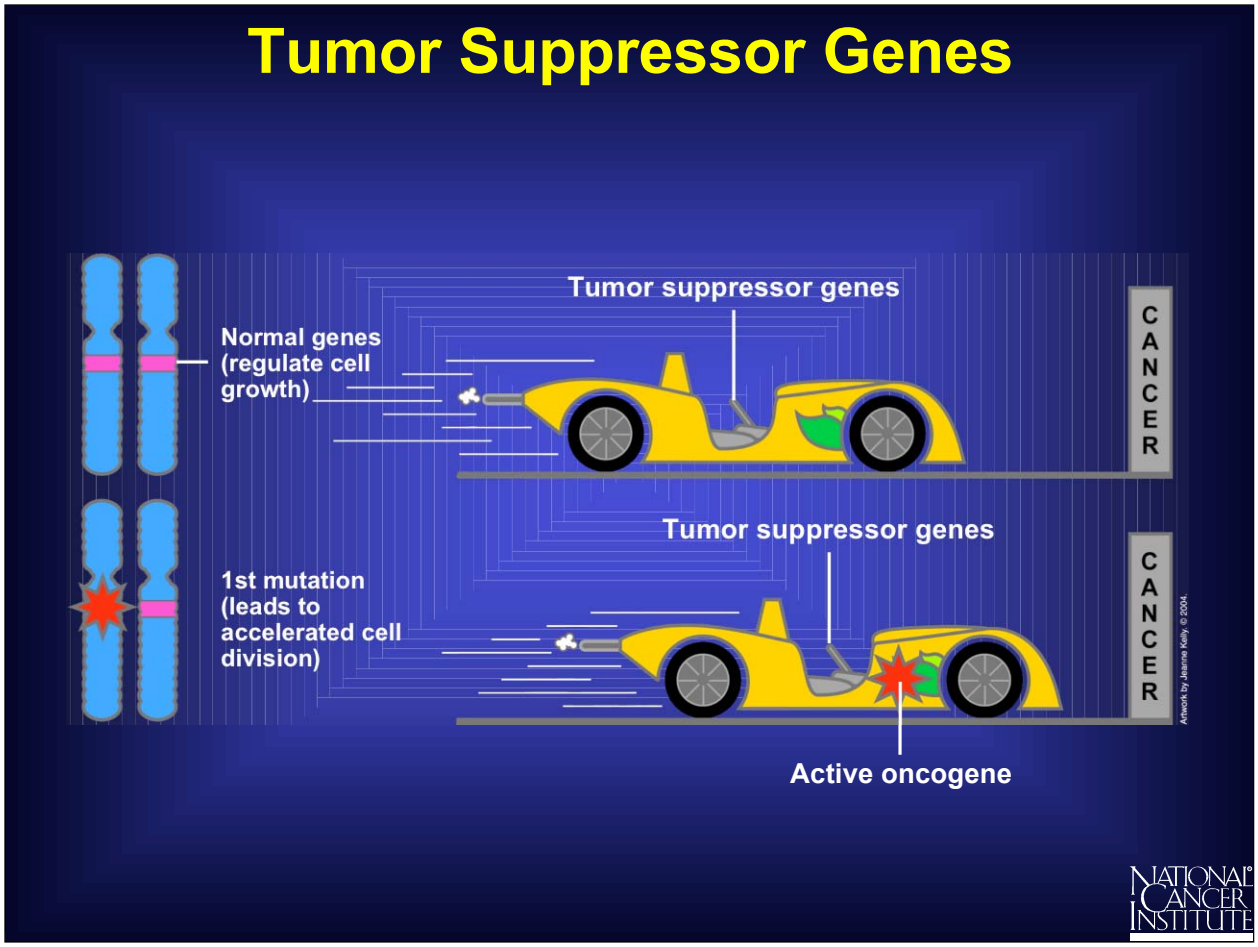
The cell cycle is a critical process that a cell undergoes in order to copy itself exactly. Most cancers have mutations in the signals that regulate the cell's cycle of growth and division. Normal cell division is required for the generation of new cells during development and for the replacement of old cells as they die.

Most cells remain in interphase, the period between cell divisions, for at least 90 percent of the cell cycle. The first part of the interphase is called G1 (for first gap), followed by the S phase (for DNA synthesis), then G2 (for second gap). During G1, there is rapid *growth* and metabolic activity, including synthesis of RNA and proteins. Cell growth continues during the S phase, and DNA is replicated. In G2, the cell continues to grow and prepares for cell division. Cell *division* (mitosis) is referred to as the M phase. Cells that do not divide for long periods do not replicate their DNA and are considered to be in G0.

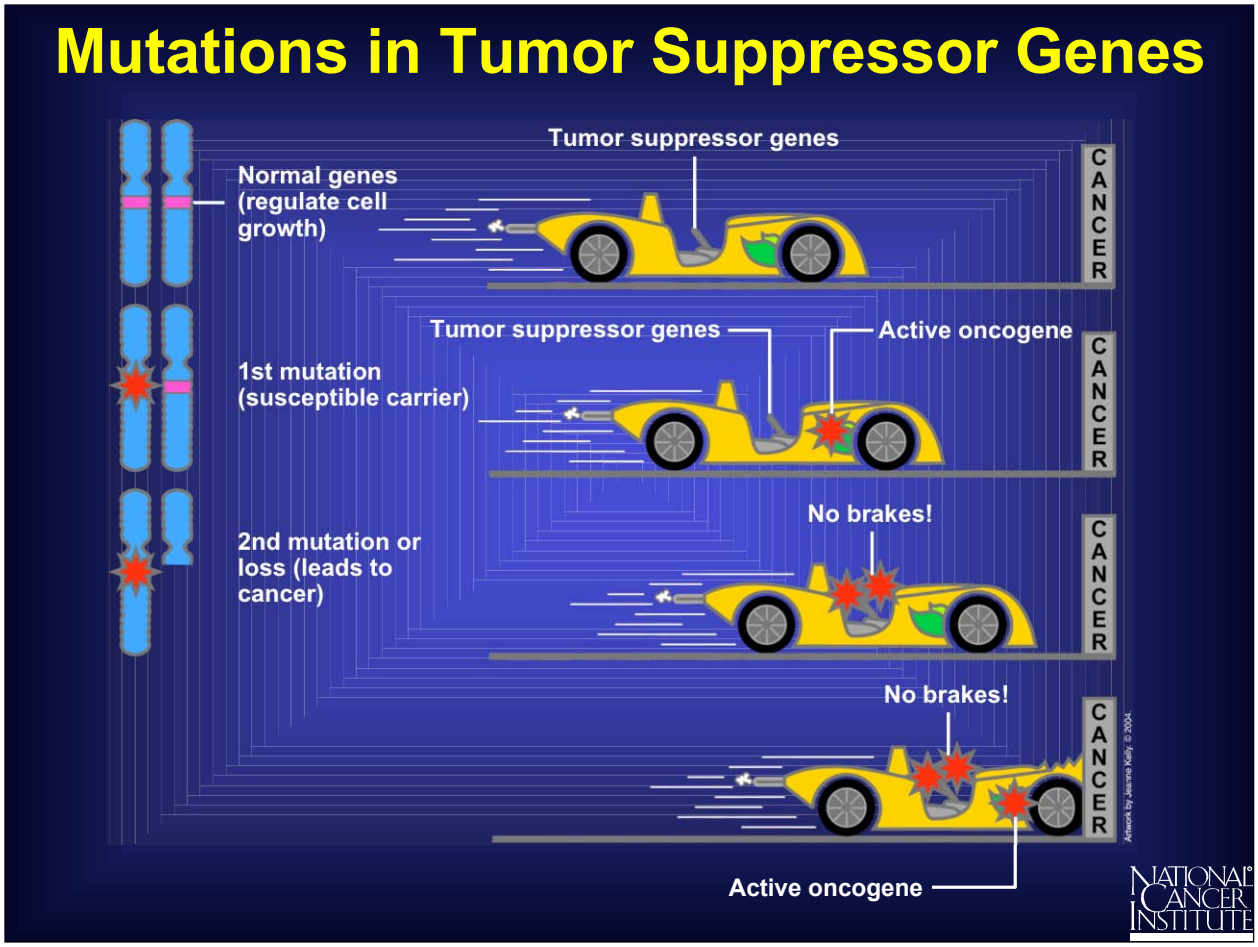
In normal cells, tumor suppressor genes act as braking signals during G1 to stop or slow the cell cycle before S phase. DNA repair genes are active throughout the cell cycle, particularly during G2 after DNA replication and before the chromosomes prepare for mitosis.



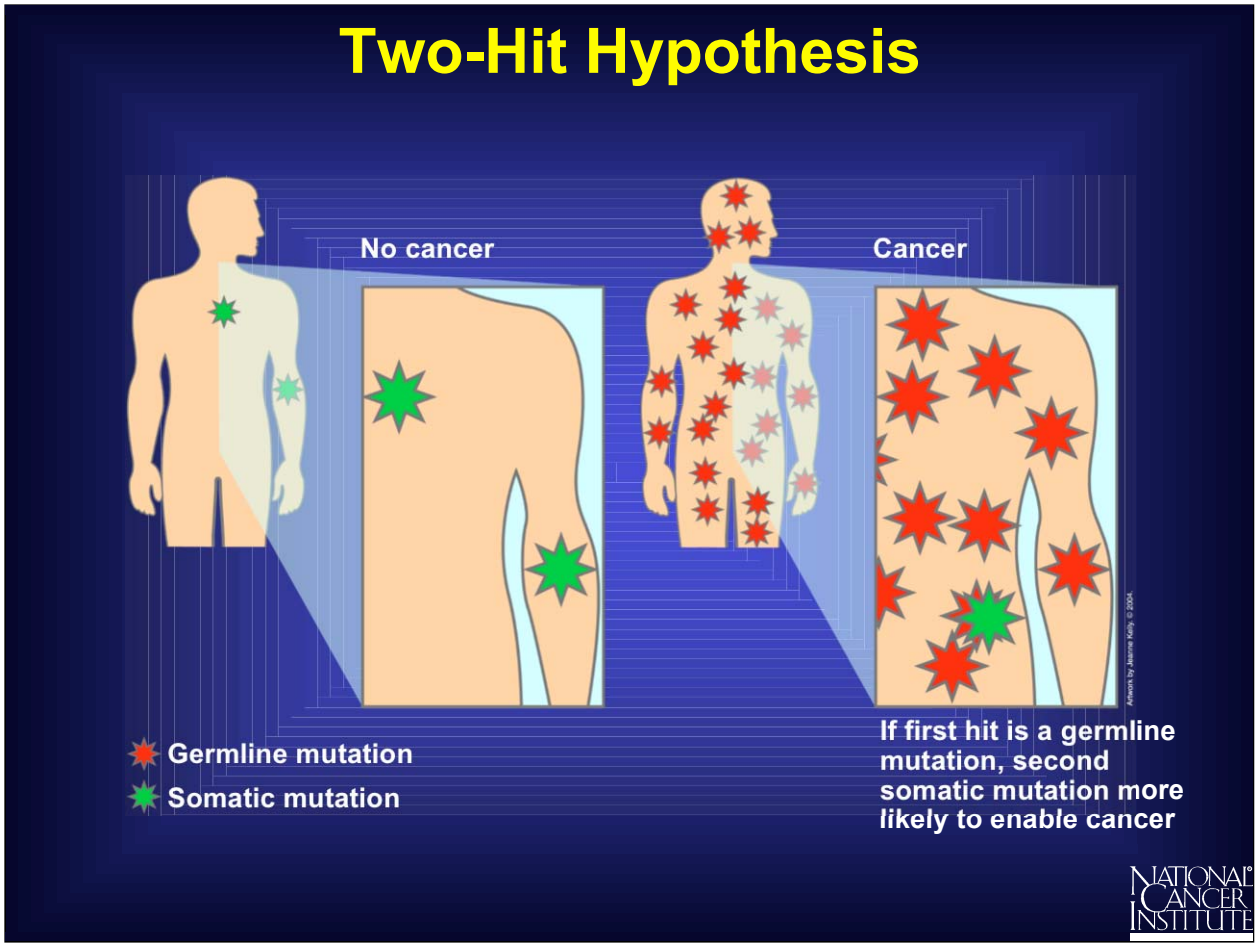
Most cancers have mutations in proto-oncogenes, the normal genes involved in the regulation of controlled cell growth. These genes encode proteins that function as growth factors, growth factor receptors, signal-relaying molecules, and nuclear transcription factors (proteins that bind to genes to start transcription). When the proto-oncogene is mutated or overregulated, it is called an oncogene and results in unregulated cell growth and transformation. At the cellular level, only one mutation in a single allele is enough to trigger an oncogenic role in cancer development. The chance that such a mutation will occur increases as a person ages.



Most cancer susceptibility genes are tumor suppressor genes. Tumor suppressor genes are just one type of the many genes malfunctioning in cancer. These genes, under normal circumstances, suppress cell growth. Some do so by encoding transcription factors for other genes needed to slow growth. For example, the protein product of the suppressor gene *TP53* is called p53 protein. It binds directly to DNA and leads to the expression of genes that inhibit cell growth or trigger cell death. Other tumor suppressor genes code for proteins that help control the cell cycle.

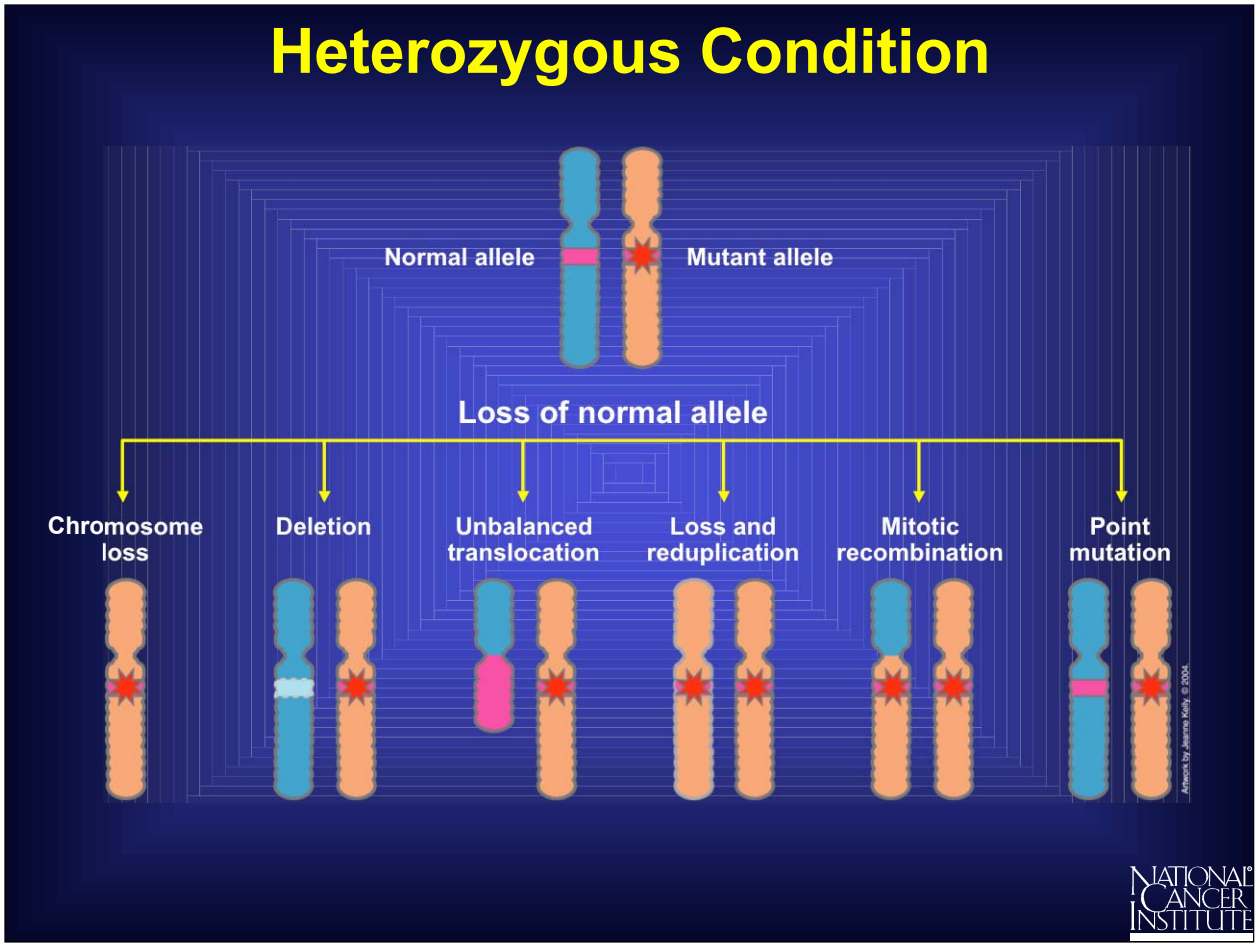


Both copies of a tumor suppressor gene must be lost or mutated for cancer to occur. A person who carries a germline mutation in a tumor suppressor gene has only one functional copy of the gene in all cells. For this person, loss or mutation of the second copy of the gene in any of these cells can lead to cancer.

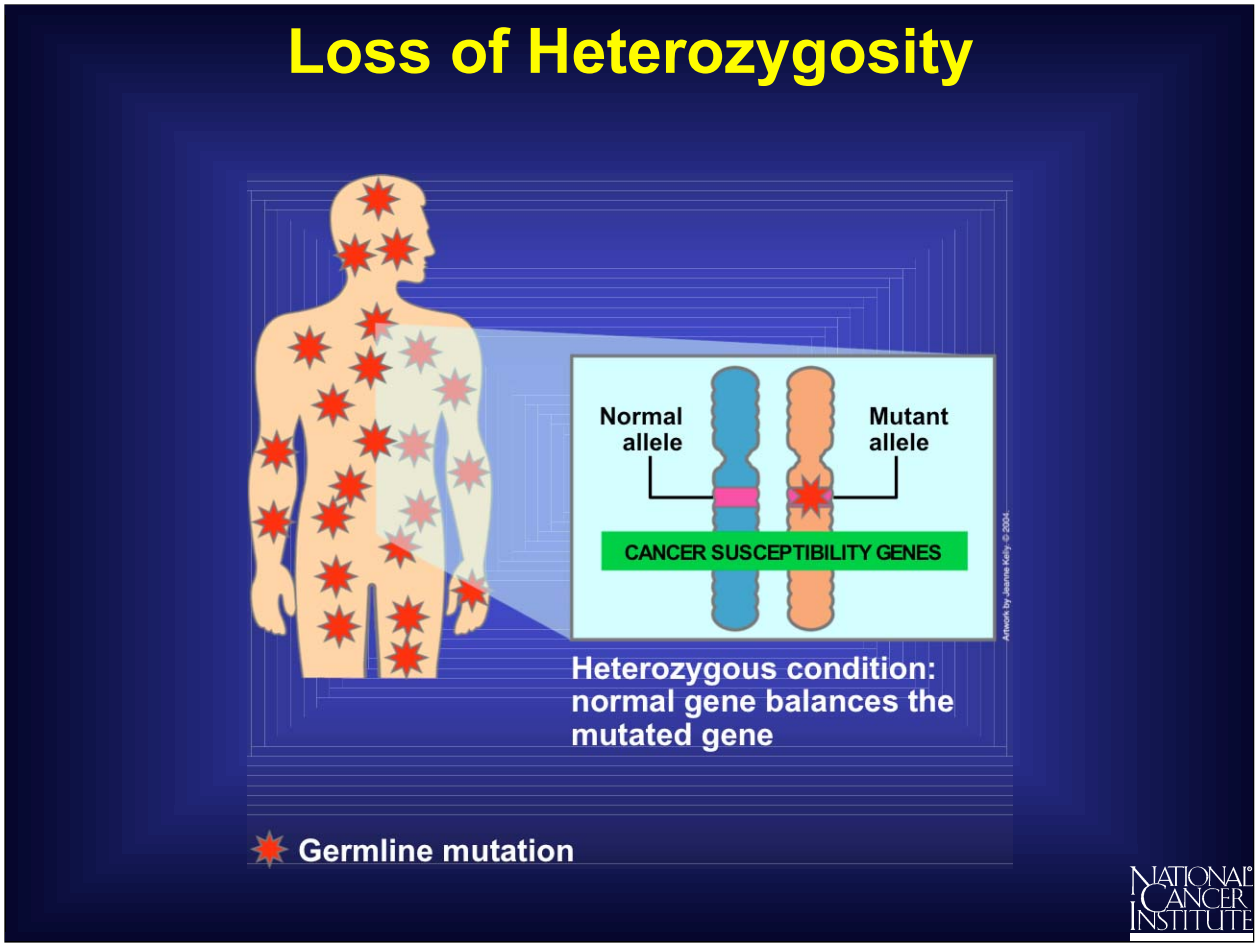


In 1971, Dr. Alfred Knudson proposed the two-hit hypothesis to explain the early onset at multiple sites in the body of an inherited form of cancer called hereditary retinoblastoma. Inheriting one germline copy of a damaged gene present in every cell in the body was not sufficient to enable this cancer to develop. A second hit (or loss) to the good copy in the gene pair could occur somatically, though, producing cancer. This hypothesis predicted that the chances for a germline mutation carrier to get a second somatic mutation at any of multiple sites in his/her body cells was much greater than the chances for a noncarrier to get two hits in the same cell.

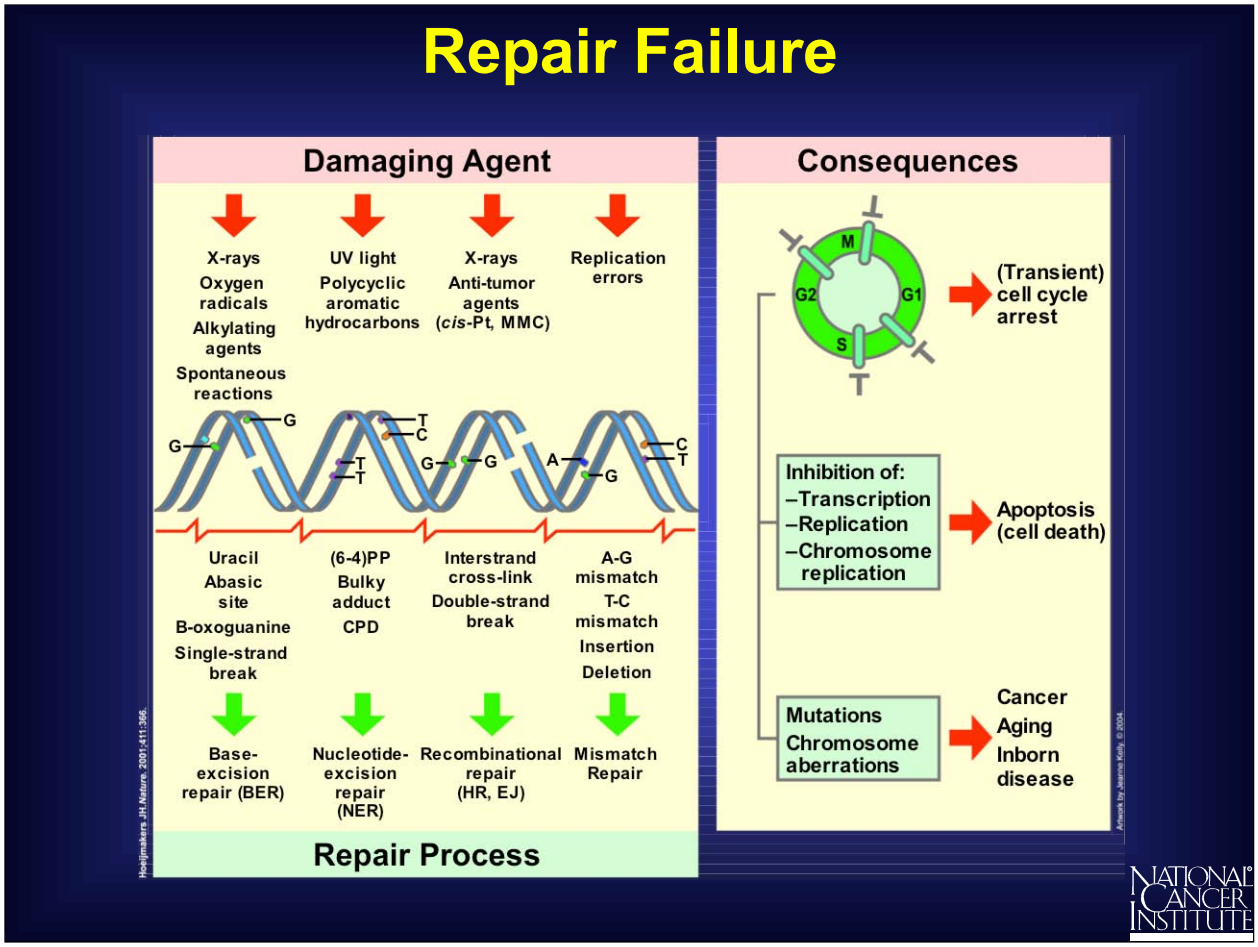
Tumor suppressors act recessive at the phenotypic level (both alleles must be mutated/lost for cancer to develop), but the "first hit" germline mutation at the genotypic level is actually inherited in an autosomal dominant fashion.



In hereditary cancer syndromes, individuals are called heterozygous (having one or more dissimilar gene pairs) because they start life with a germline mutation in one of the alleles linked to cancer susceptibility, but it is balanced by a normal counterpart. These individuals are predisposed to cancer because all their cells have already sustained the first hit to cancer-linked genes. If the critically needed normal suppressor gene that balances this germline mutation is lost at some time during an individual's life, a condition called loss of heterozygosity (LOH) occurs.



There are several ways a cell can suffer loss of heterozygosity. An entire chromosome containing a normal allele may be lost due to failure of the chromosomes to segregate properly at mitosis (nondisjunction). Alternatively, an unbalanced exchange of genetic material can occur in a process called translocation, resulting in loss of a chromosomal region containing the normal gene. Sometimes when a normal gene is lost, a reduplication of the remaining chromosome with an abnormal gene occurs, leaving the cell with two abnormal gene copies. Normal genes may also be lost during normal mitotic recombination events or as a consequence of a point mutation in the second allele, leading to inactivation of the normal counterpart.



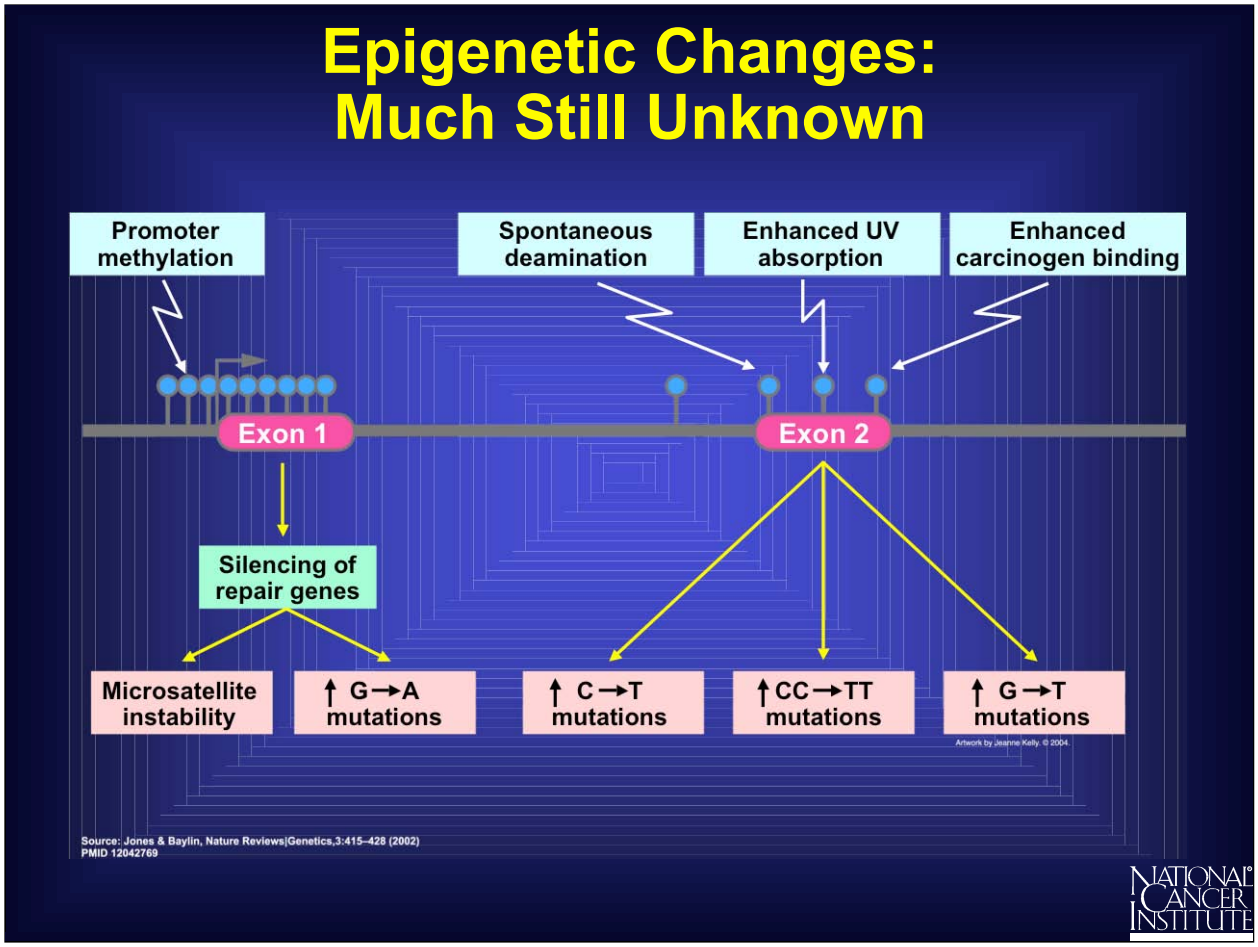
Some mutations linked to cancer appear to involve a failure of one or many of the cell's repair systems. One example of such error involves DNA mismatch repair. After DNA copies itself, proteins from mismatch repair genes act as proofreaders to identify and correct mismatches. If a loss or mutation occurs in the mismatch repair genes, sporadic mutations will more likely accumulate. Other errors in repair may involve incorrect cutting out of bases--or whole nucleotides--as repair proteins try to fix DNA after bulky molecules, such as the carcinogens in cigarettes, have attached. This is faulty excision repair. Sometimes both strands of DNA suffer breaks at the same time, and faulty recombinational repair occurs. Any of these mistakes may enable mutations to persist, get copied, and eventually contribute to cancer's development.

Much remains elusive in our understanding of cancer susceptibility. Breast cancer is a good example of how incomplete a picture we have.

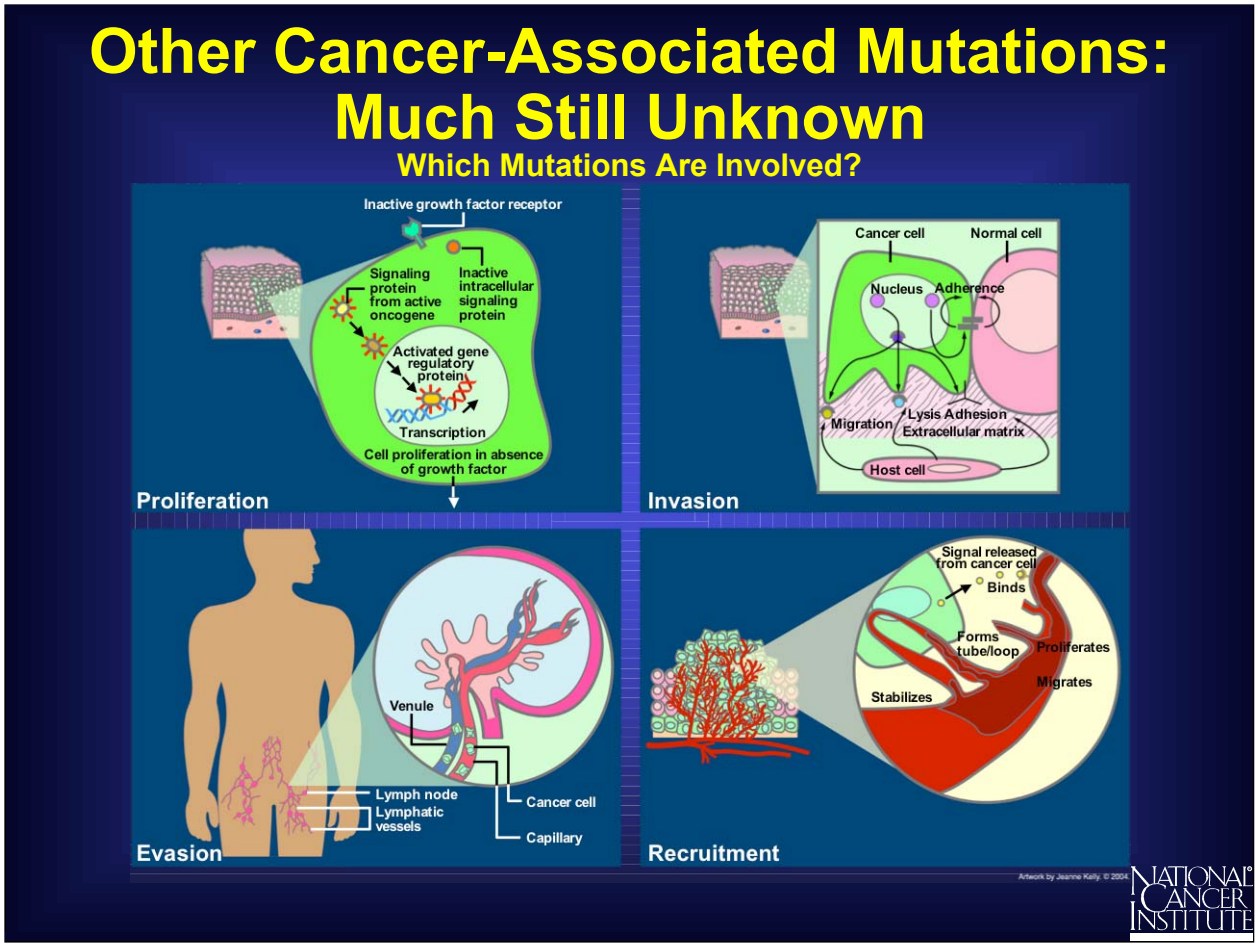
Most women with a family history of breast cancer DO NOT carry germline mutations in the single highly penetrant cancer susceptibility genes, yet familial clusters continue to appear with each new generation.

About 5 to 10 percent of breast cancer cases are linked to germline mutations in single, highly penetrant cancer susceptibility genes such as *BRCA1* and *BRCA2*. Strong genetic predisposition and cancer susceptibility in these families is passed down in an autosomal dominant fashion.

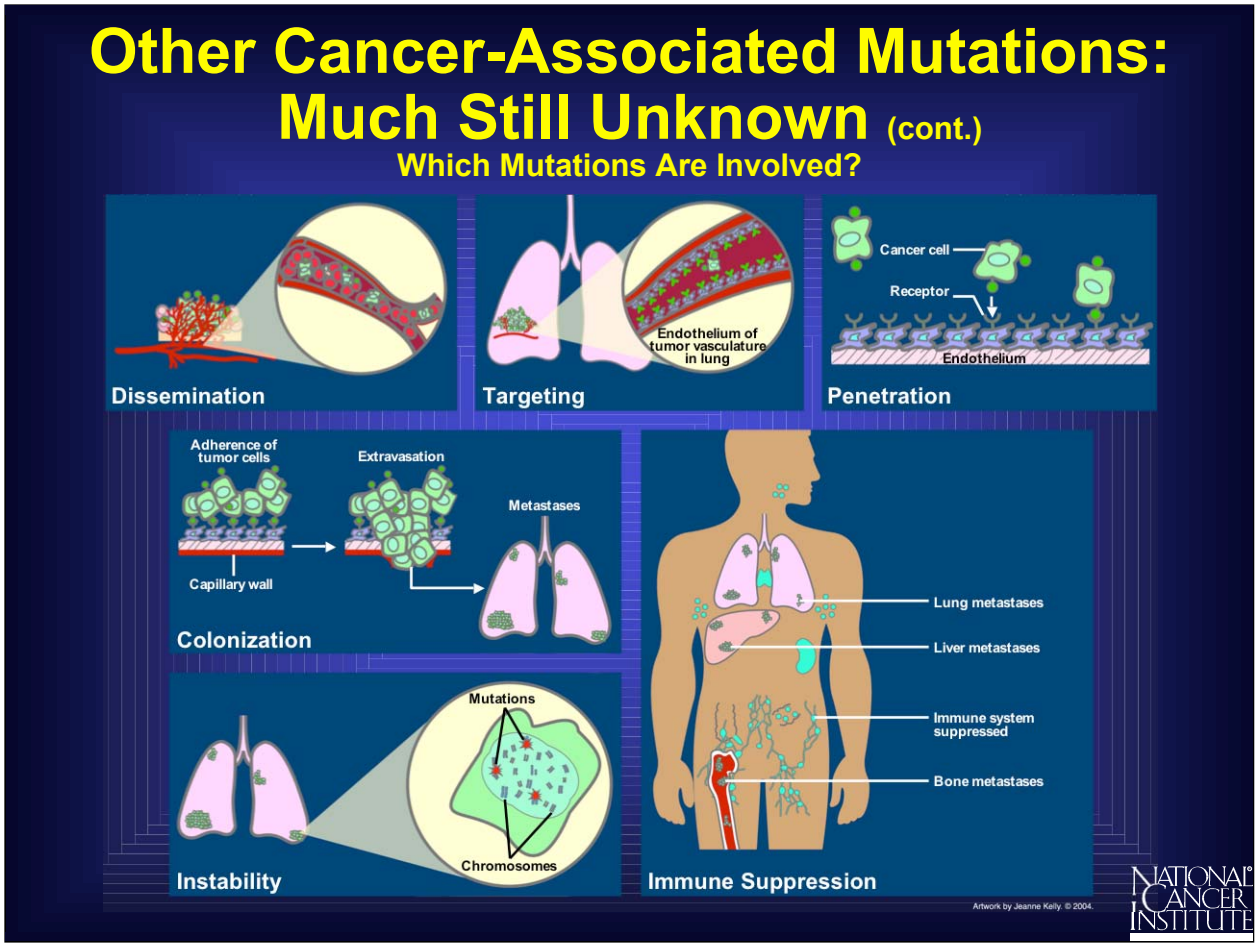
Another 15 to 20 percent of breast cancers, however, are associated with some family history *but no evidence of such autosomal dominant transmission*. These cases are not well understood. Possibly environmental or multiple gene interactions contribute to very low penetrance of susceptibility genes, or possibly *yet undiscovered mutations* are involved.



Much remains unknown about the role of epigenetic factors and cancer. Epigenetic changes are reversible modifications to genes or proteins that occur in the tumor and its microenvironment. Epigenetic modifier molecules have been observed making tumor-friendly, nonmutational changes in an already confused biosystem. For example, by heavily methylating genes or promoter regions, gene activity critical to counteract a tumor's drive toward metastasis gets turned off. Or noncoding ribonucleic acids meddle in epigenetic fashion, interfering with a cell's regulation of growth or attempt to repair damage.



In addition to oncogenes and tumor suppressor genes, most cancers acquire several other key mutations that enable cancer to progress. While researchers don't yet know all the mutations involved, they have organized them in terms of their activities in support of tumor growth and metastasis. In addition to the contributions of oncogenes and mutated suppressor genes, additional genomic mutations enable the invasion of neighboring tissue, evasion of immune system detection, recruitment of a new blood supply, dissemination and targeting of new sites, and the penetration and reinvasion through new blood and tissue layers. Over time, successful metastasis occurs.


Other Cancer-Associated Mutations: Much Still Unknown (cont.)
Which Mutations Are Involved?
Dissemination
Targeting
Endothelium of tumor vasculature in lung
Cancer cell
Receptor
Endothelium
Penetration
Adherence of tumor cells
Extravasation
Metastases
Capillary wall
Colonization
Mutations
Chromosomes
Instability
Lung metastases
Liver metastases
Immune system suppressed
Bone metastases
Immune Suppression
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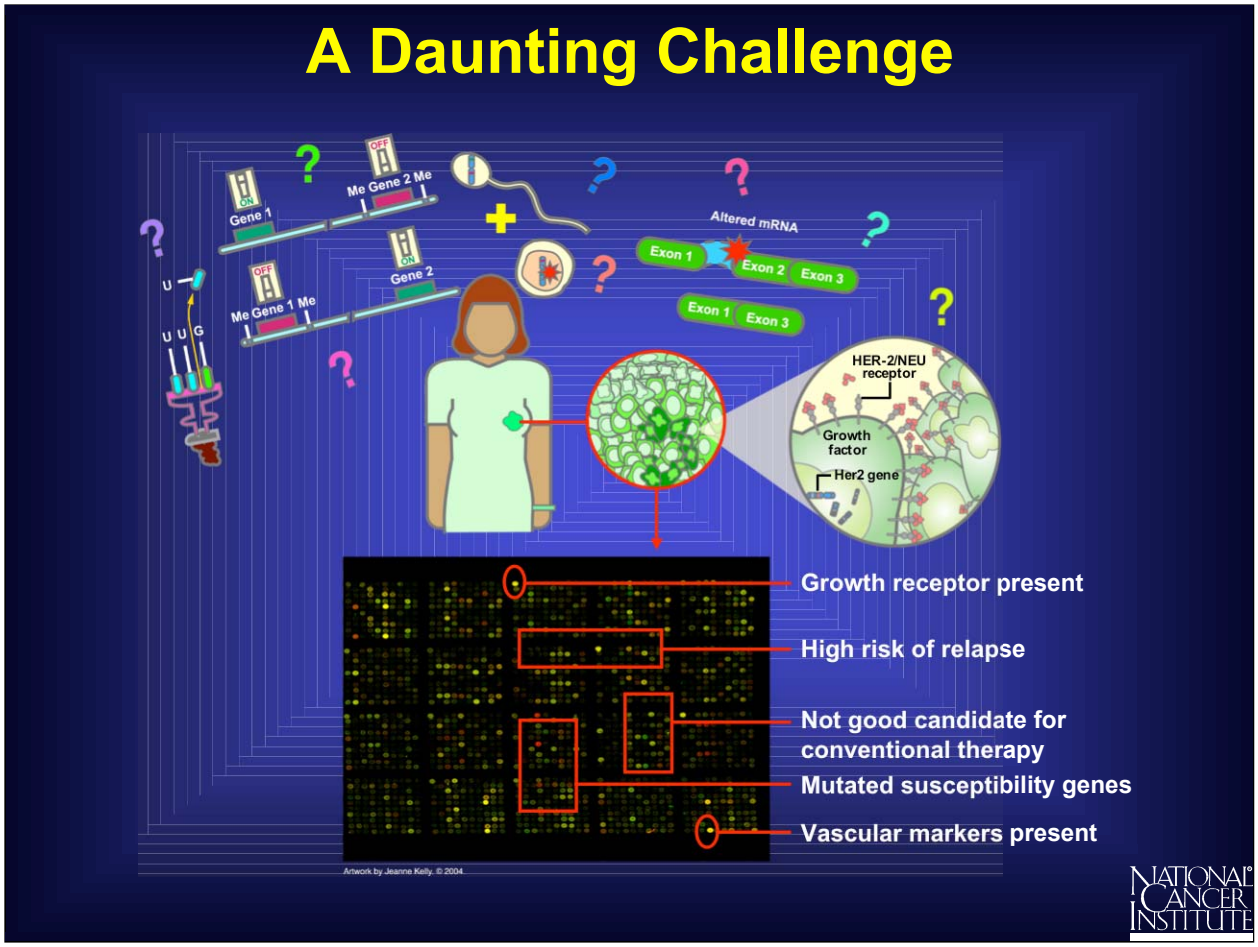
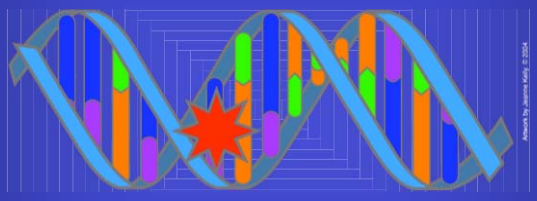


A comprehensive analysis of the cancer genome remains a daunting challenge. There is no single technology at present that will detect all the types of abnormality--deletions, rearrangements, point mutations, frameshift insertions, amplifications, imprinting, and epigenetic changes--implicated in cancer. Microarrays and gene chip analysis, however, are beginning to unveil some key genomic drivers. (Please see Molecular Diagnostics for more information.)

Many clinical trials now include genomic profiles of cancer patients as prognostic and diagnostic indicators. Genomic profiles are even used to monitor where and how the cancer genome has been hit during molecularly targeted therapies. Mining and sharing all this data should eventually help oncologists to better integrate the genotypic and phenotypic changes that occur in a biosystem during cancer's progression. This knowledge will be used to bring earlier and better interventions to cancer patients.



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