Ciências ULisboa

REPÚBLICA PORTUGUESA
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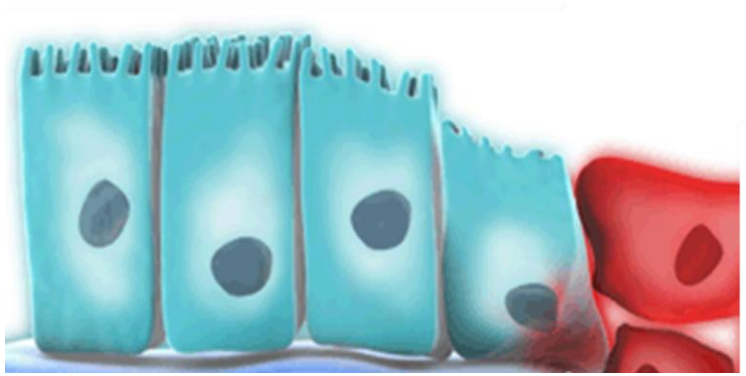
Instituto_Nacional de Saúde Doutor Ricardo Jorge



Oncobiology

Margarida Gama-Carvalho (DQB/FCUL) and Peter Jordan (INSA)

Hereditary and familial forms of cancer

Lecture 1- Some take-home concepts

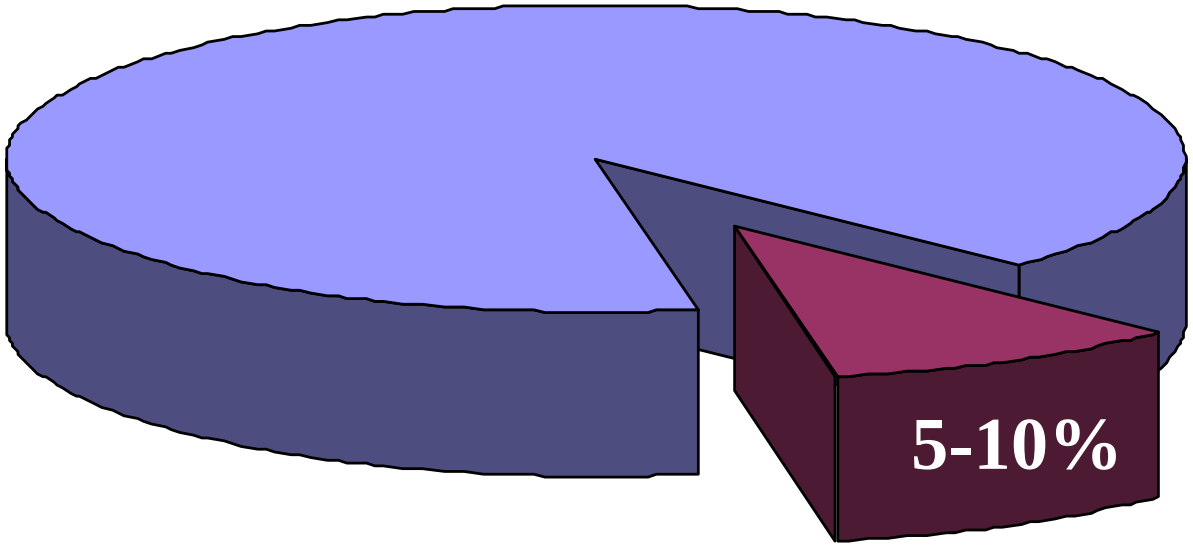
- **Cancer is a disease of uncontrolled growth of our own cells following their genetic transformation**
- **Infection with microbes, viruses or parasites can promote the formation of certain tumour types**
- **Cancer cells display several hallmark properties**

- **Tumours develop slowly over decades and cells accumulate genetic changes through clonal selection**
- **Cells with a tumour-initiating mutation often require tumour-promoting stimuli for malignant progression**
- **The local microenvironment has an important role in tumour promotion**

- **Cancer types differ in Incidence and Mortality rates**
- **Epidemiologic studies of migrant populations highlight the role of environmental and life-style factors**

CANCER PATIENTS

90-95% sporadic



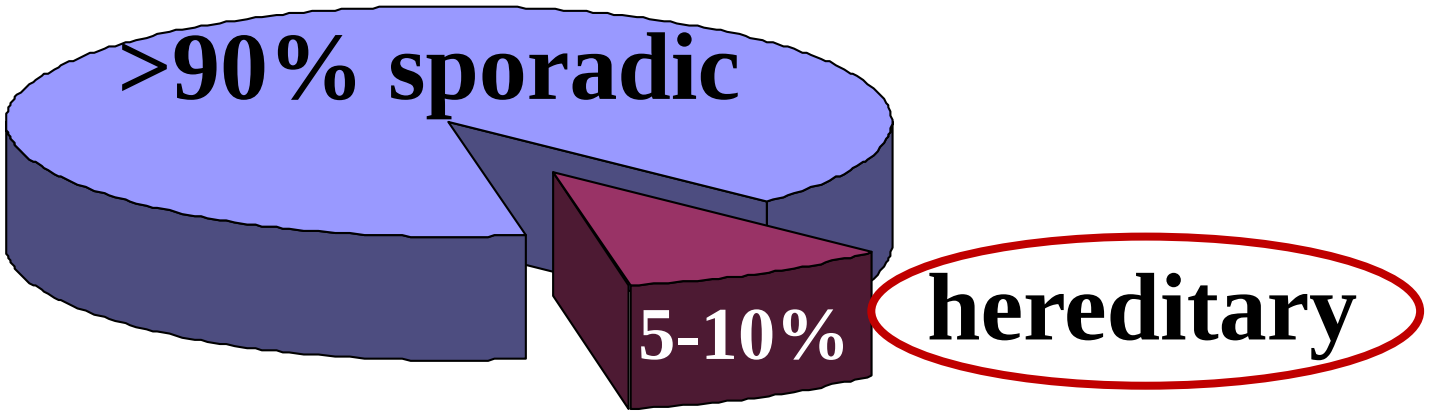
hereditary

Clinical signs of hereditary cancer

- Cases of the same type of cancer occurring in several generations (like grandfather, father, and son) or first-degree relatives;
- Cancers occurring at younger ages than usual (e.g. colon cancer at the age of 20);

- More than one type of cancer in a single person (like a woman with both breast and ovarian cancer);
- Cancers occurring in both of a pair of organs (like both eyes, both kidneys, or both breasts);
- Cancer occurring in the sex not usually affected (like breast cancer in a man)
- Certain rare cancer syndromes

CANCER CASES



Germline mutation in a *tumour suppressor gene*

Most frequent hereditary forms of cancer

…frequently, these TSG are also inactivated during sporadic tumorigenesis

Familial adenomatous polyposis APC	Hereditary non-polyposis colon cancer MMR genes	Hereditary breast and ovarian cancer BRCA	Hereditary diffuse gastric cancer CDH1

Li-Fraumeni syndrome
TP53

….. (more than 50 genes and syndromes)

tumour suppressor genes

control normal cell proliferation

('antigrowth genes')

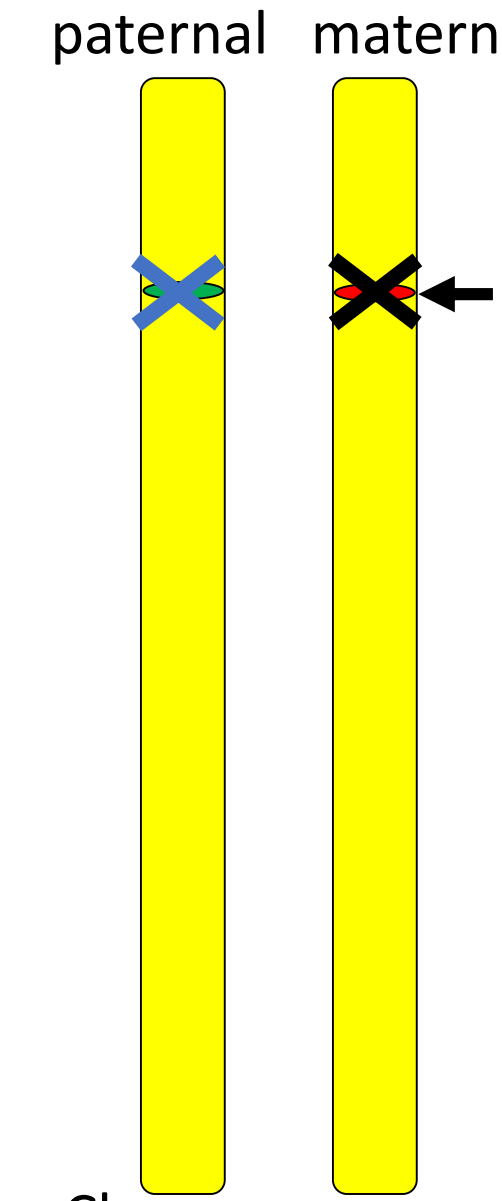
gatekeepers

- Control or suppress cell division
- Promote apoptosis

caretakers

- DNA damage repair

Hereditary cancer



Tumour suppressor gene mutation in the germline

1st copy
is mutated in <u>all</u> cells

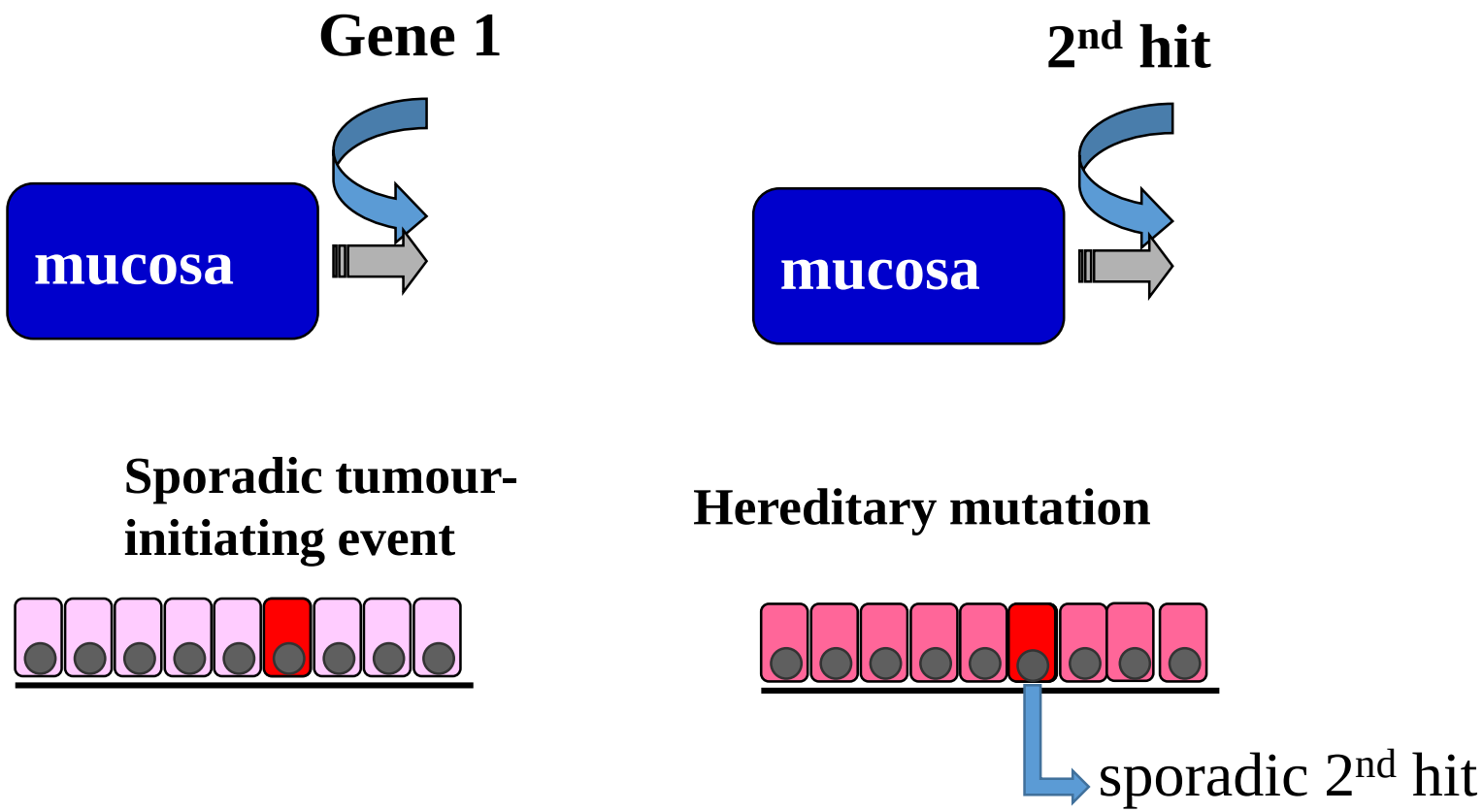
↓ 2nd copy allows embryonic develpoment and infancy

2nd copy becomes inactivated
(*2-hit hypothesis)*
(Alfred Knudson 1971)

↓

Cancer occurs at much younger ages

Sporadic vs hereditary tumorigenesis in the *clonal selection* model



Loss of tumour suppressor genes: molecular mechanisms for the 1st hit

Point Mutation

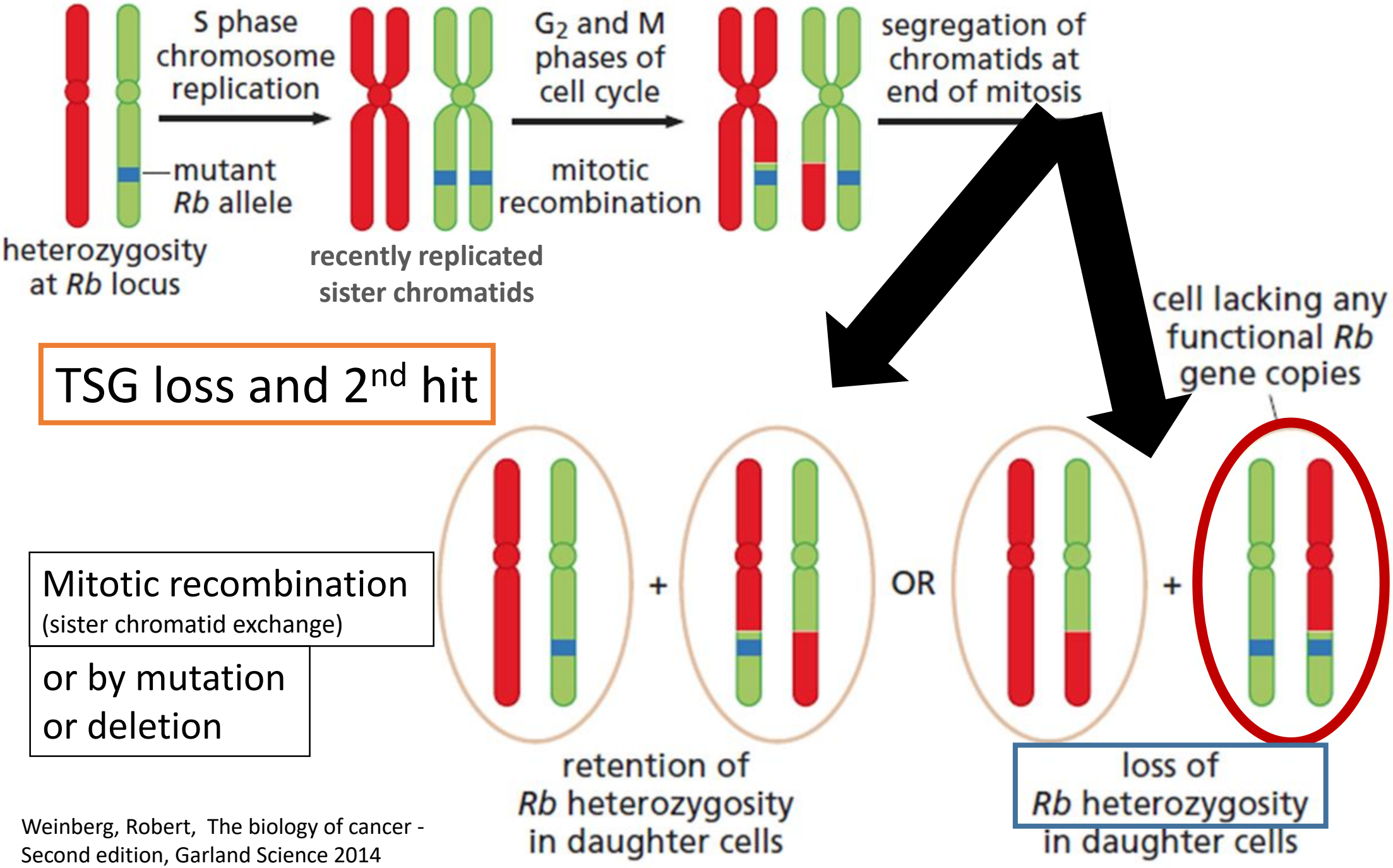
Truncated or non-functional gene product

Deletion

Promoter methylation

mostly in sporadic tumours,
but affecting the same genes

Gene without mutation but silenced



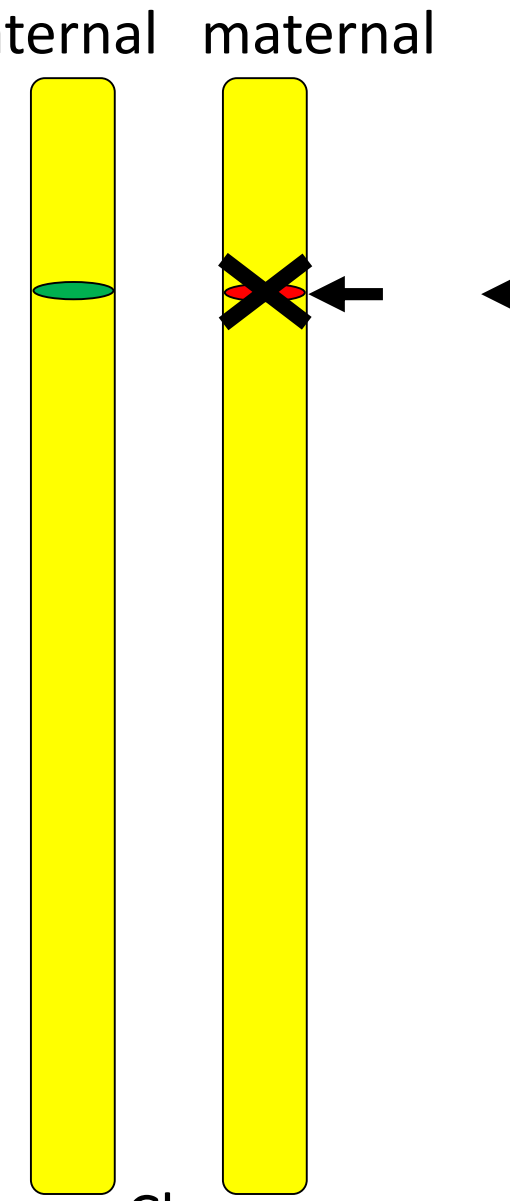
TSG loss and 2nd hit

Mitotic recombination
(sister chromatid exchange)

or by mutation
or deletion

Weinberg, Robert, The biology of cancer - Second edition, Garland Science 2014

Hereditary cancer



tumour suppressor gene in the germline

1st copy
is mutated in all cells

↓

2nd copy becomes
inactivated
(*2-hit hypothesis*)

↓

Cancer occurs at
much younger ages

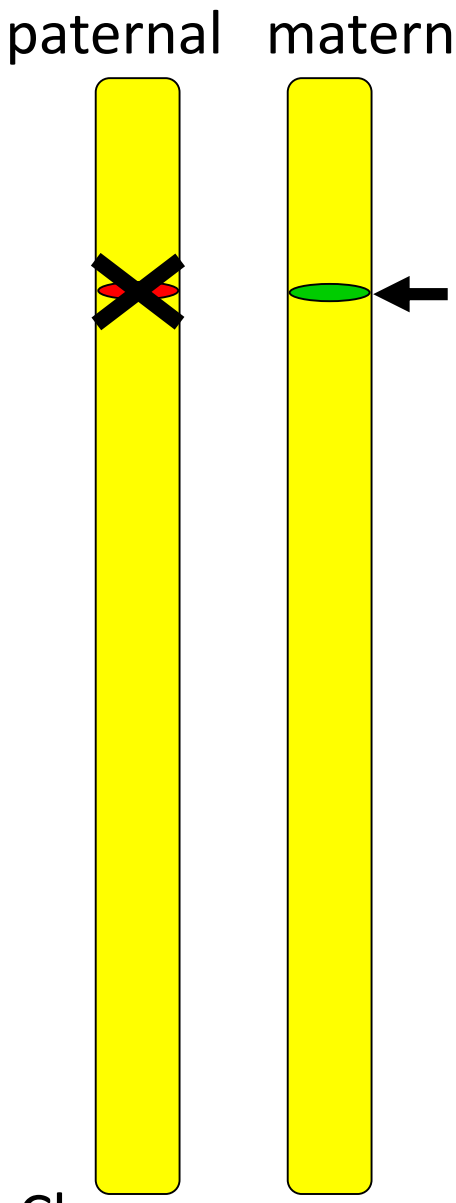
Dominant or Recessive??

Germline mutations may be "dominant" or "recessive".

In **autosomal dominant** diseases, one parent has a normal copy of the gene and a mutated copy; there is a 50-50 chance a child will inherit the mutation and be at risk for the disease.

In **autosomal recessive** diseases, two copies of the mutated gene are required to cause the disease. Each parent has one normal and one mutated allele, but only 25% of their children will inherit two mutated gene copies and be at risk of the disease.

Hereditary cancer



tumour suppressor gene in the germline

1st copy
is mutated in all cells

↓

2nd copy becomes
inactivated
(*2-hit hypothesis*)

↓

Cancer occurs at
much younger ages

heterozygous

Dominant or Recessive??

Usually dominant phenotype, but 2nd copy is lost

Dominant phenotype, however

…not everyone who carries a BRCA mutation develops breast cancer

Germline mutations can vary in their **penetrance**, i.e. the proportion of mutation carriers who will eventually express the disease.

Incomplete penetrance due to:

- type of mutation (may be less aggressive),
- the individual carries protective modifier genes,
- protective environmental or life style factors?

tumour suppressor genes

control normal cell proliferation

('antigrowth genes')

gatekeepers

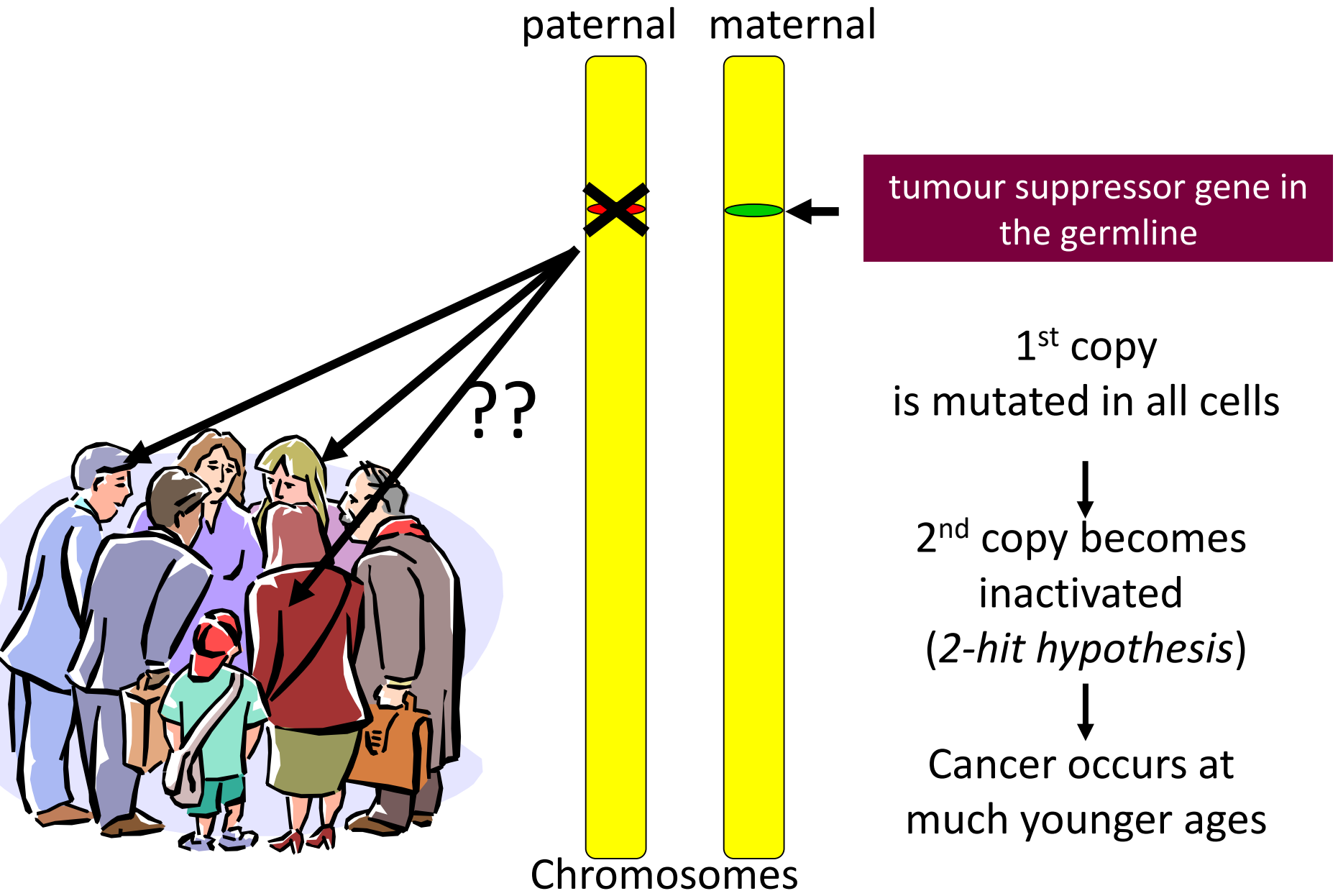
- **Control or suppress cell division**
- **Promote apoptosis**

caretakers

- **DNA damage repair**

can hereditary cancer be caused by germline mutations in *oncogenes*???

Hereditary cancer allows for presymptomatic genetic testing



tumour suppressor gene in the germline

1st copy
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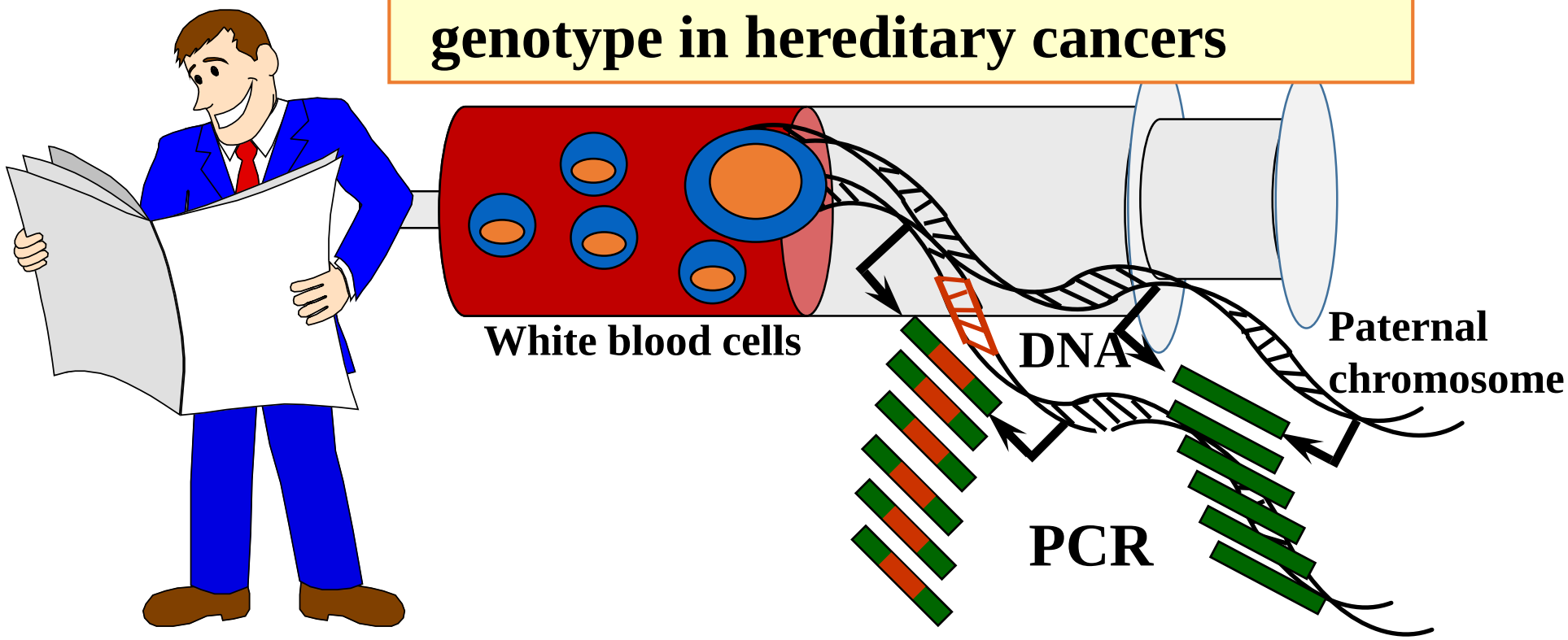
2nd copy becomes
inactivated
(*2-hit hypothesis*)

↓

Cancer occurs at
much younger ages

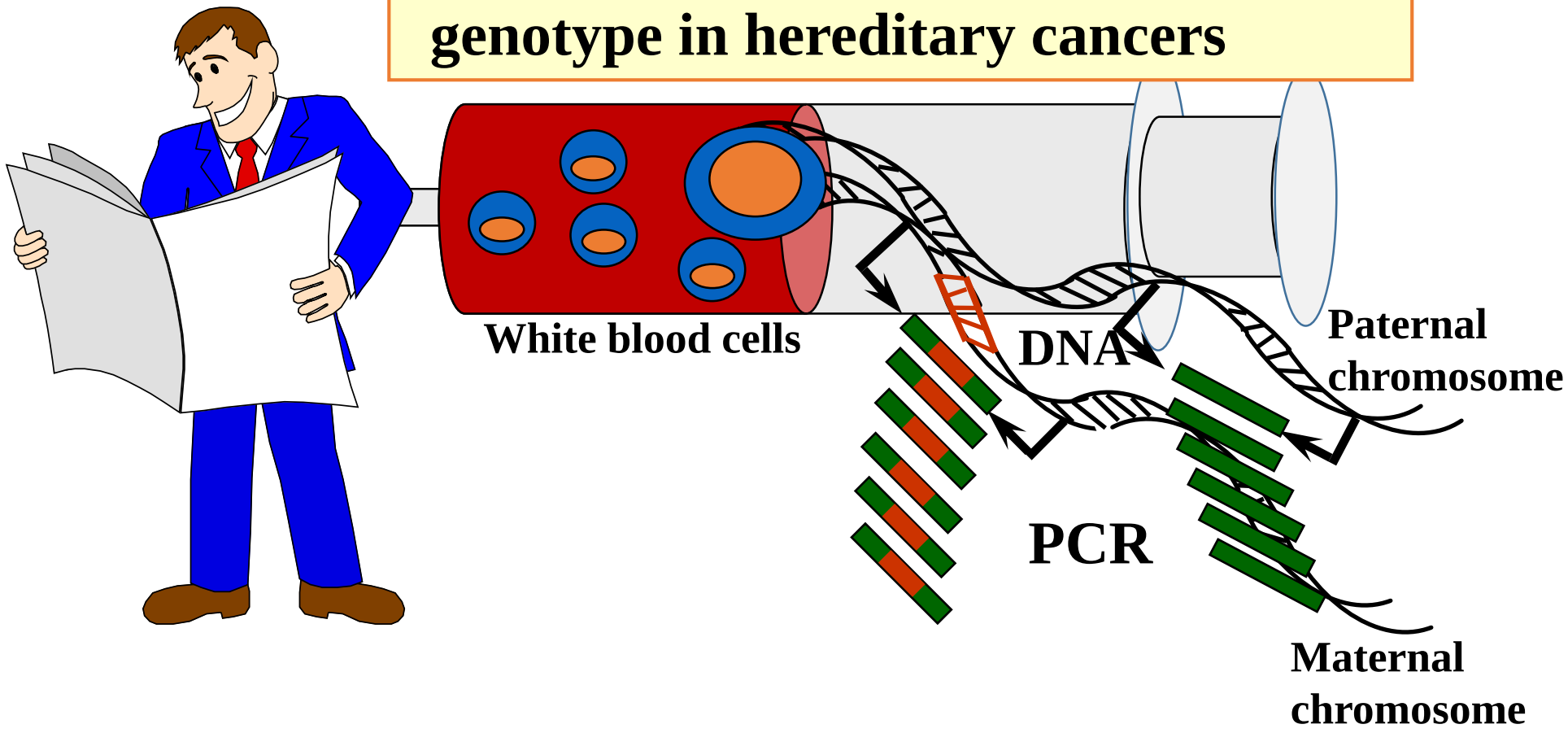
Genetic testing of tumor suppressor genotype in hereditary cancers

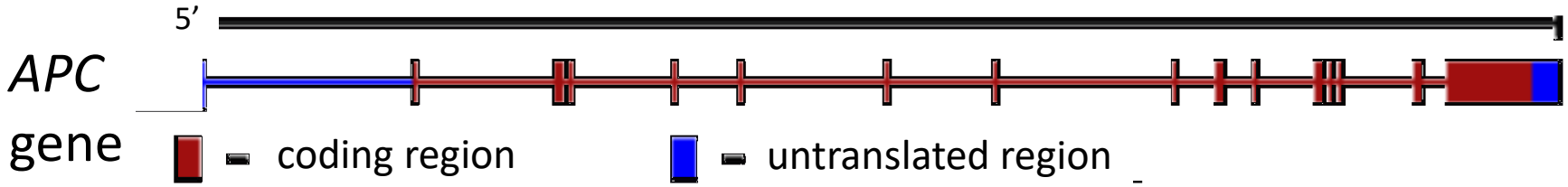


??

DNA sequencing, Mutation ?

Genetic testing of tumor suppressor genotype in hereditary cancers





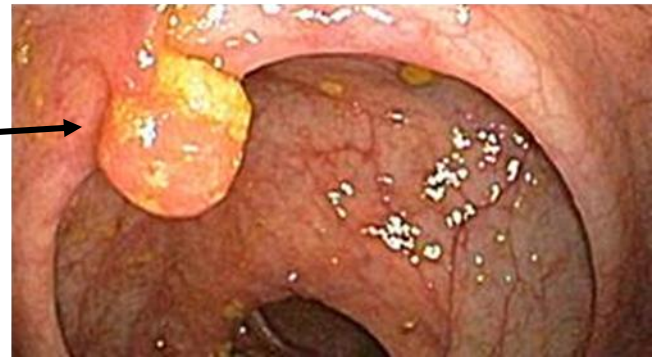
Exon-by-exon versus NGS

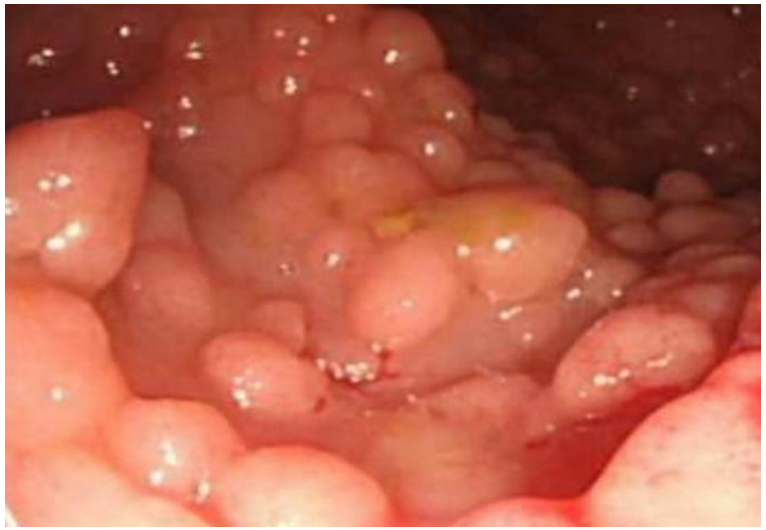
Examples of frequent hereditary cancer syndromes

Example 1: Hereditary colorectal cancer syndromes

Syndrome	Gene	Features
Familial adenomatous polyposis (FAP)	APC	>100 **polyps** (adenomas) in the colon detectable in second decade of life; autosomal dominant inheritance/phenotype

Colonoscopy image of a polyp



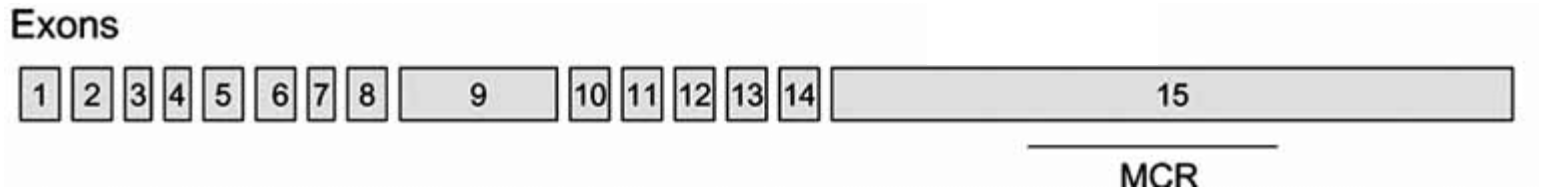


Polyps also initiate the majority of sporadic colon tumours
-> colonoscopic screening programs

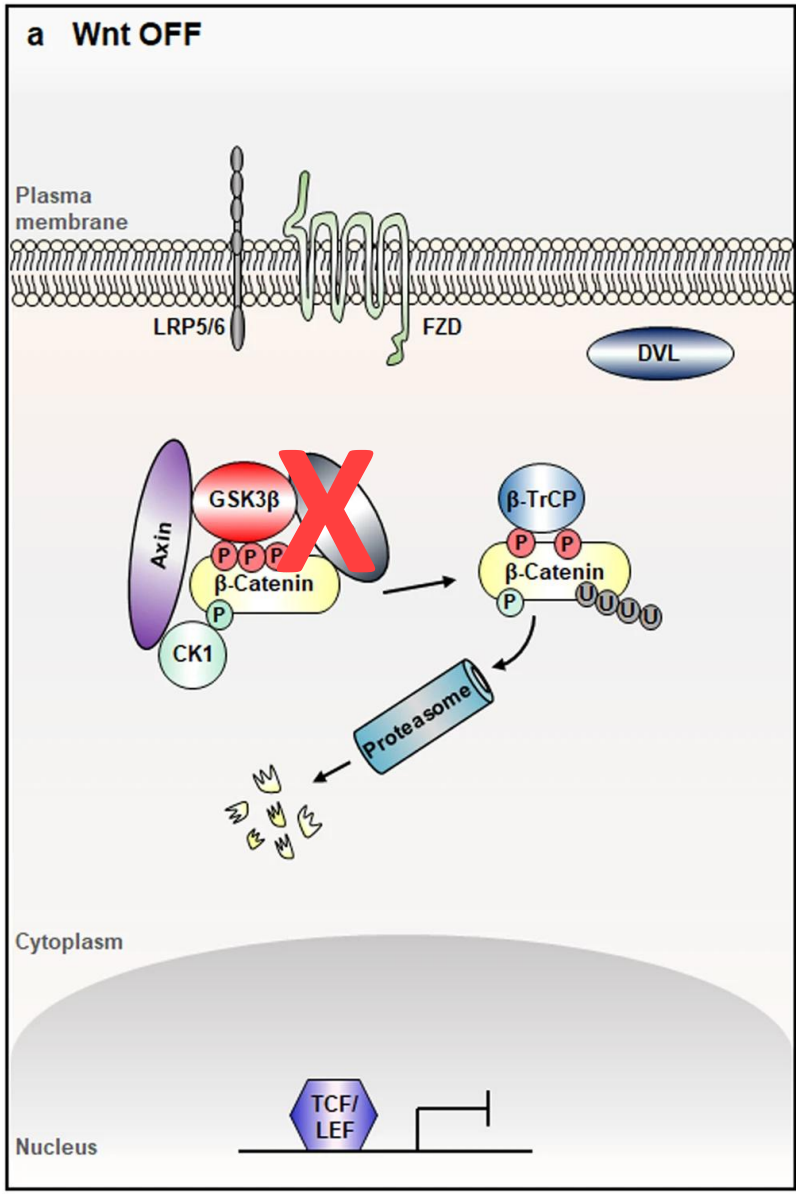
Hereditary colorectal cancer syndromes

Syndrome	Gene	Features
Familial adenomatous polyposis (FAP)	APC	>100 **polyps** (adenomas) in the colon detectable in second decade of life; autosomal dominant inheritance/phenotype
Attenuated FAP	APC	20 -100 **polyps** in the colon,

APC Gene



APC controls the transcriptional cofactor β-catenin in the Wnt pathway



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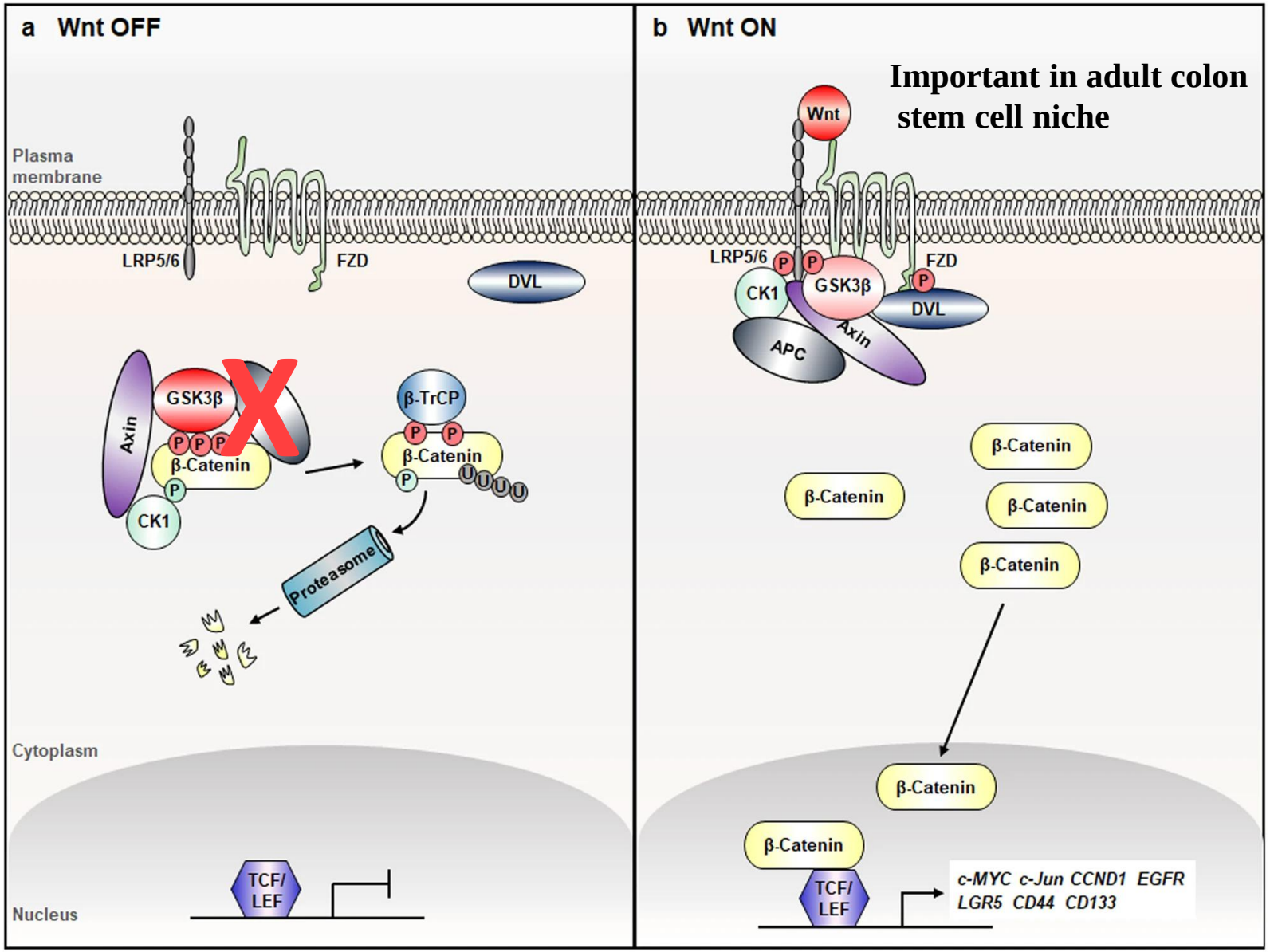
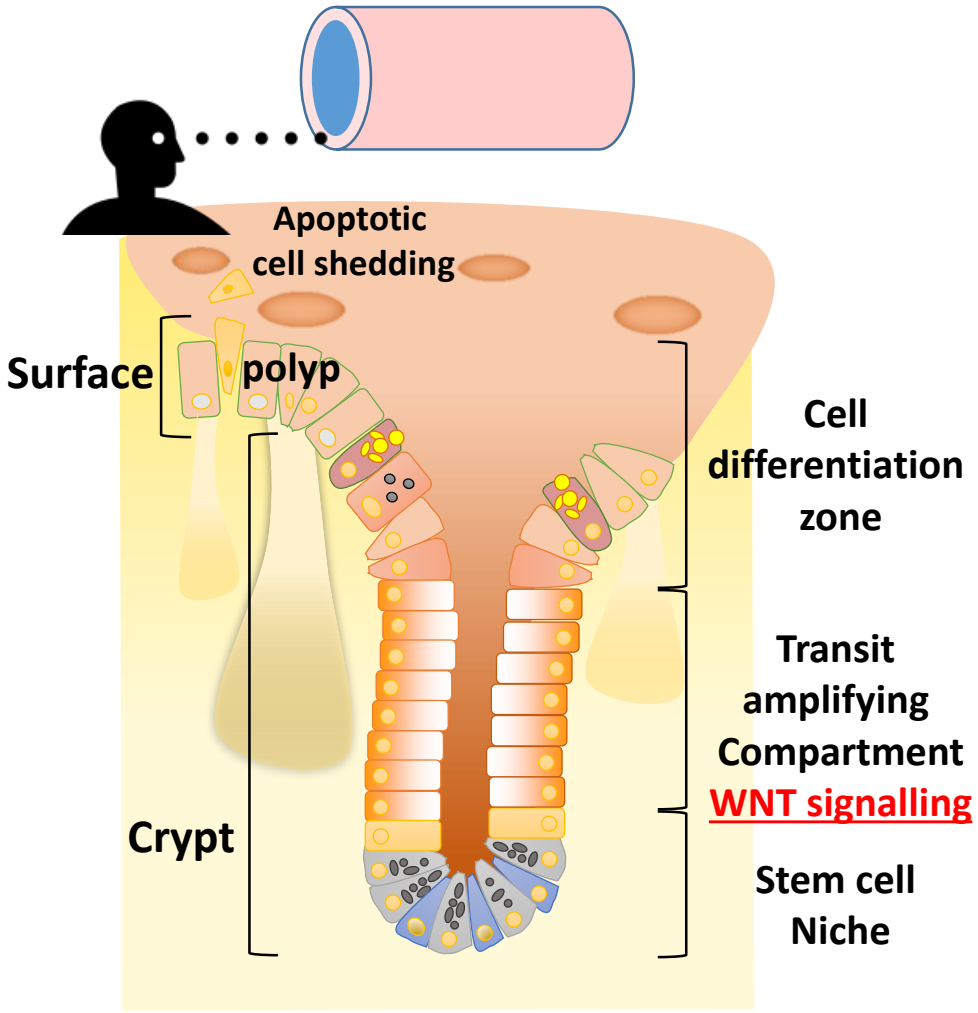


Why is the APC gene so important for colon cancer?



Pereira et al. (2016) Cell. Mol. Life Sci 73, 3971-89

colon crypt organization with stem cells:

- Wnt signalling controls cell renewal
- Suscetible environment for malignant transformation

Hereditary colorectal cancer syndromes

Syndrome	Gene	Features
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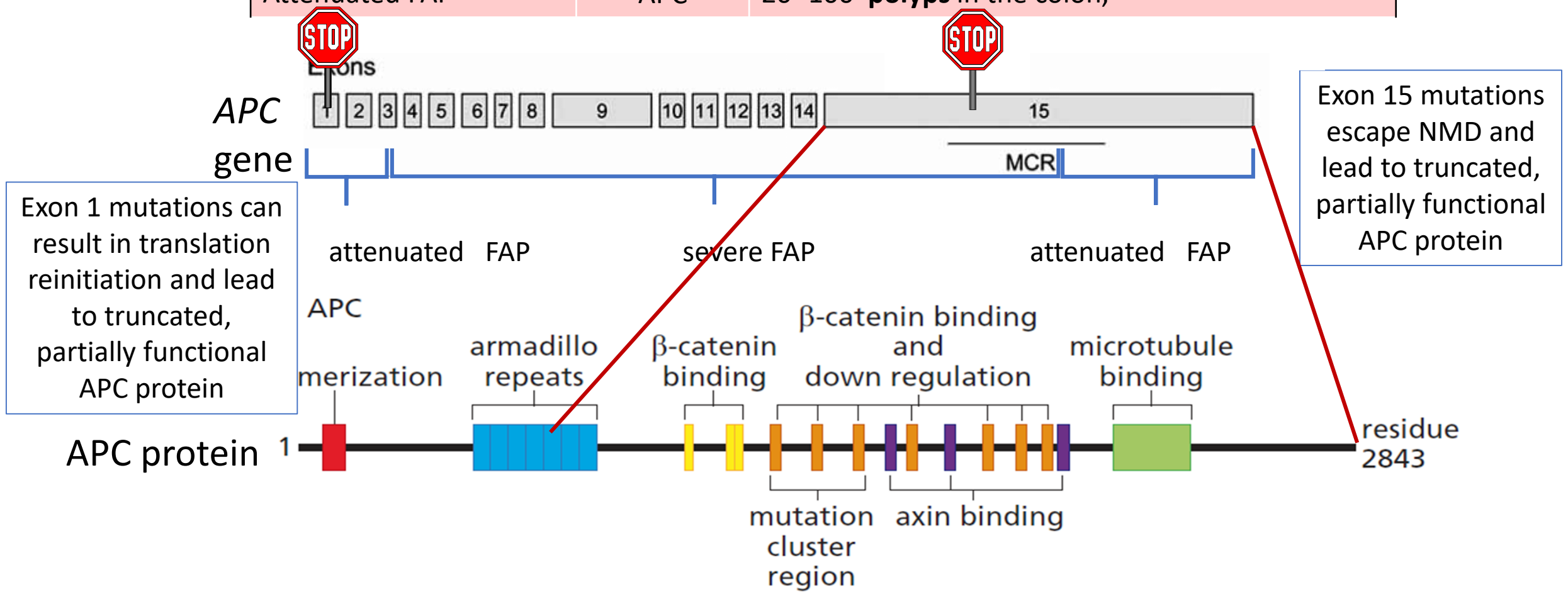
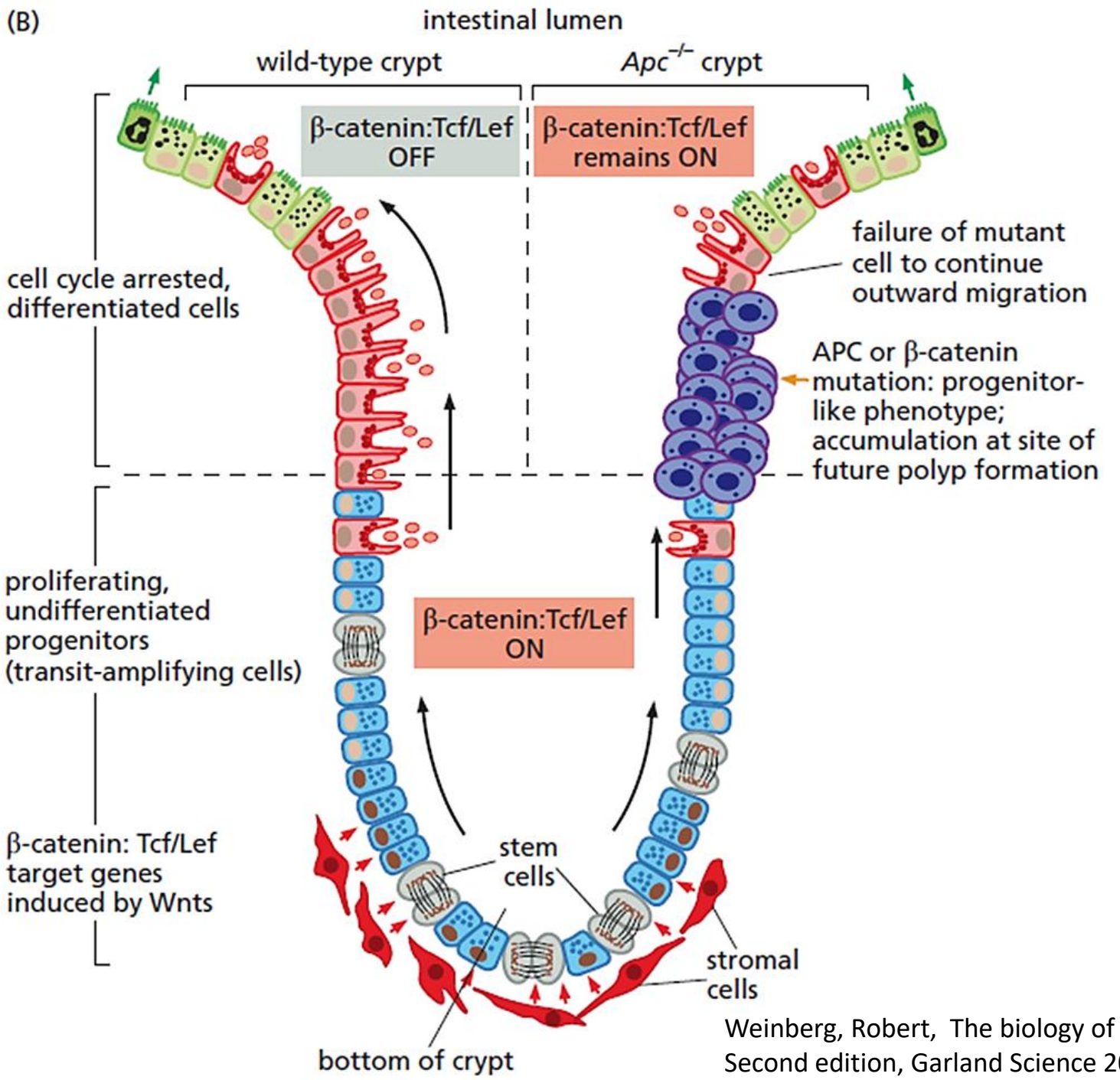


APC-dependent control of β-catenin signalling in the colon



Weinberg, Robert, The biology of cancer - Second edition, Garland Science 2014

Hereditary colorectal cancer syndromes

Syndrome	Gene	Features
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Attenuated FAP	APC	20 -100 **polyps** in the colon,
MUTYH polyposis	MYH	~10 **polyps** in the colon, **recessive** inheritance

MUTYH is a base excision repair glycosylase, which repairs oxidative damage to DNA to prevent G>T transversion mutations

➡ mutational signature in MUTYH tumours shows somatic G>T mutations in KRAS codon 12 (GGT > GTT) and in APC gene

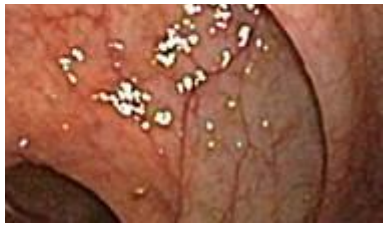
Hereditary colorectal cancer syndromes

Syndrome	Gene	Features
Familial adenomatous polyposis (FAP)	APC	>100 polyps (adenomas) in the colon detectable in second decade of life; autosomal dominant inheritance
Attenuated FAP	APC	20 -100 polyps in the colon,
MYH polyposis	MYH	~10 polyps in the colon, recessive inheritance
HNPCC or Lynch syndrome	MSH2 or MLH1 or MSH6 or PMS2	- **no polyps** formed; - high frequency of DNA sequence mutations; - most common hereditary syndrome, - can also cause endometrial or ovarian cancer;

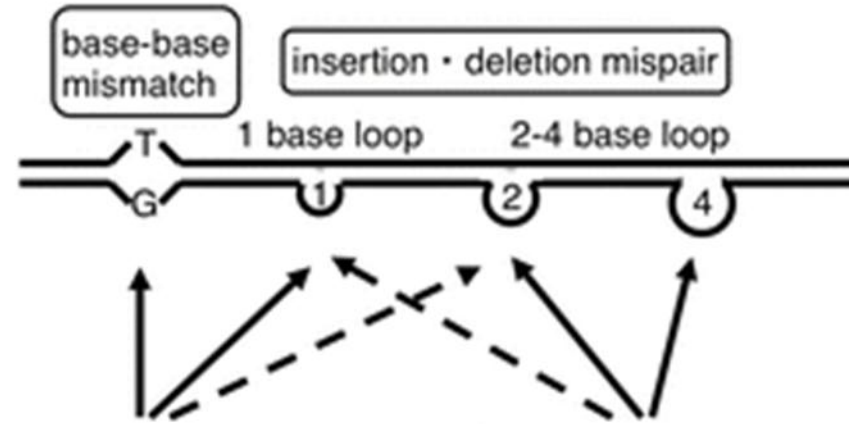
MMR= DNA mismatch repair machinery

Hereditary mutations at the 3´-end of the **EPCAM gene** can lead to subsequent epigenetic silencing of the neighbouring MSH2 gene, causing Lynch syndrome.

Colonoscopy image



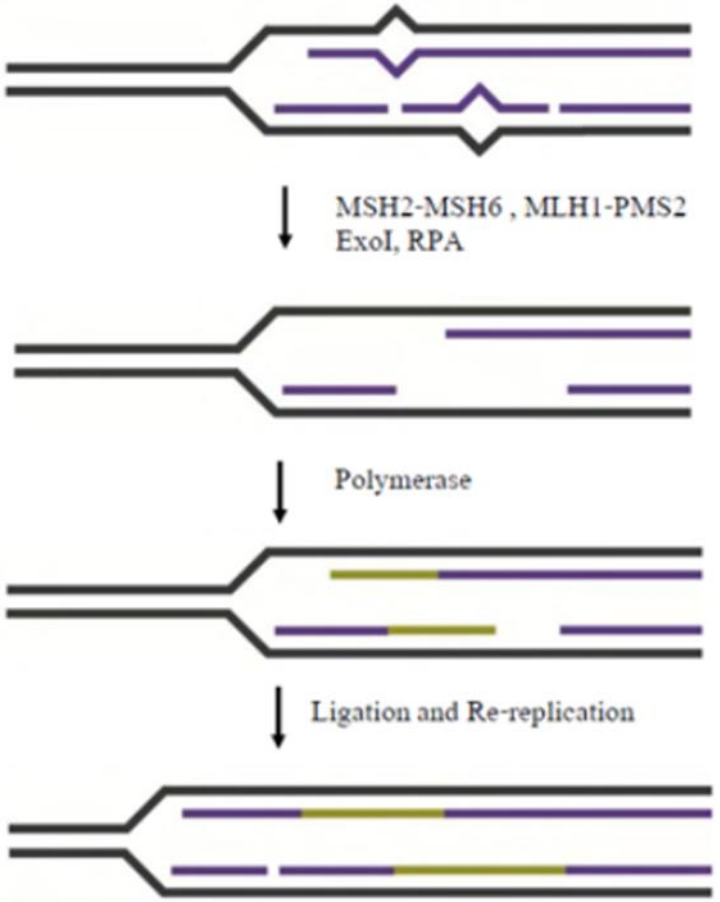
Mismatch error recognition



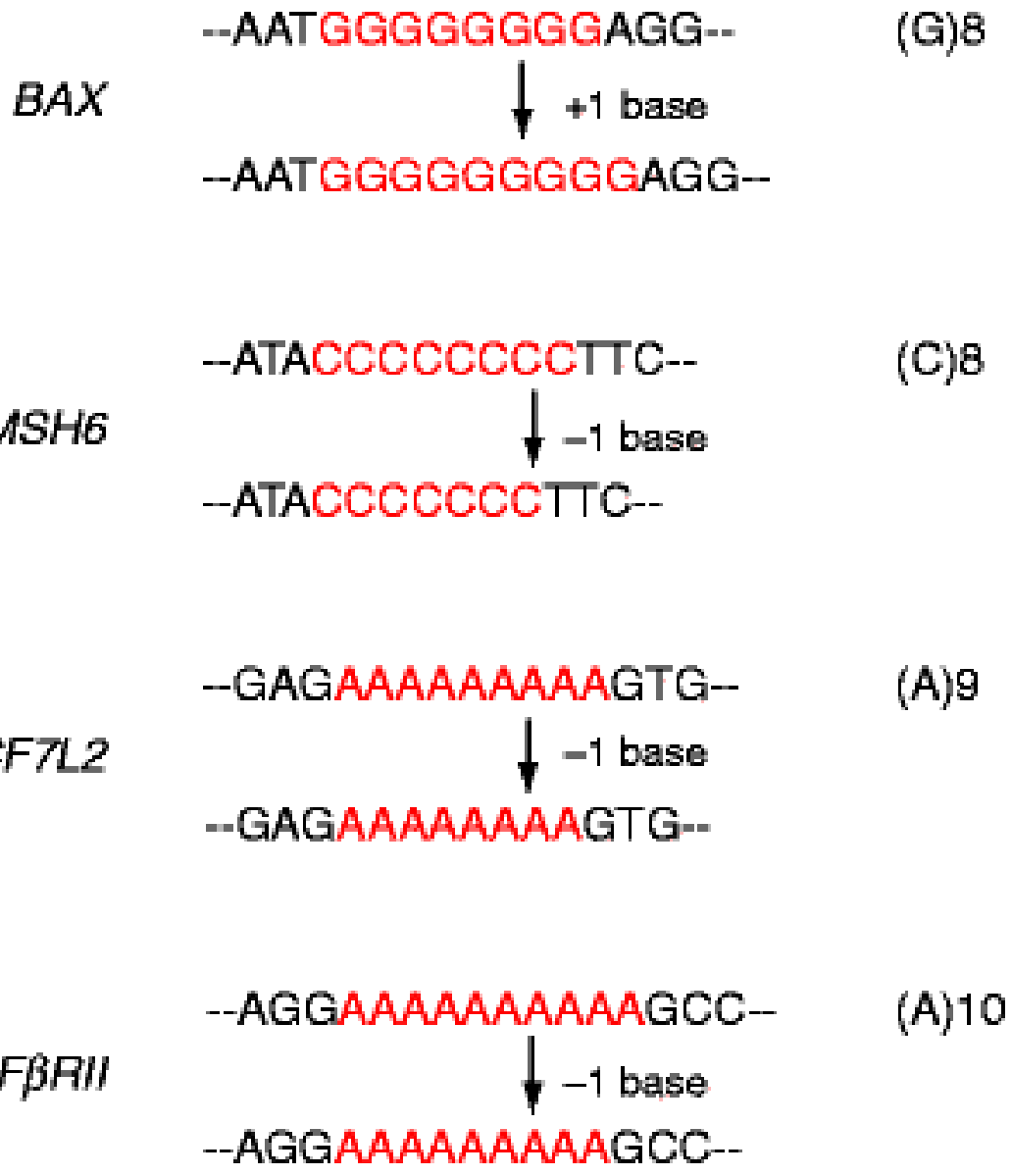
DNA MMR gene

..typically detected by analyzing repetitive microsatellite DNA sequences

Error repair



..what happens in microsatellites also happens genome-wide,
therefore also in coding sequences of some tumor supressor genes



Designations:

Microsatellite instability (or MSI),

Mismatch repair deficiency,

DNA sequence instability phenotype,

Mutator Phenotype

Normal counterpart:

Microsatellite stability (or MSS),

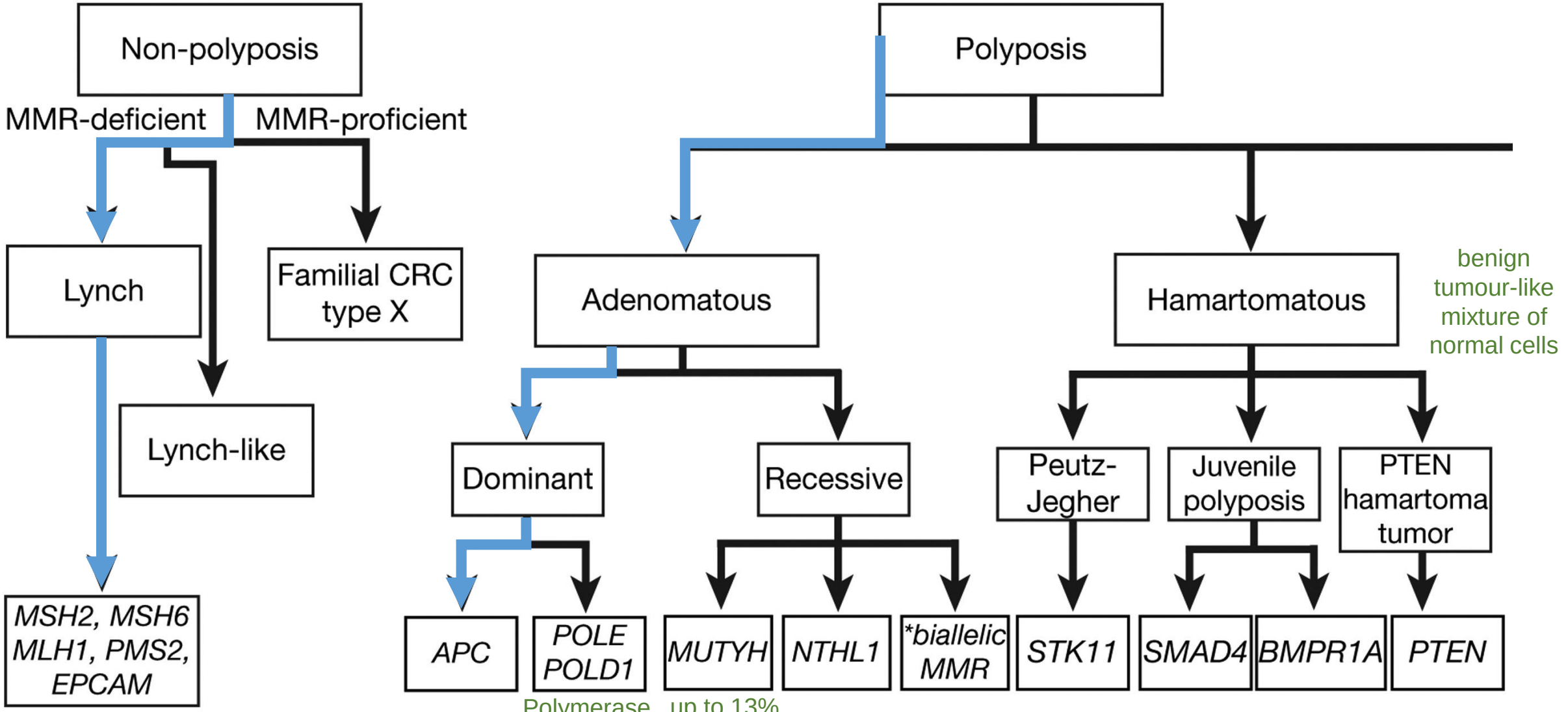
Mismatch repair proficiency,

DNA sequence stability

HNPCC or Lynch syndrome	2 or MLH1 or MSH6 or PMS2	- **no polyps** formed; - high frequency of DNA sequence mutations; - most common hereditary syndrome, - can cause endometrial or ovarian cancer;

All HNPCC are MSI

Recent Discoveries in the Genetics of Familial Colorectal Cancer and Polyposis



> multigene NGS panel for CRC genetic testing

doi: 10.1016/j.cgh.2016.09.148

Hereditary colon cancer genes panel (22 genes):

APC, AXIN2, GREM1, BMPR1A, SMAD4, STK11, PTEN,
NTHL1, POLD1, POLE, MUTYH,

MLH1, MLH3, MSH2, MSH6, PMS2, CHEK2, EPCAM, FAN1,

CDH1, TP53, GALNT12,

Eample 2: Hereditary Diffuse Gastric Cancer

-average age of diagnosis for HDGC is 38 years

- E-cadherin gene (CDH1) mutated, high mortality

- prophylactic total gastrectomy between 20 and 30 years of age

- "diffuse" because this cancer tends to be invasive rather than developing at a single area (20% of sporadic stomach cancers are also diffuse);

- estimated HDGC penetrance is 42% for males and 33% for females;

- the risk of other cancer types is not significantly increased by pathogenic *CDH1* variants, except for Lobular Breast Cancer

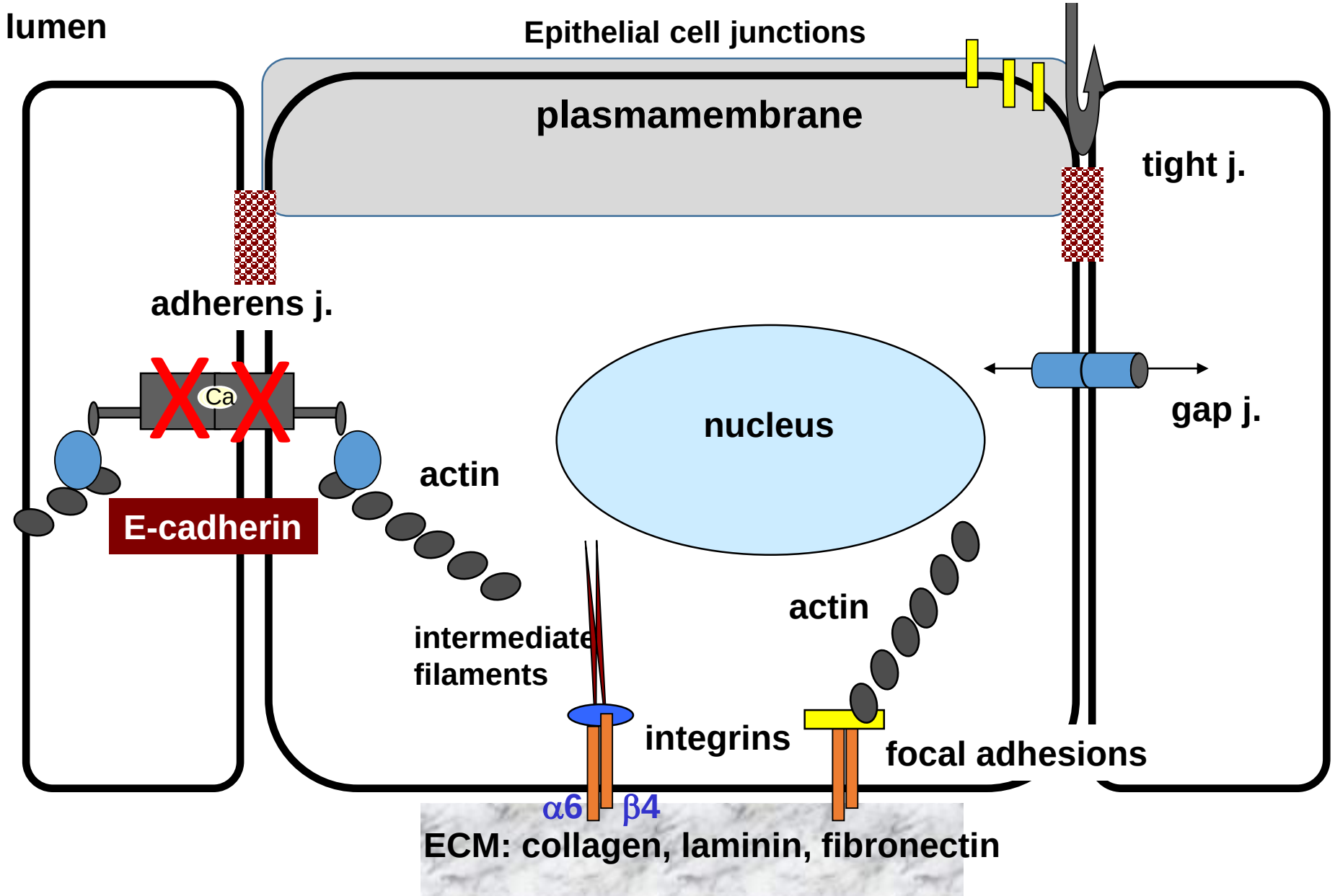
Well-differentiated epithelial cells have separate apical and basolateral membrane compartments

CDH1

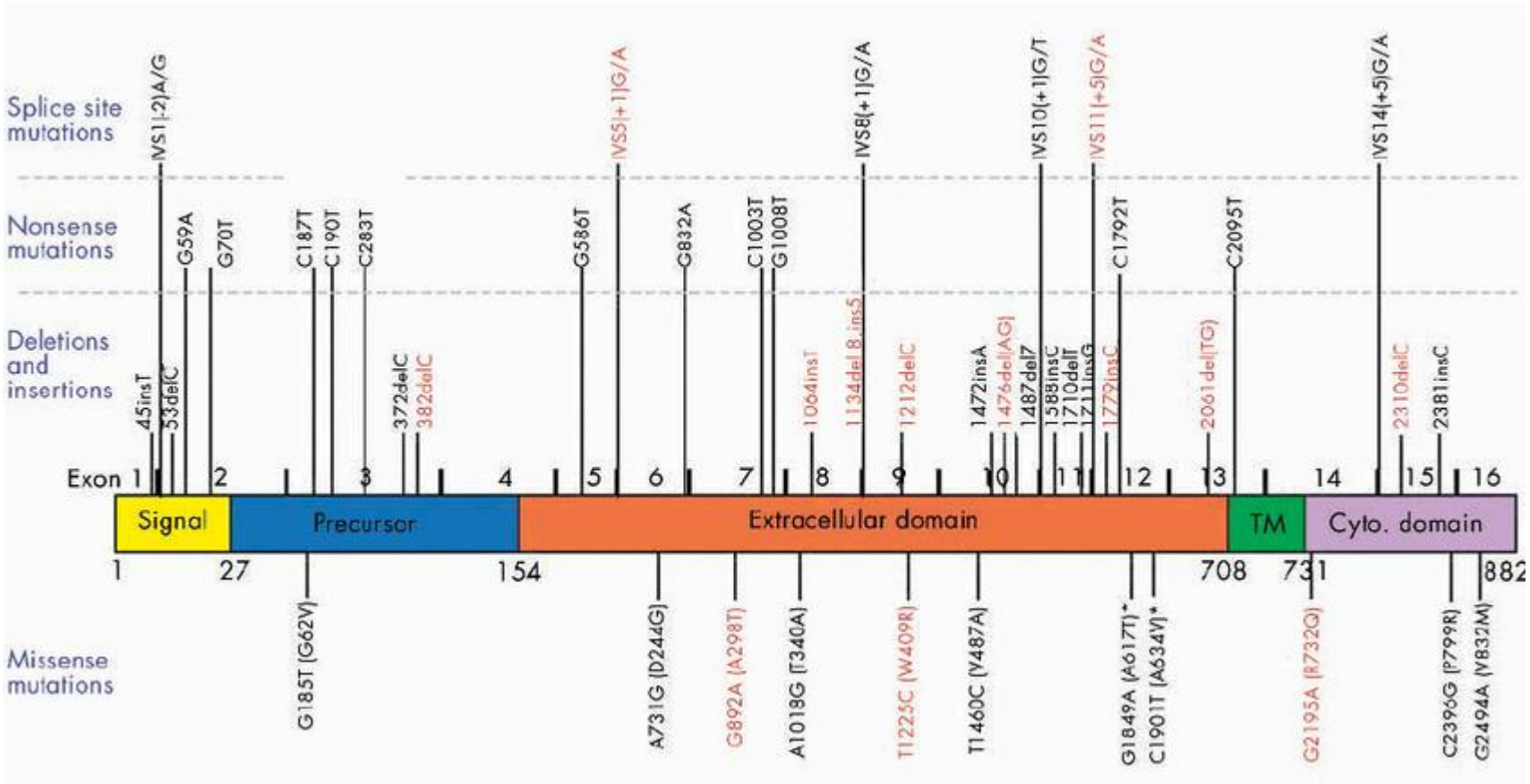
Gene deletion, point mutation or gene silencing

↓

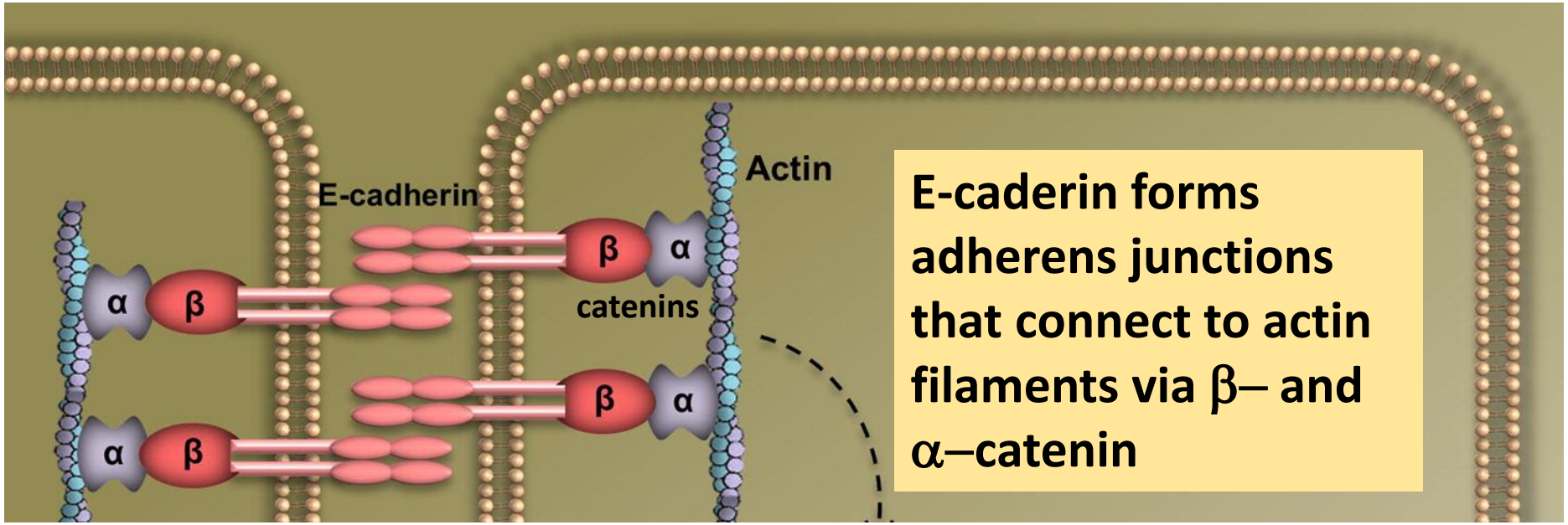
Familial gastric cancer



DOI:10.1136/jmg.2004.018275



- no major hot spots for mutations in CDH1 gene;
- 75% truncating mutations or large deletions;
- 25% missense variants that disrupt E-cadherin homophilic adhesion;
- some families present monoallelic expression of *CDH1* in the germline.



E-caderin forms adherens junctions that connect to actin filaments via β– and α–catenin

Mutations in the α-catenin gene (CTNNA1) are also found in a small percentage of HDGC families

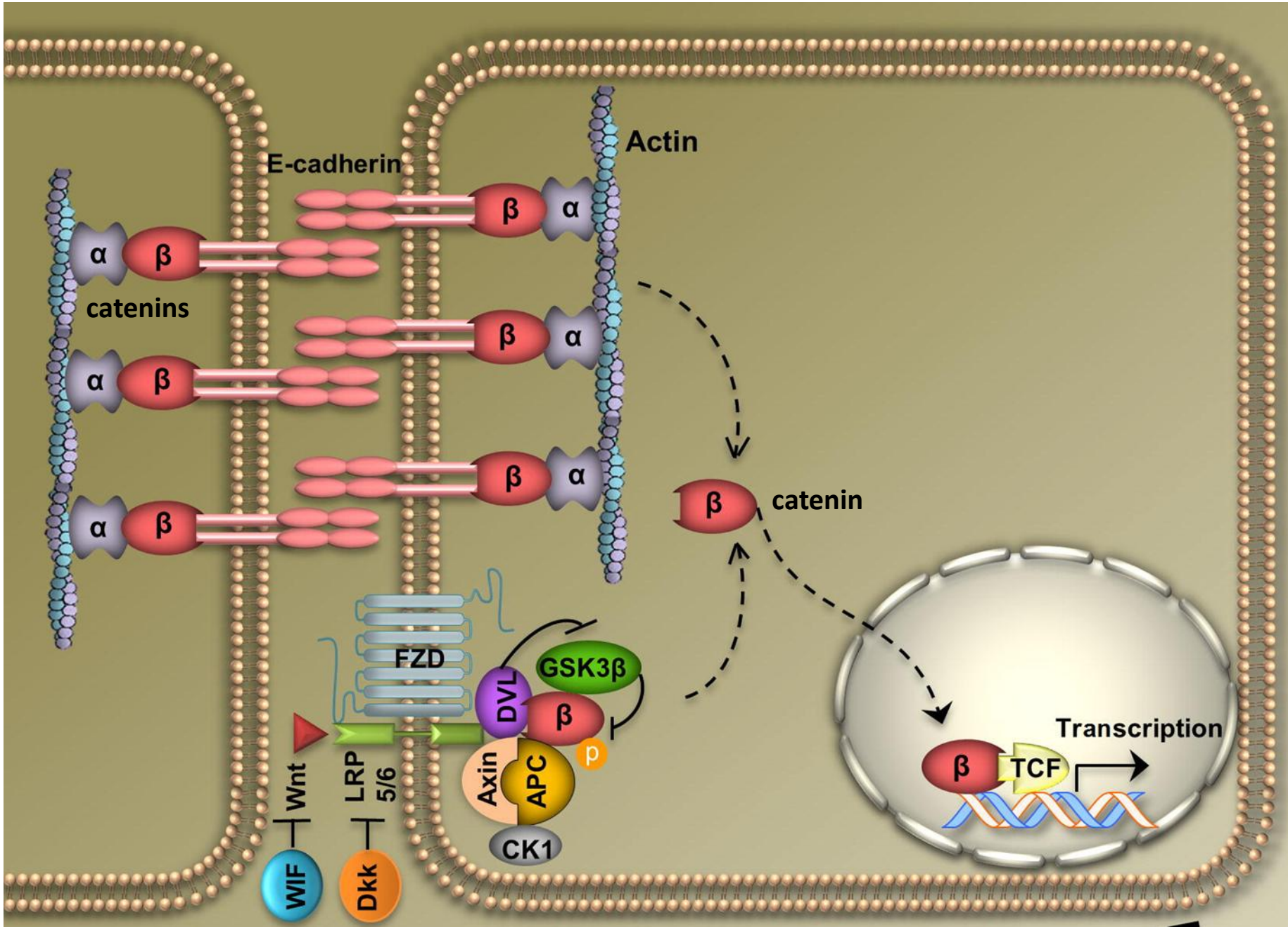
CDH1

Gene deletion, point mutation or gene silencing

Familial gastric cancer

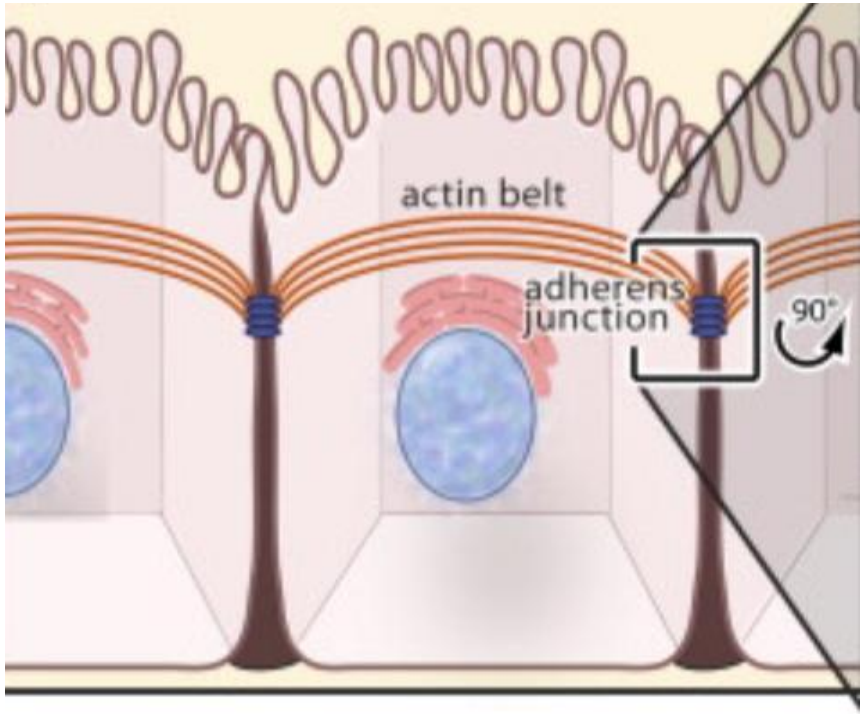
What is the cellular effect of losing E-cadherin?

1- increased Wnt/β-catenin signalling

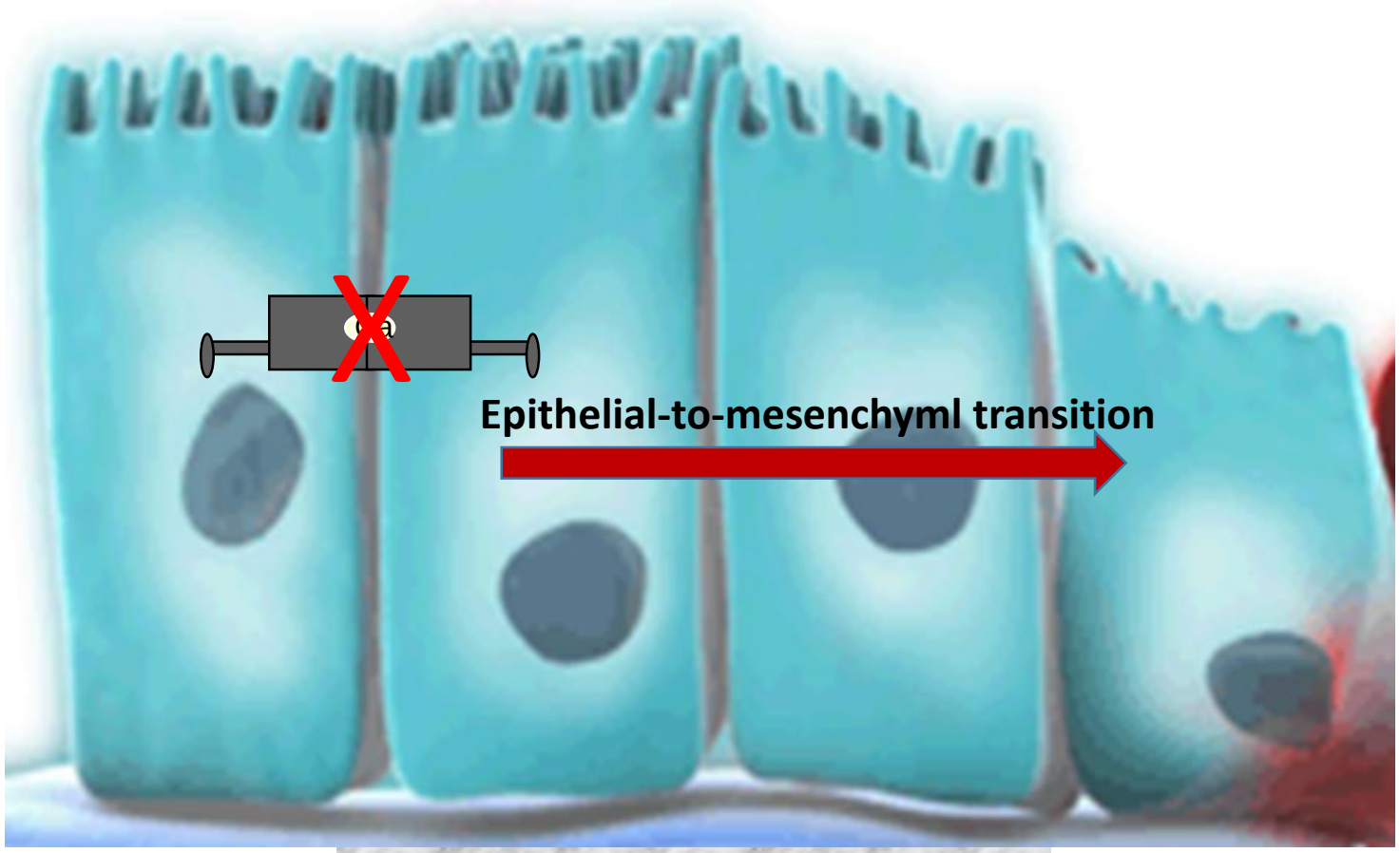


2- higher tumour cell invasiveness

Differentiated epithelial cells rely on an <u>apical actin belt</u> linked to adherens junctions for their organization



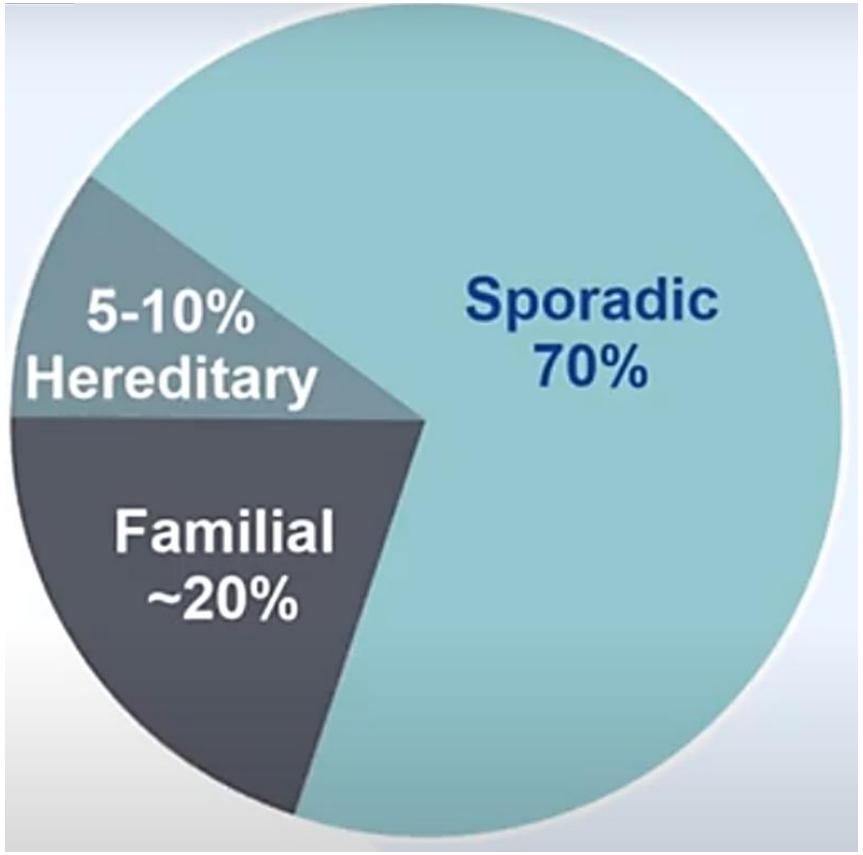
E-cadherin loss in well-differentiated epithelial cells affects cell layer organization and promotes invasive properties



From hereditary cancer syndromes to genetic predisposition

Hereditary or Familial cancer??

often used as synonyms, but sometimes distinguished



Cancer risk moderately increased (low penetrance)

Multiple genes involved, combined with environmental factors

Familial cancer (genetic predisposition)

Cancer that occurs in families more often than would be expected by chance.

These cancers often occur at an earlier age and may indicate the presence of a genetic predisposition that increases the risk of cancer.

The genetic susceptibility is mostly associated with multiple genes, each with a negligible effect on the risk of cancer, but when occurring together they increase the individuals' susceptibility.

Familial cancer may also be a sign of shared environmental or lifestyle factors.

Genetic predisposition to develop Cancer

(conclusions from genome-wide studies; also for other complex diseases)

High-penetrance gene mutations (hereditary cancer)

- Frequency: Rare (≤0.1% of population)
- Cancer risk**:** 10 - 20 x higher

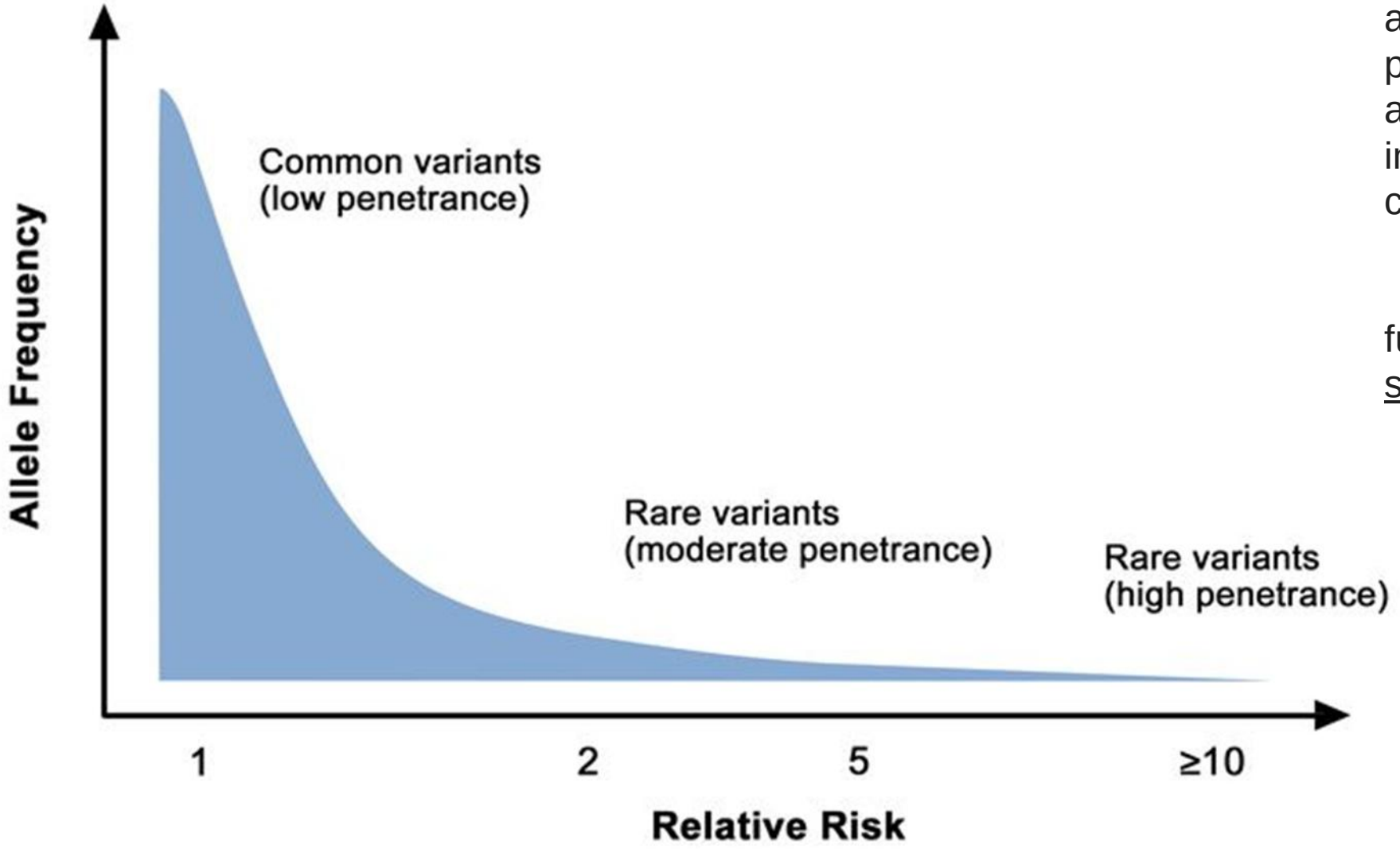
Moderate-penetrance gene mutations

- Frequency: Rare (≤0.6% of population)
- Cancer risk**:** 2 - 4 x higher

Low-penetrance susceptibility genes

- Frequency: common SNPs (5–50% of population)
- Cancer risk**:** 1,25 to 1,65 x (hetero-/homozygous)

Genetic Architecture of Cancer Risk



a number of common low penetrance alleles are associated with a slightly increased or decreased risk of cancer

future utility of polygenic risk scores

Lecture on Breast cancer genetic testing

Lecture 2- Some take-home concepts

- **Hereditary Cancer accounts for 5-10% of cases**
- **Characteristics include cancer in two or more relatives on the same side of the family, in several generations, occurring at early ages or with more than one primary cancer**

- **Germline mutations occur in certain tumour suppressor genes, allowing pre-symptomatic genetic testing**
- **2-hit hypothesis**
- **Dominant phenotype but variable penetrance**

- **Most frequent hereditary cancers are colon, breast or stomach cancer, and Li-Fraumeni syndrome**
- **Respective tumour suppressor genes are APC, MLH1, MSH2, BRCA1, BRCA2, CDH1, TP53**