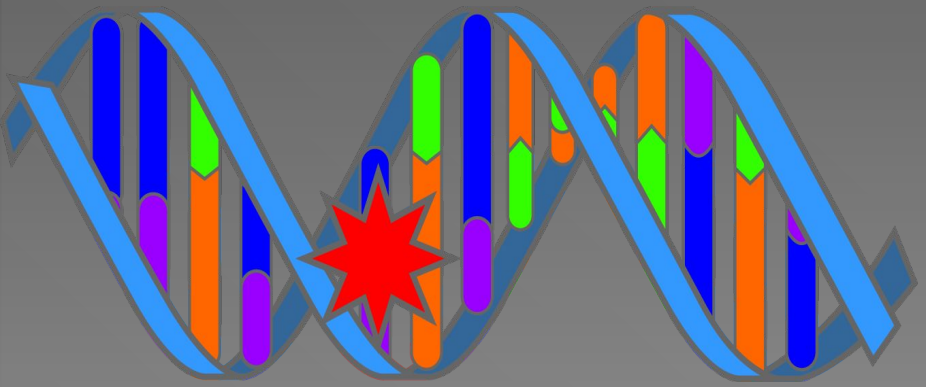
ГЕНЕТИКА РАКА
Understanding Cancer Genomics



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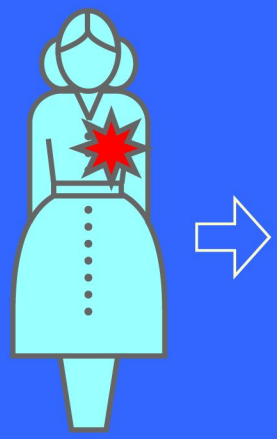
DR. SEMENISTY V.
27.09.2017

Mutations: Somatic and Germline

Somatic mutations

- Occur in nongermline tissues
- Are nonheritable

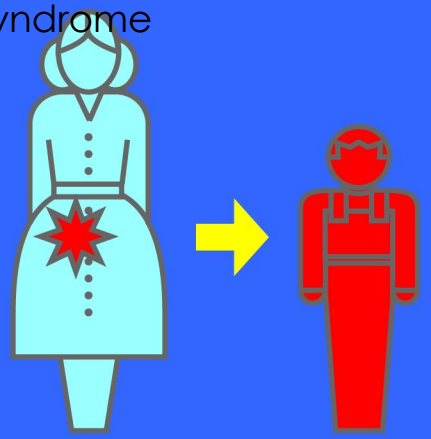


Somatic mutation (e.g., breast)

Nonheritable

Germline mutations

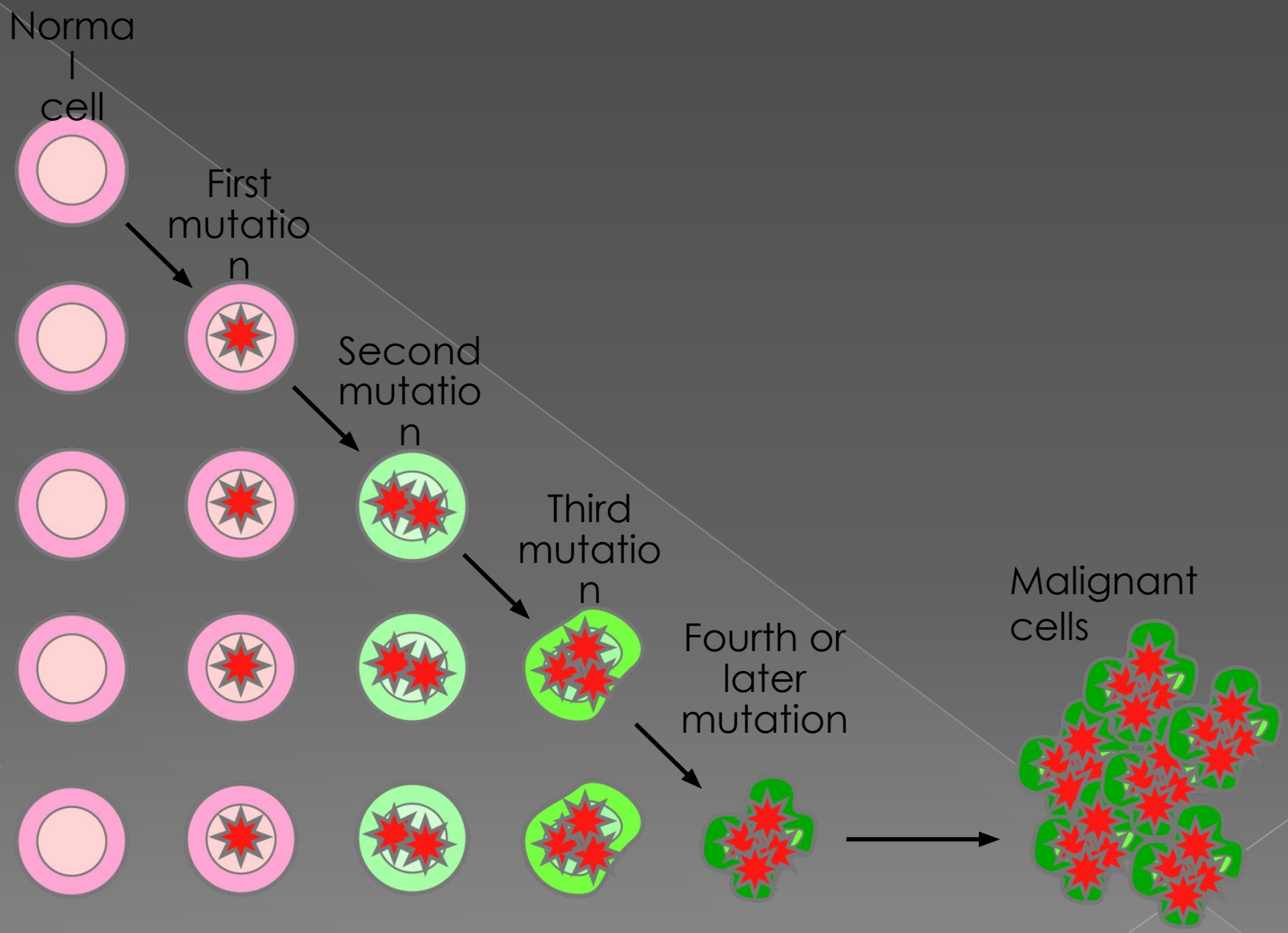
- Present in egg or sperm
- Are heritable
- Cause cancer family syndrome



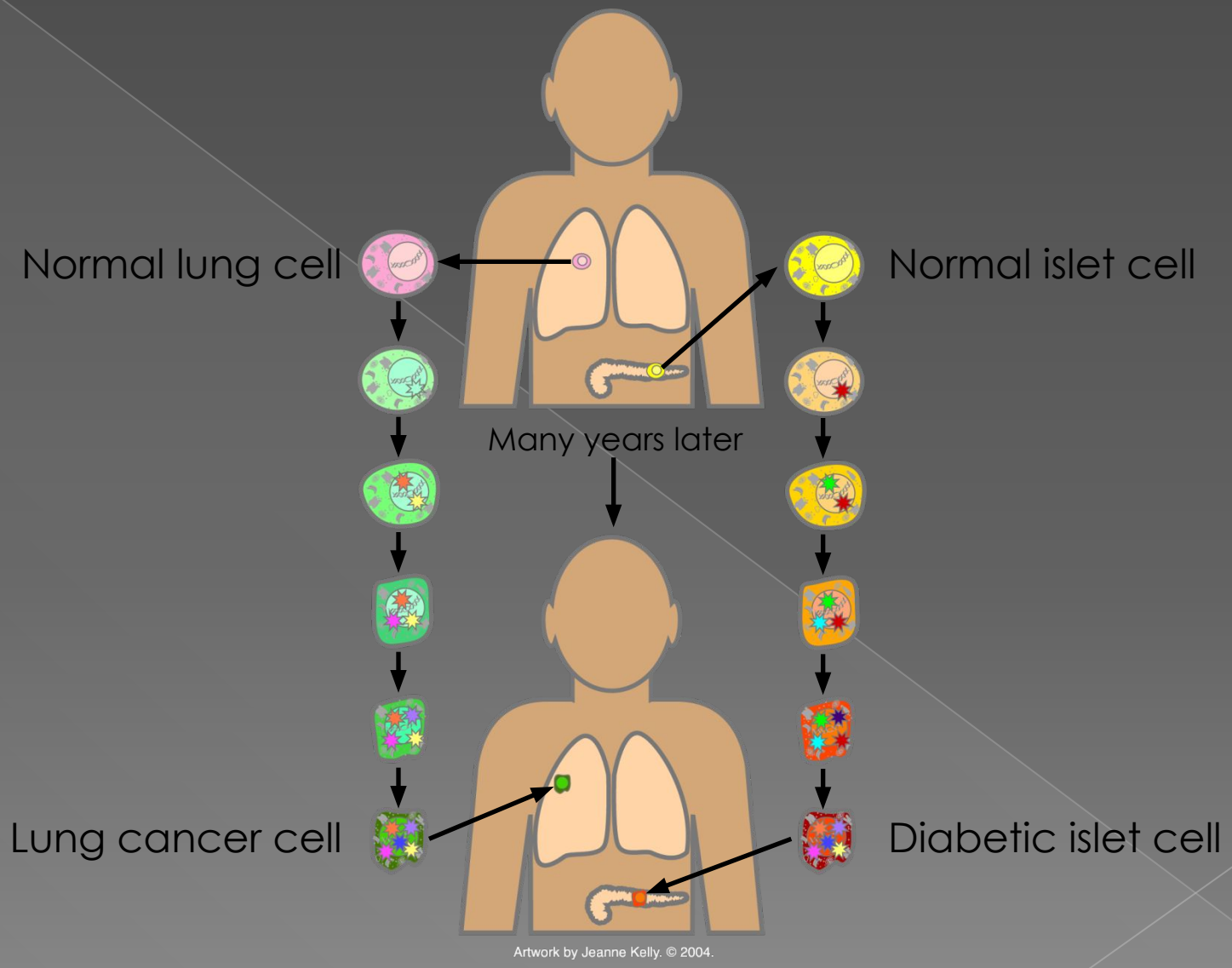
Mutation in egg or sperm

All cells affected in offspring

Tumors Are Clonal

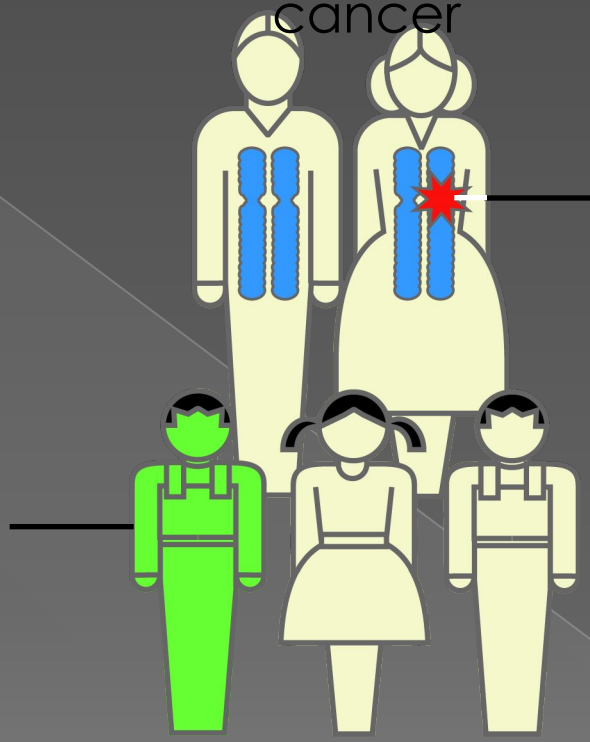


Somatic Mutations



De Novo Mutations

No family history of hereditary cancer



De novo mutations common in:

Familial adenomatous polyposis	30%
Multiple endocrine neoplasia 2B	50%
Hereditary retinoblastoma	50%

теория двойного удара или двойной мутации

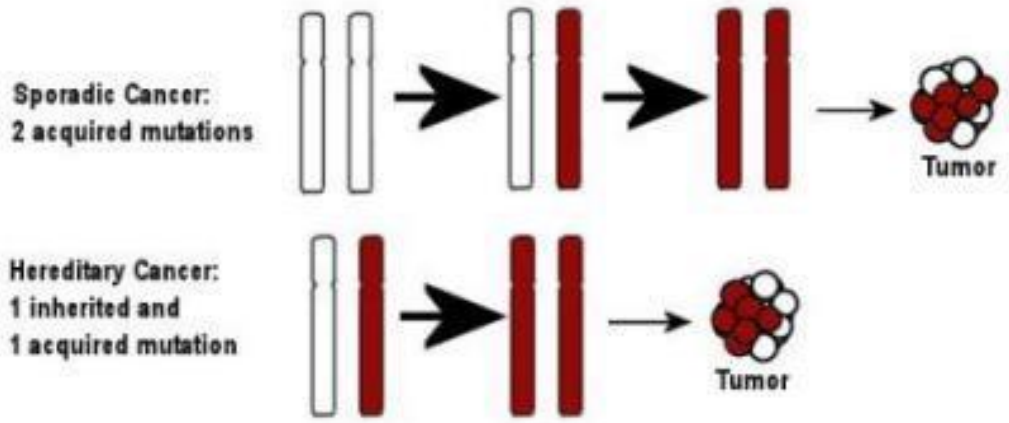
- В 1971 году Альфред Кнудсон предложил гипотезу, известную сейчас как теория двойного удара или двойной мутации, объясняющую механизм возникновения наследственной и спорадической форм ретинобластомы — злокачественной опухоли сетчатки глаза.
- для возникновения опухоли в клетке должны произойти две последовательные мутации. В случае наследственной ретинобластомы первая мутация происходит в клетках зародышевой линии (наследственная мутация), а вторая мутация (второй удар) — в соматических. Спорадическая ретинобластома встречается реже и является результатом двух мутаций в соматической клетке. Вероятность того, что в одной клетке произойдёт две последовательные мутации, невелика, поэтому спорадическая ретинобластома встречается реже, чем наследственная, опухоли при этом формируются позже и в меньшем количестве

Two-hit theory of carcinogenesis (Knudson hypothesis)

- A cell can initiate a tumor only when it contains TWO mutant alleles
- A person who inherits a mutant allele must experience a second somatic mutation to initiate tumorigenesis
- Persons with inherited mutations frequently develop cancer in more than one site

Knudson's 2-Hit Hypothesis

Gene Mutations May be Inherited or Acquired During a Person's Life



- ОНКОГЕН — это ген, продукт которого может стимулировать образование злокачественной опухоли. Мутации, вызывающие активацию онкогенов, повышают шанс того, что клетка превратится в раковую клетку.
- гены-супрессоры опухолей (ГСО) предохраняют клетки от ракового перерождения
- рак возникает либо в случае нарушения работы генов-супрессоров опухолей, либо при появлении онкогенов

- Протоонкоген — это обычный ген, который может стать онкогеном из-за мутаций или повышения экспрессии. Многие протоонкогены кодируют белки, которые регулируют клеточный рост и дифференцировку. Протоонкогены часто вовлечены в пути передачи сигнала и в регуляцию митоза, обычно через свои белковые продукты. После активации (которая происходит из-за мутации самого протоонкогена или других генов) протоонкоген становится онкогеном и может вызвать опухоль.

- Примерами продуктов протоонкогенов являются белки, вовлеченных в сигнальные пути — белок RAS, а также белки WNT, Myc, ERK и TRK.

- Протоонкоген может стать онкогеном путем относительно незначительной модификации его естественной функции.

три основных пути активации:

1. Мутация внутри протоонкогена, которая меняет структуру белка и
- повышает активность белка (фермента)

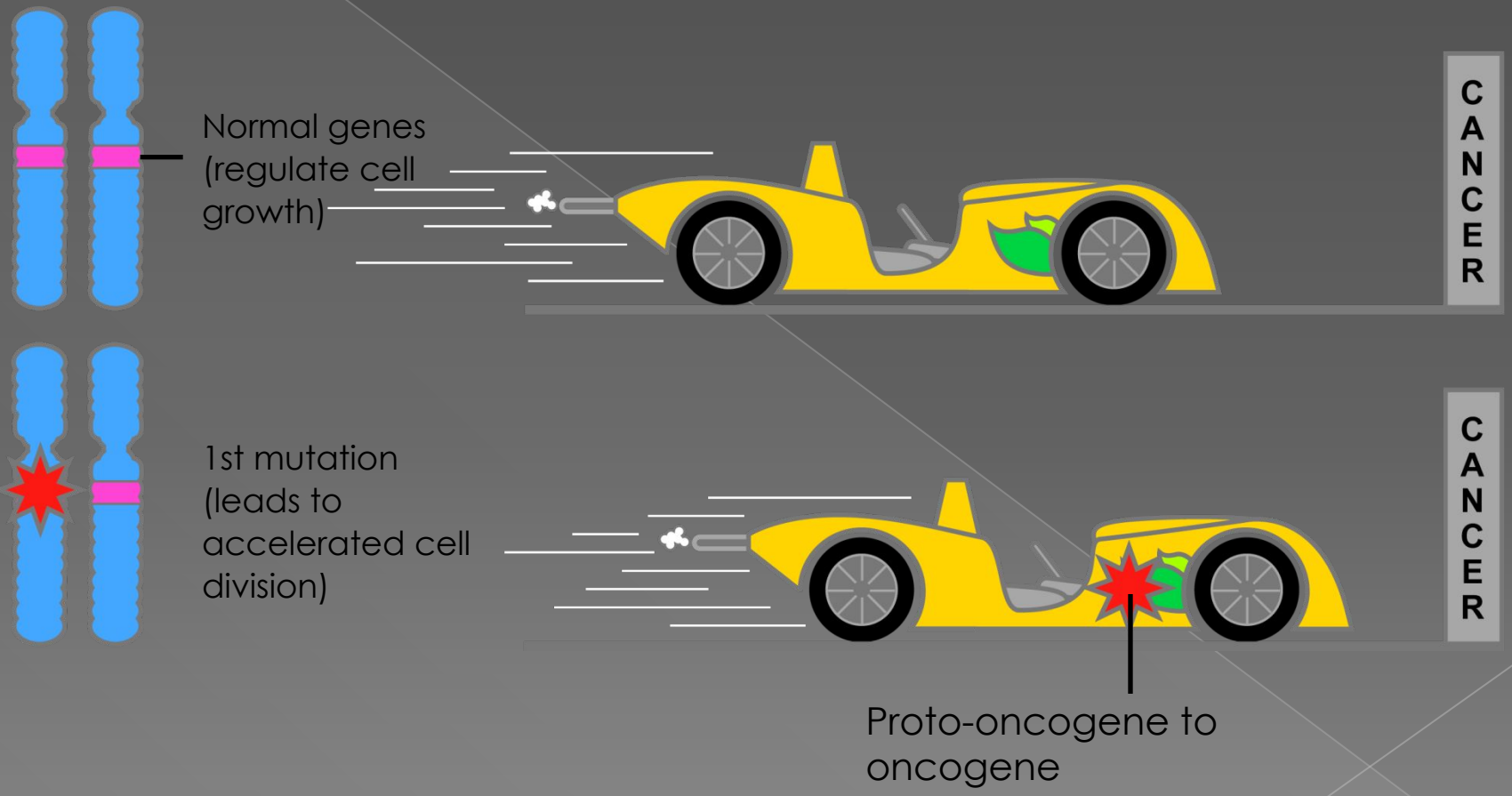
  при этом утрачивается регуляция экспрессии соответствующего гена

2. Повышение концентрации белка путем
- повышения экспрессии гена (нарушение регуляции экспрессии)
- повышение стабильности белка, увеличение периода полужизни и, соответственно, активности в клетке
- дупликация гена (хромосомная перестройка), в результате чего повышается концентрация белка в клетке

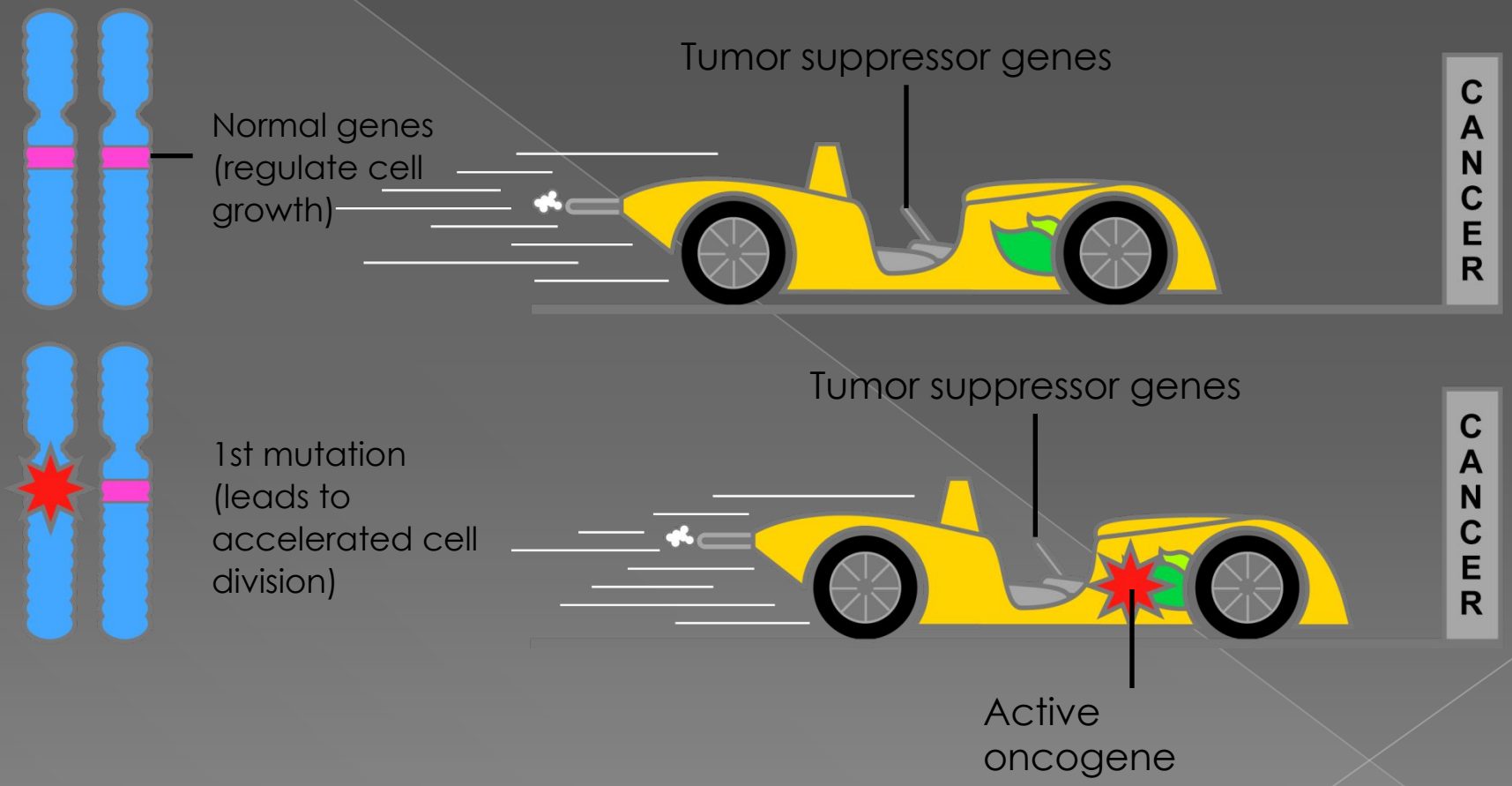
3.Транслокация (хромосомная перестройка), которая вызывает
- повышение экспрессии гена в нетипичных клетках или в нетипичное время
- экспрессия постоянно активного гибридного белка. Такой тип перестройки в делящихся стволовых клетках костного мозга приводит к лейкемии у взрослых.

Мутации в микроРНК могут также приводить к активации онкогенов Исследования показали, что малые молекулы РНК длиной 21-25 нуклеотидов, называемые микроРНК, контролируют экспрессию генов путем понижения их активности. Антисмысловые мРНК могут теоретически быть использованы для блокировки действия онкогенов.

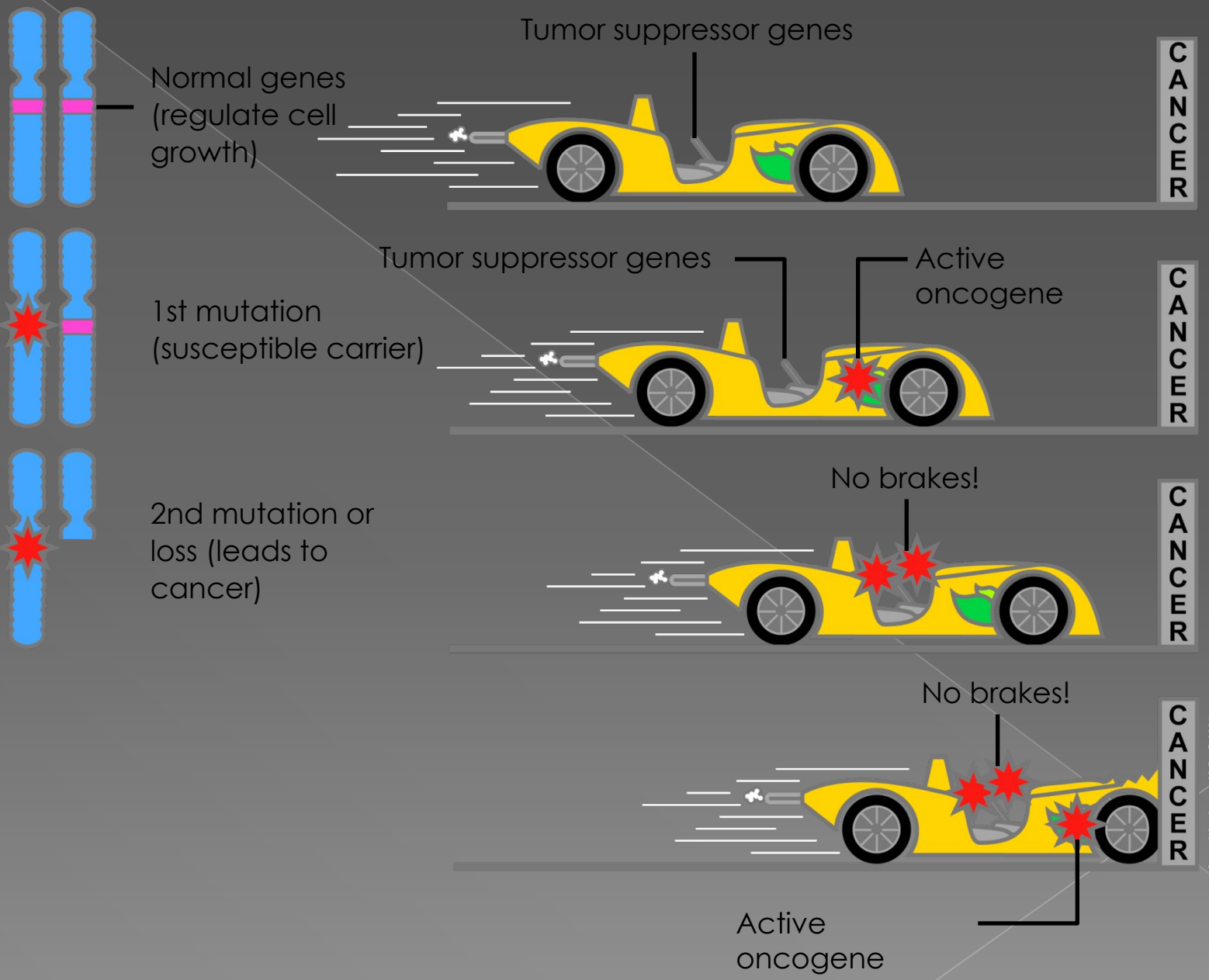
Abnormal Cell Growth: Oncogenes



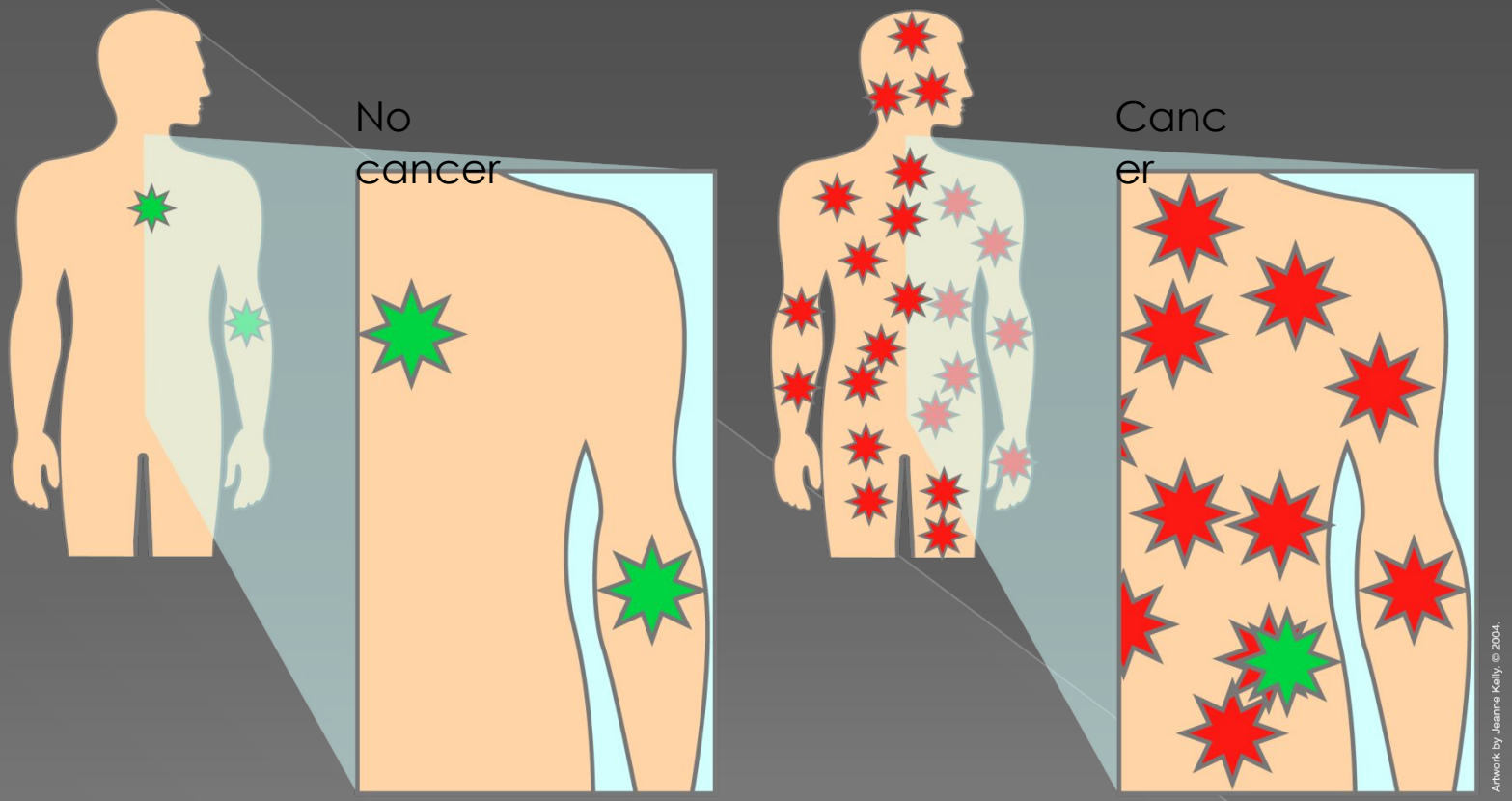
Tumor Suppressor Genes



Mutations in Tumor Suppressor Genes



Two-Hit Hypothesis

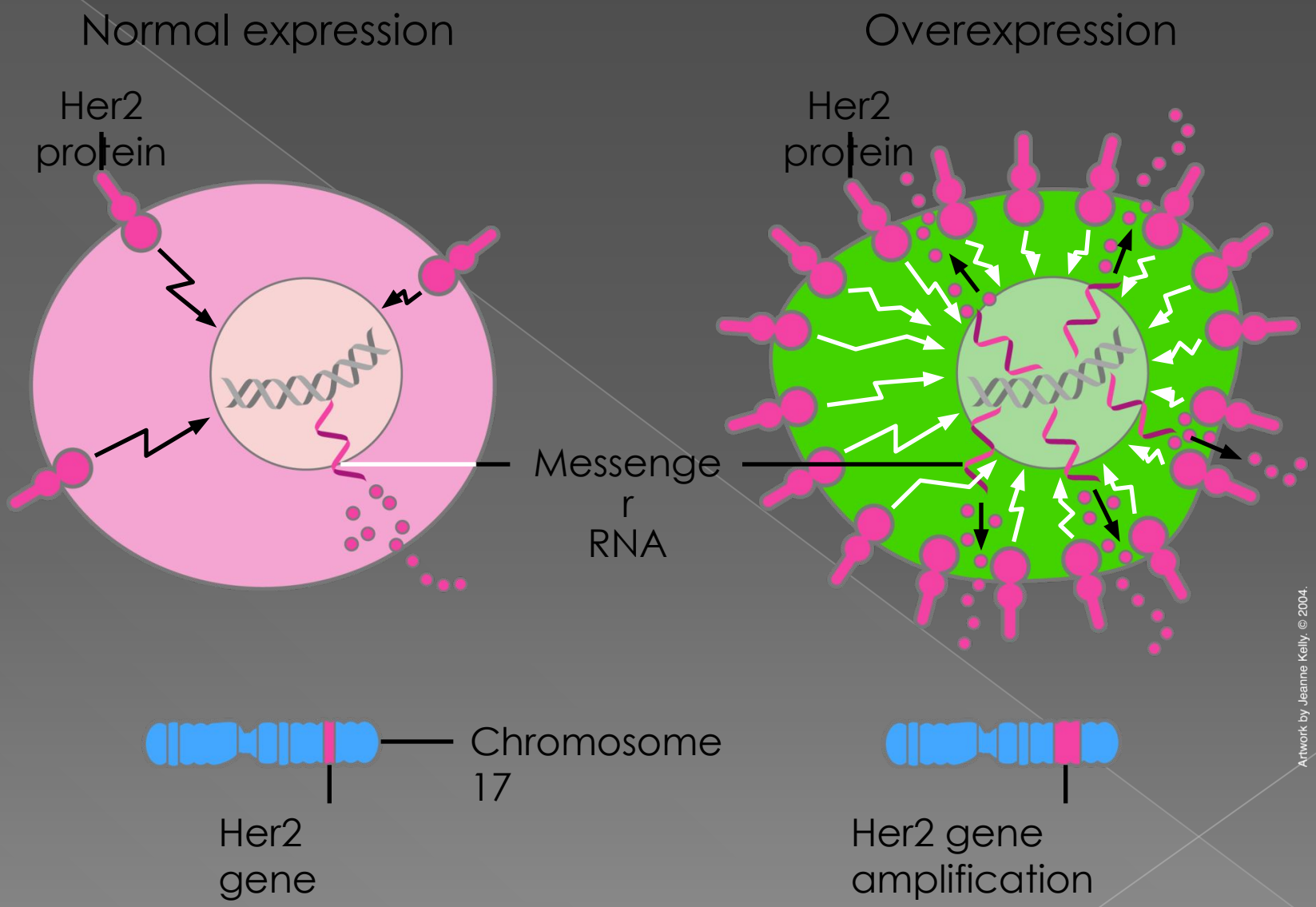


Germline mutation

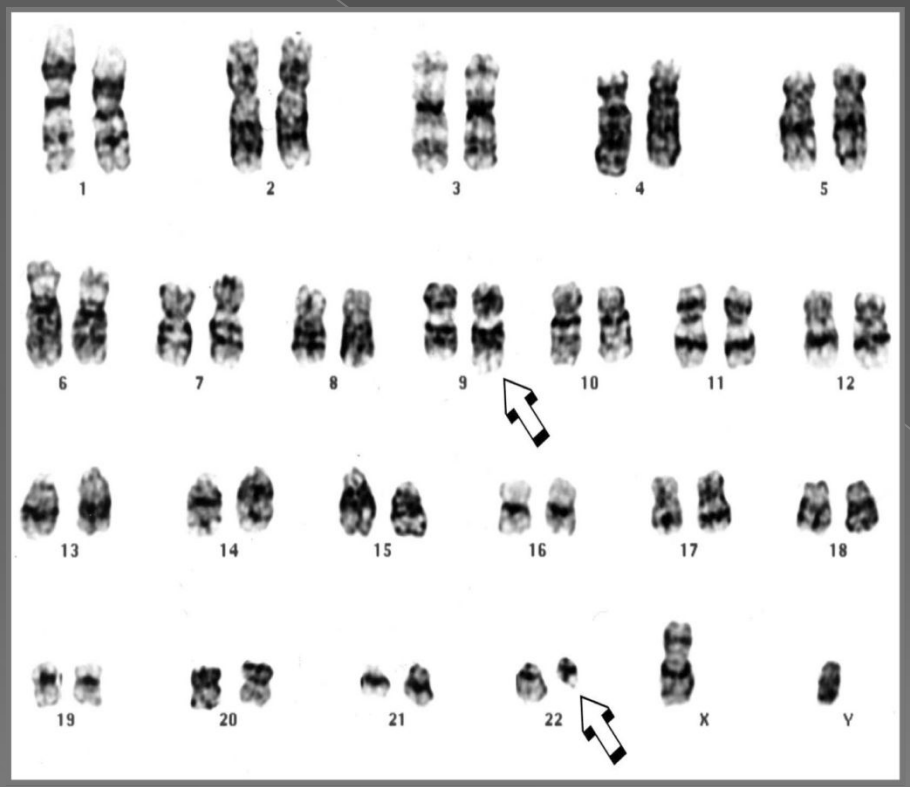
Somatic mutation

If first hit is a germline mutation, second somatic mutation more likely to enable cancer

Regulatory Mutations



Translocation of *Bcr-Abl* Genes



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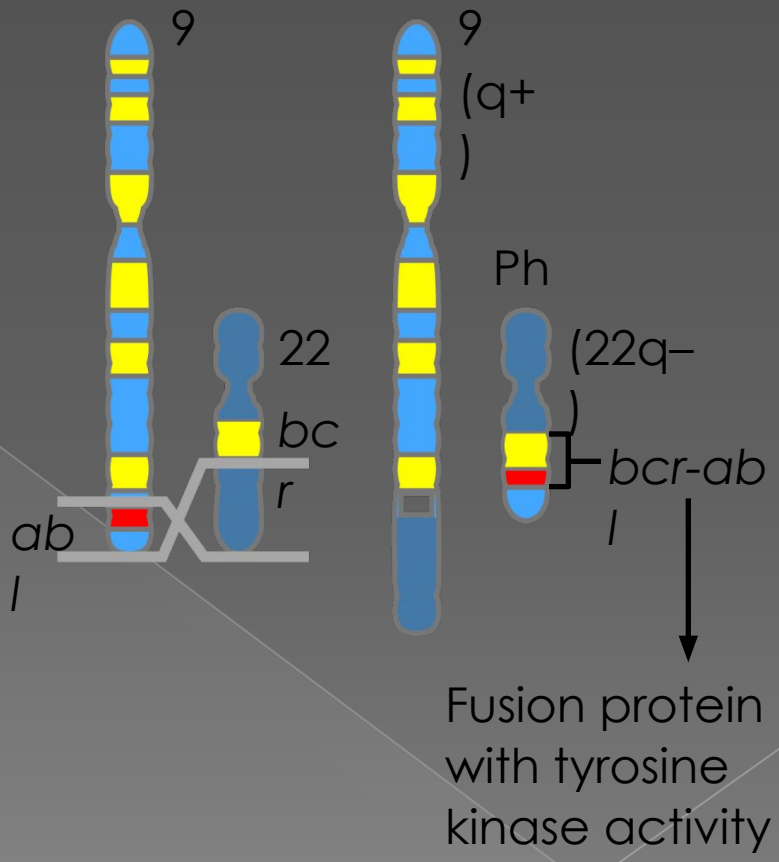
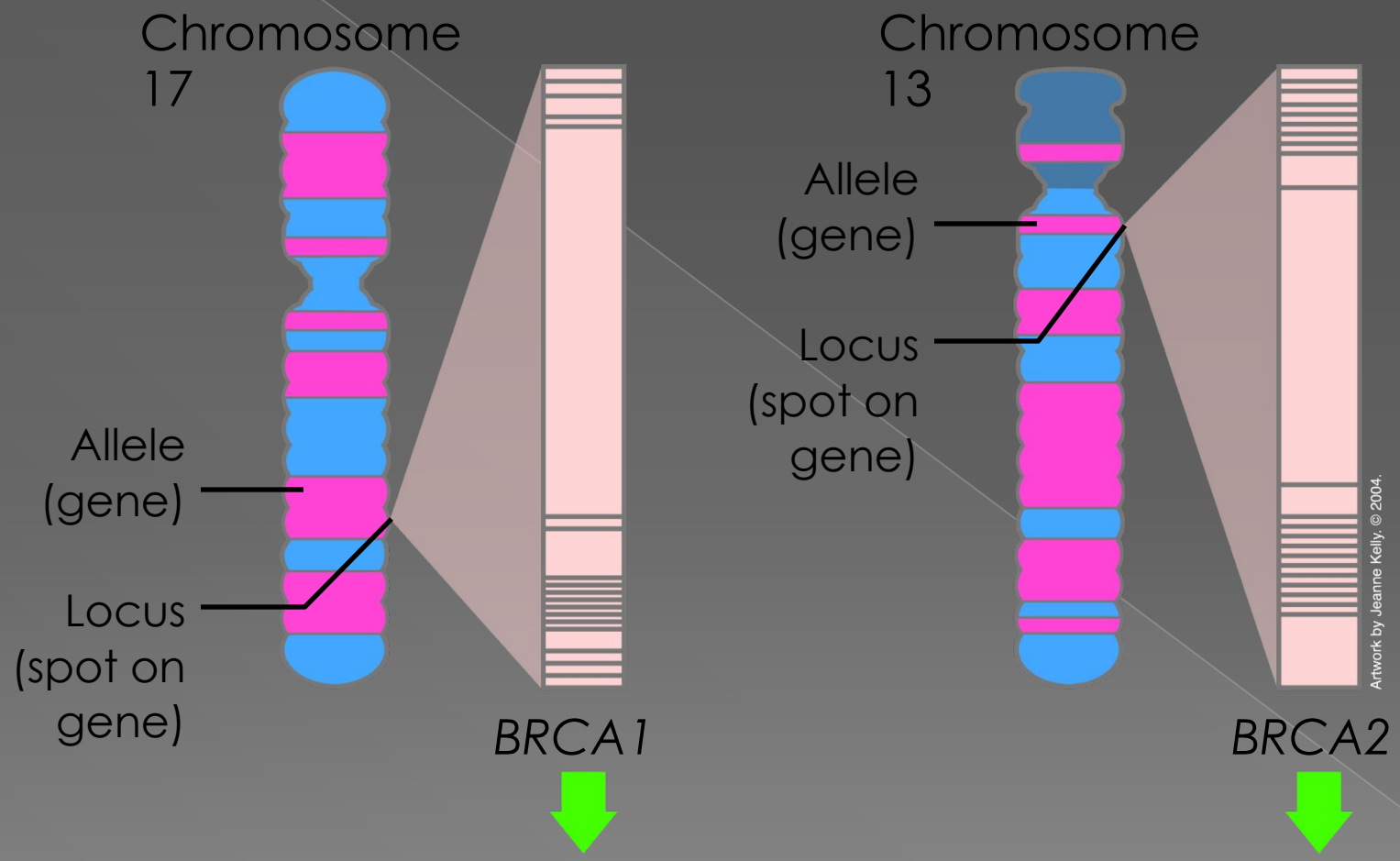


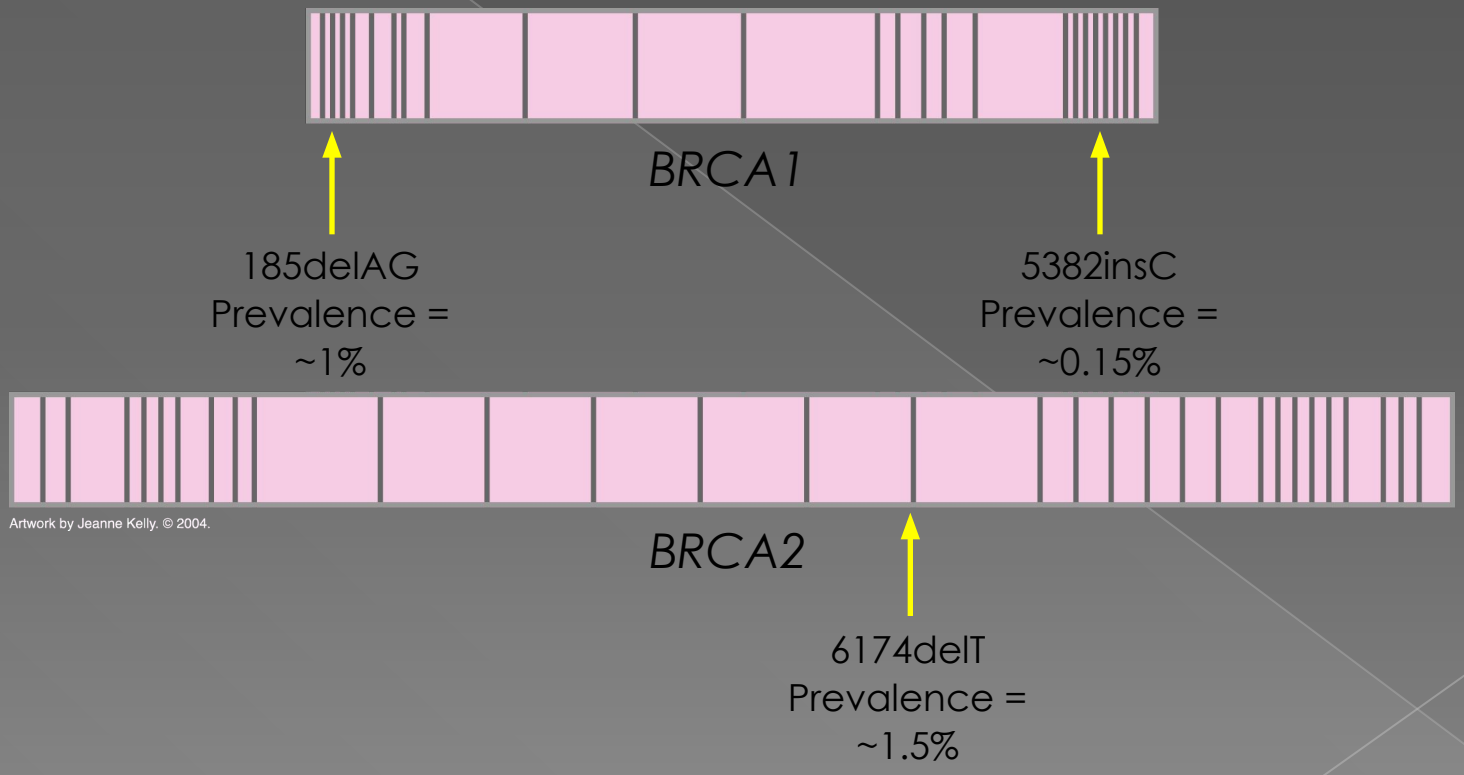
Different Locus, Different Allele, Same Phenotype



Hereditary breast and ovarian cancer

Founder Effect in Ashkenazi Jewish Population

An estimated 1 in 40 Ashkenazi Jews carries a *BRCA1* or *BRCA2* mutation



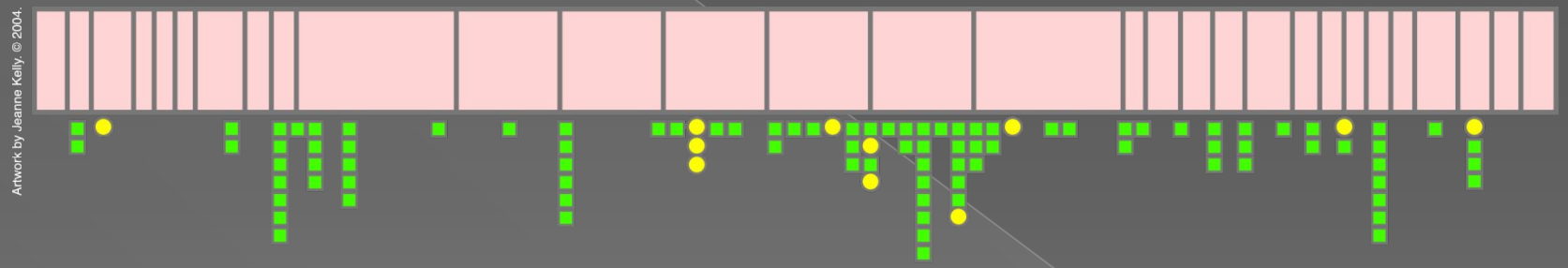
Mutations in Cancer Susceptibility Genes: *BRCA1*

- On chromosome 17
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~500 different mutations reported

- Nonsense/Frameshift
- Missense
- Splice-site

Mutations in Cancer Susceptibility Genes: *BRCA2*

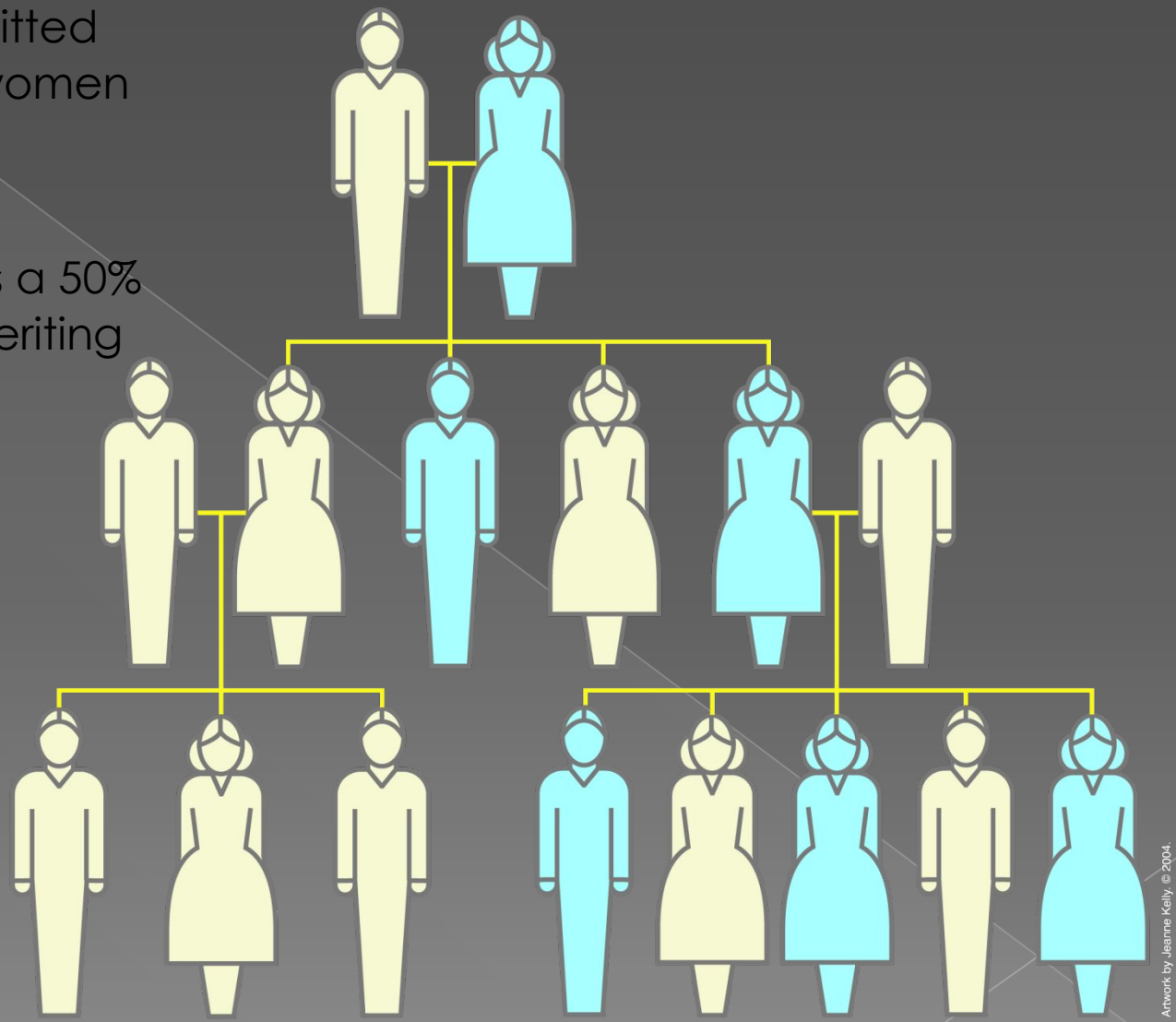
- On chromosome 13
- Autosomal dominant transmission
- Protein has role in genomic stability
- ~300 different mutations reported



- Nonsense/Frameshift
- Missense

Autosomal Dominant Inheritance

- Equally transmitted by men and women
- No skipped generations
- Each child has a 50% chance of inheriting the mutation



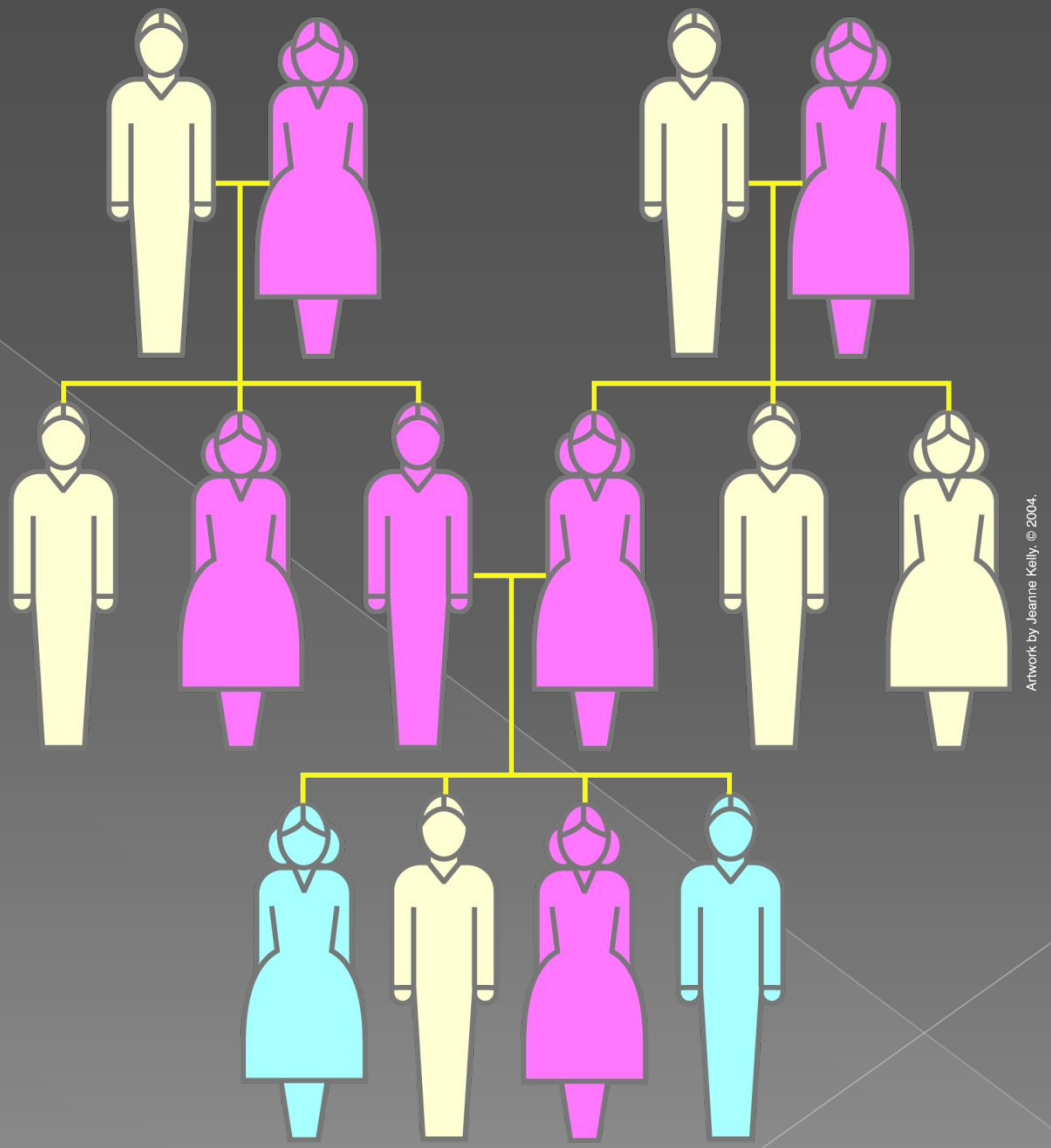
Examples of Dominantly Inherited Cancer Syndromes

Syndrome	Associated Gene
Familial retinoblastoma	*RB1*
Li-Fraumeni	*TP53* (p53 protein)
Familial adenomatous polyposis	*APC*
Hereditary nonpolyposis colorectal cancer	*MLH1, MSH2, MSH6 PMS1, PMS2*
Wilms' tumor	*WT1*
Breast and ovarian cancer	*BRCA1, BRCA2*
von Hippel-Lindau	*VHL*
Cowden	*PTEN*

Autosomal Recessive Inheritance

Two germline mutations (one from each parent)
to develop disease

Equally transmitted by men and women



Nonaffected carrier

Noncarrier

Affected carrier

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*

Other Genetic Conditions Linked to Increased Cancer Risk

Syndrome	Gene Mutation
Li-Fraumeni	*TP53*
Cowden	*PTEN*
Muir-Torre	*MSH2* *MLH1*
Peutz-Jeghers	*STK11*

Repair Failure

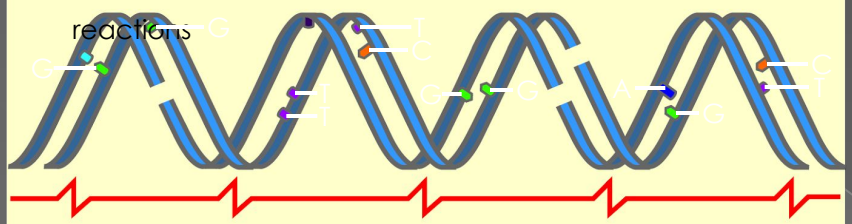
Damaging Agent

X-rays
Oxygen radicals
Alkylating agents
Spontaneous reactions

UV light
Polycyclic aromatic hydrocarbons

X-rays
Anti-tumor agents (*cis*-Pt, MMC)

Replication errors



Uracil
Abasic site
B-oxoguanine
Single-strand break

(6-4)PP
Bulky adduct
CPD

Interstrand cross-link
Double-strand break

A-G mismatch
T-C mismatch
Insertion
Deletion

Base-excision repair (BER)

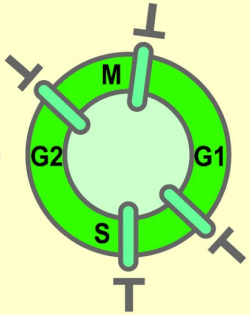
Nucleotide-excision repair (NER)

Recombinational repair (HR, EJ)

Mismatch Repair

Repair Process

Consequences



(Transient) cell cycle arrest

Inhibition of:
–Transcription
–Replication
–Chromosome replication

Apoptosis (cell death)

Mutations
Chromosome aberrations

Cancer
Aging
Inborn disease

Hoeijmakers JH. *Nature*. 2001;411:366.

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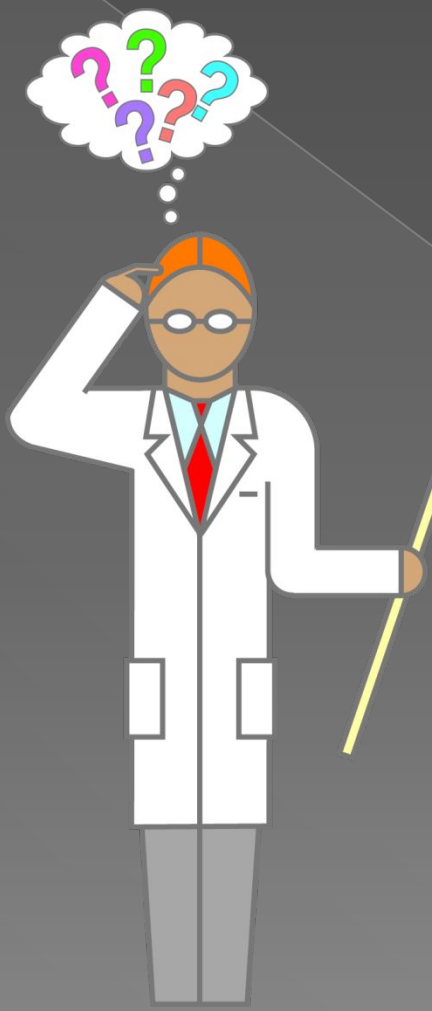
Cancer Susceptibility: Much Still Unknown



Who Gets Breast Cancer?

- 5-10 percent cases have BRCA1/BRCA2 mutations
- 10-20 percent cases have family history, no BRCA1/BRCA2 mutations
- Most cases have no BRCA1/BRCA2 mutations. Family clusters of cases persist.

How do people know if they should consider genetic testing for BRCA1 and BRCA2 mutations?

- For women who are not of Ashkenazi Jewish descent:
- two first-degree relatives (mother, daughter, or sister) diagnosed with breast cancer, one of whom was diagnosed at age 50 or younger;
- three or more first-degree or second-degree (grandmother or aunt) relatives diagnosed with breast cancer regardless of their age at diagnosis;
- a combination of first- and second-degree relatives diagnosed with breast cancer and ovarian cancer (one cancer type per person);
- a first-degree relative with cancer diagnosed in both breasts (bilateral breast cancer);
- a combination of two or more first- or second-degree relatives diagnosed with ovarian cancer regardless of age at diagnosis;
- a first- or second-degree relative diagnosed with both breast and ovarian cancer regardless of age at diagnosis; and
- breast cancer diagnosed in a male relative.

- For women of Ashkenazi Jewish descent:
- any first-degree relative diagnosed with breast or ovarian cancer; and
- two second-degree relatives on the same side of the family diagnosed with breast or ovarian cancer.

- These family history patterns apply to about 2 percent of adult women in the general population. Women who have none of these family history patterns have a low probability of having a harmful BRCA1 or BRCA2 mutation.

Li-Fraumeni Syndrome

- Li-Fraumeni Syndrome (LFS) was first described in 1969 by Drs. Frederick Li and Joseph F. Fraumeni, Jr., who were working at the NCI. Their study identified four families with sarcomas, breast cancer, brain tumors, and leukemia, many of which were diagnosed at much younger-than-usual ages. Additional studies showed that other tumors, including cancers of the adrenal cortex, gastrointestinal tract, lung, and non-Hodgkin lymphoma, also occurred more often than expected in these families.

Classic Li-Fraumeni Syndrome (LFS):

Three features must be present in a family to fit the classic LFS criteria. Often more than 3 family members have had cancers.

- A person with a sarcoma diagnosed under the age of 45; AND
- At least one first-degree relative (meaning parents, brothers, sisters and children) with a cancer of any kind diagnosed under the age of 45; AND
- A third family member who is either a first- or second-degree relative (such as grandparents, aunts, uncles, nieces, nephews, and grandchildren) with cancer diagnosed under the age of 45, or having a sarcoma at any age

Li-Fraumeni-Like Syndrome (LFL):

- A person with any childhood cancer or sarcoma, brain tumor, or adrenal cortical tumor diagnosed under the age of 45 AND
- A first- or second-degree relative with a typical LFS cancer (soft tissue and bone sarcomas, brain tumors, breast cancer, adrenocortical carcinomas, leukemia, and many others) at any age AND
- An additional first- or second-degree relative with any cancer diagnosed under the age of 60.

What Causes LFS?

- Changes in a "tumor suppressor" gene called "TP53" were discovered in 1990 as the most common cause of LFS. Everyone has two copies of the TP53 gene – one inherited from the mother, the other from the father – in every cell of their body. This gene is very important for the normal growth, function, and division of cells. The gene causes cells that are damaged beyond repair to die, a process that stops damaged cells from becoming cancerous. If there is a change (or mutation) in TP53, the gene fails to work properly and cancer may develop. The kind of cancer that develops depends on where in the body the abnormal cell is located. The fact that TP53 is so important to the normal functioning of most cells in the body may explain why so many different kinds of cancer occur in LFS.

- About 7 out of every 10 patients (or 70%) with classic LFS, and 4 out of every 10 (40%) of patients with LFL, have a detectable change in the TP53 gene. We don't yet fully understand what causes LFS in families that do not have a TP53 mutation, but there are several ideas. For example there could be an unusual mutation in TP53 that is not easily found by the usual testing methods. Or there may be other genes which have not yet been identified, that can cause LFS.

Risk of Cancer in Patients with LFS

- The lifetime risk of cancer – all types combined - in a person who carries a TP53 mutation ranges from 70% to 90% by age 70. Women with LFS have a higher lifetime cancer risk than men with LFS, most likely due to the high risk of female breast cancer. The lifetime cancer risk for women reaches almost 100%. At present, we cannot predict which individual with a TP53 mutation will eventually develop cancer and, if they do develop cancer, which type and when.

- If a family member has a known mutation in the TP53 gene, genetic testing can identify other family members with the same mutation who would also be at high cancer risk. For those at high risk, early cancer detection and risk reduction strategies are desirable, but not yet standardized. Currently, management recommendations are based on our best clinical judgment.

- For now, in persons with a TP53 gene mutation, we can try to find cancers as early as possible (a process called screening) in the hope that finding cancer early will lead to more successful treatment.

Cowden syndrome

mutations in the PTEN gene

- Cowden syndrome is a disorder characterized by multiple noncancerous, tumor-like growths called hamartomas and an increased risk of developing certain cancers.

Cowden syndrome

mutations in the PTEN gene (TSG)

- Cowden syndrome is associated with an increased risk of developing several types of cancer, particularly cancers of the breast, thyroid, and the lining of the uterus (the endometrium).
- Other cancers that have been identified in people with Cowden syndrome include colorectal cancer, kidney cancer, and melanoma. Compared with the general population, people with Cowden syndrome develop these cancers at younger ages, often beginning in their thirties or forties. Other diseases of the breast, thyroid, and endometrium are also common in Cowden syndrome. Additional signs and symptoms can include an enlarged head (macrocephaly) and a rare, noncancerous brain tumor called Lhermitte-Duclos disease.

Что такое ОНКОГЕН ?

- 1.ген, стимулирующий образование опухоли
- 2. гены, предохраняющие клетки от ракового перерождения
- 3. ген, продукт которого может стимулировать образование злокачественной опухоли

Рак груди встречается при следующих генетических синдромах, кроме:

1. BRCA-1/2 мутация
2. Cowden syndrom
3. Li-Fraumeni syndrom
4. Все верно