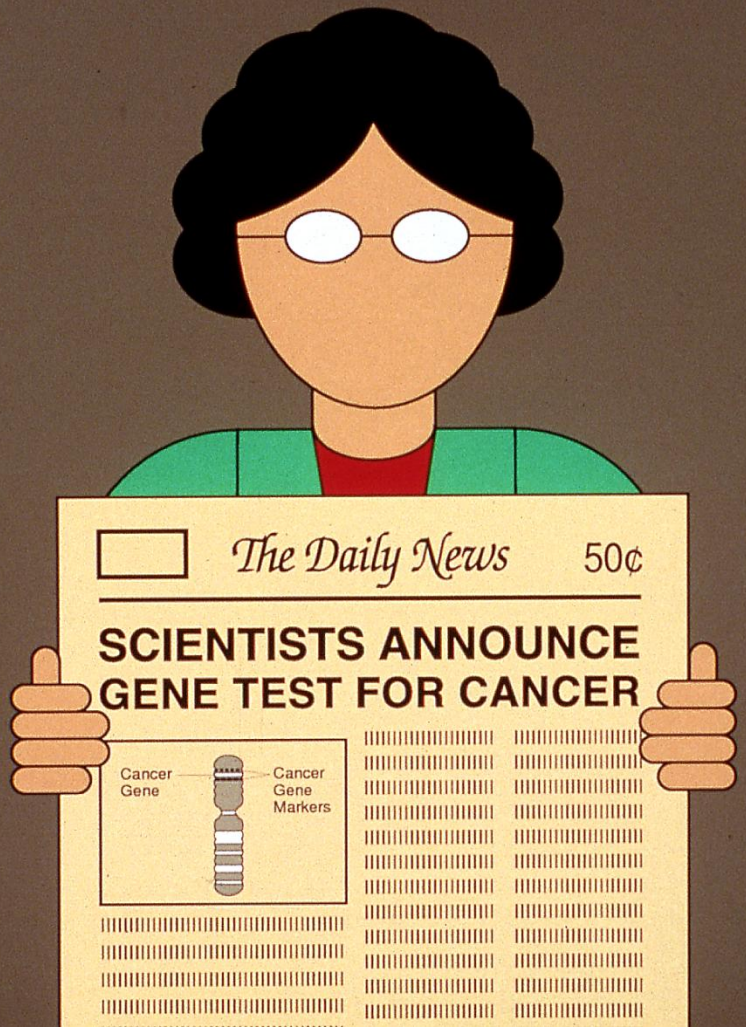
The molecular basis for cancer development in the individual patient are largely unknown

Possible risk factors:

- Genetic damage - Mutation
- Induced alteration of gene expression
- Chemical agents
- Radiation
- Viruses
- „epigenetic“ factors
- ?????????????

Alone or in Combination

Genes in the News



"All the News That's Fit to Print"

The

NY TIMES 11/3/95

VOL.CXLV.... No. 50,234

Research Links One Gene To Most Breast Cancers

New Hope for Predicting and Treating Disease

By GINA KOLATA

A gene that was thought to cause only a small proportion of breast cancers now appears to be at the heart of nearly all of them, researchers report.

The finding may lead to new ways to give a prognosis and to treat breast cancer, but there is no immediate action recommended for women who have breast cancer or are concerned about a genetic predisposition to the disease.

ed a mutated form of the gene had about a 90 percent chance of developing breast cancer and about a 6[illegible] percent chance of developing ovarian cancer in their lifetimes.

But women with familial breast cancers constitute just 5 percent of all women with the disease, so the importance of the finding seemed of minor importance for the vast majority of women who might contract

The role of genes in cancer development

1. Strong hereditary factors,
   Mendelian-Genetics of inherited risk, high penetrance

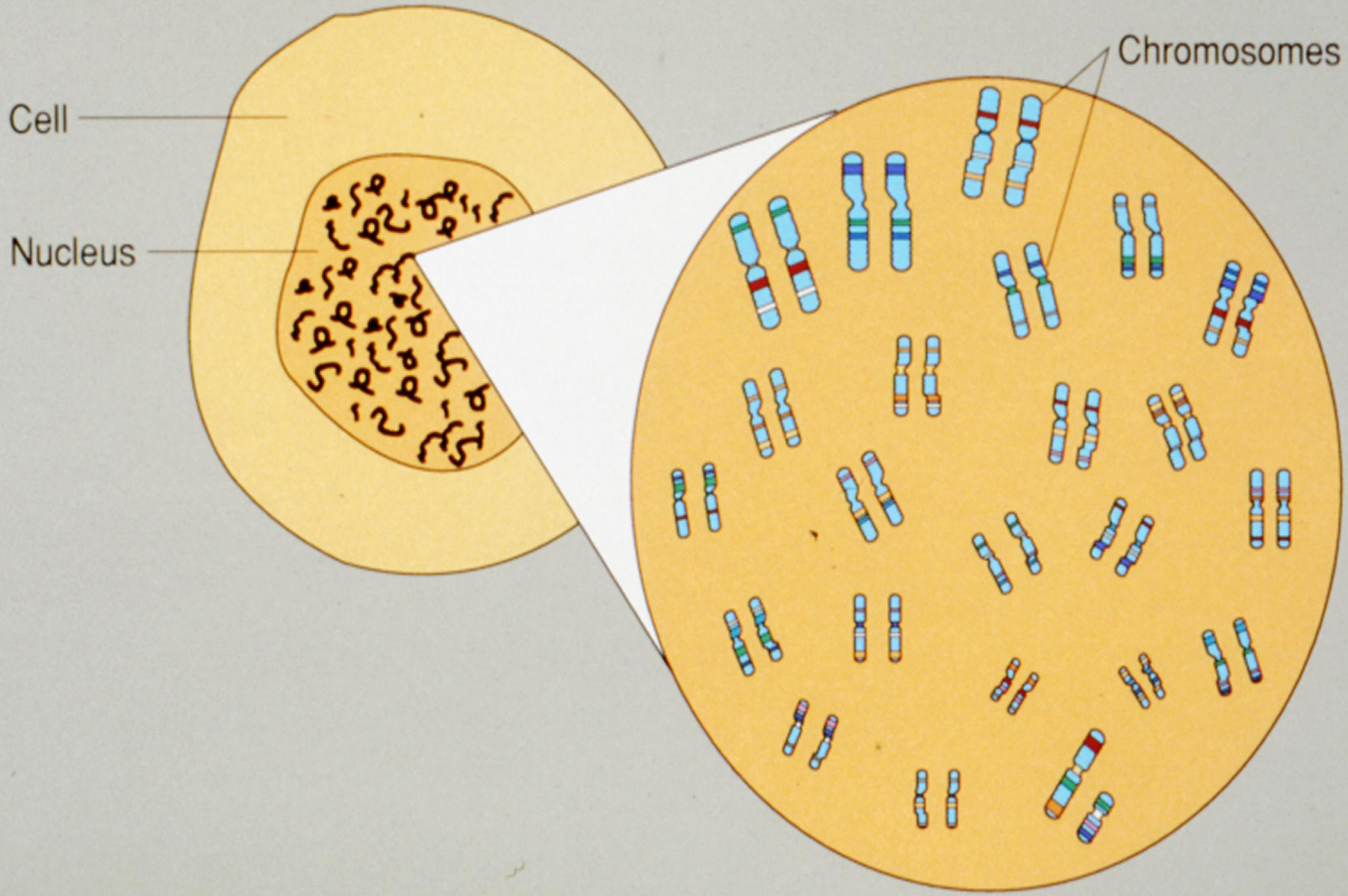
2. Medium inherited influence,
   penetrance limited

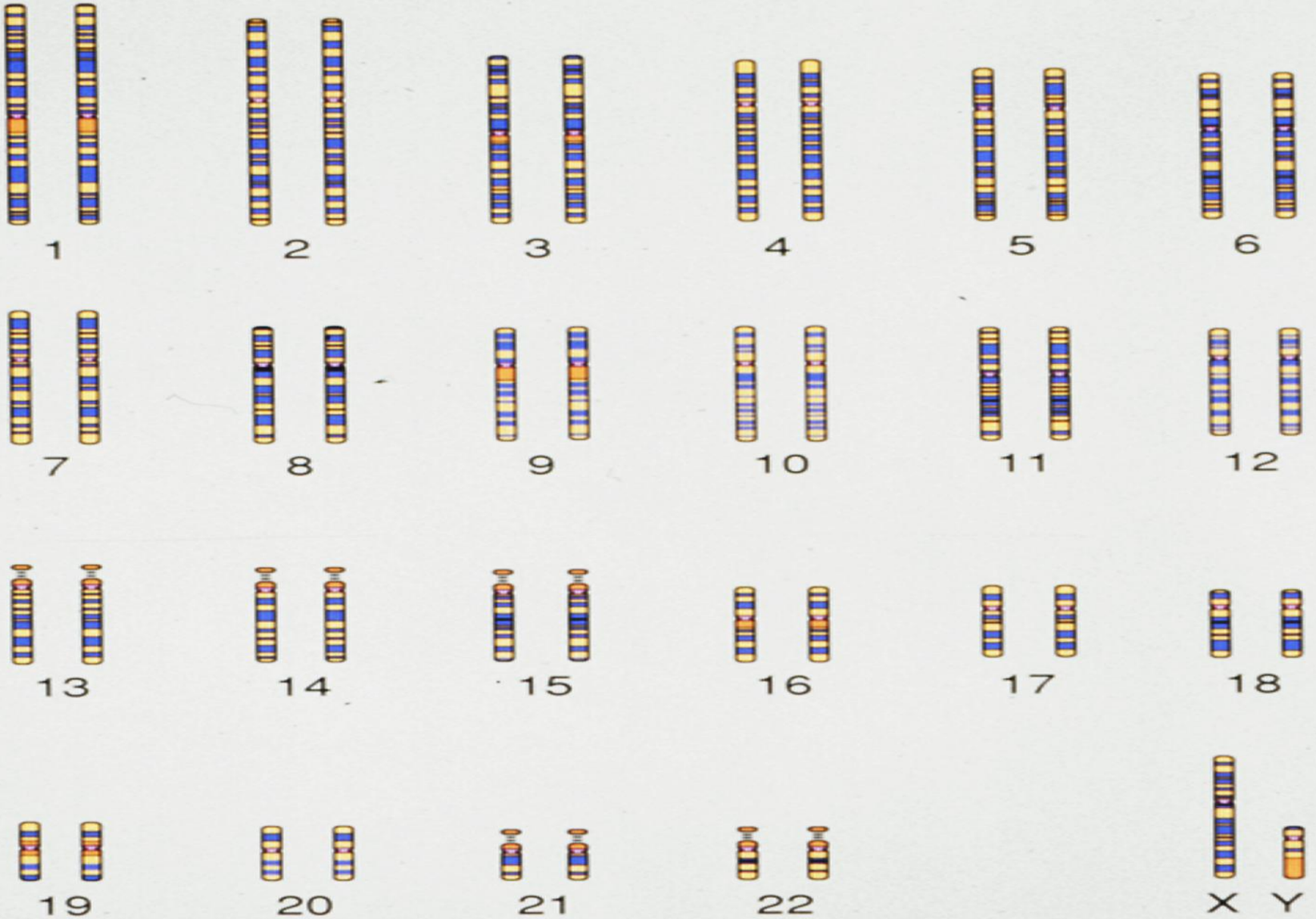
3. Weak inherited influence, often can only be diffusely delineated

4. Somatic mutation without recognizable inherited basis
   erbliche Basis

5. „Epigenetic“ alterations of gene expression

DNA Molecules

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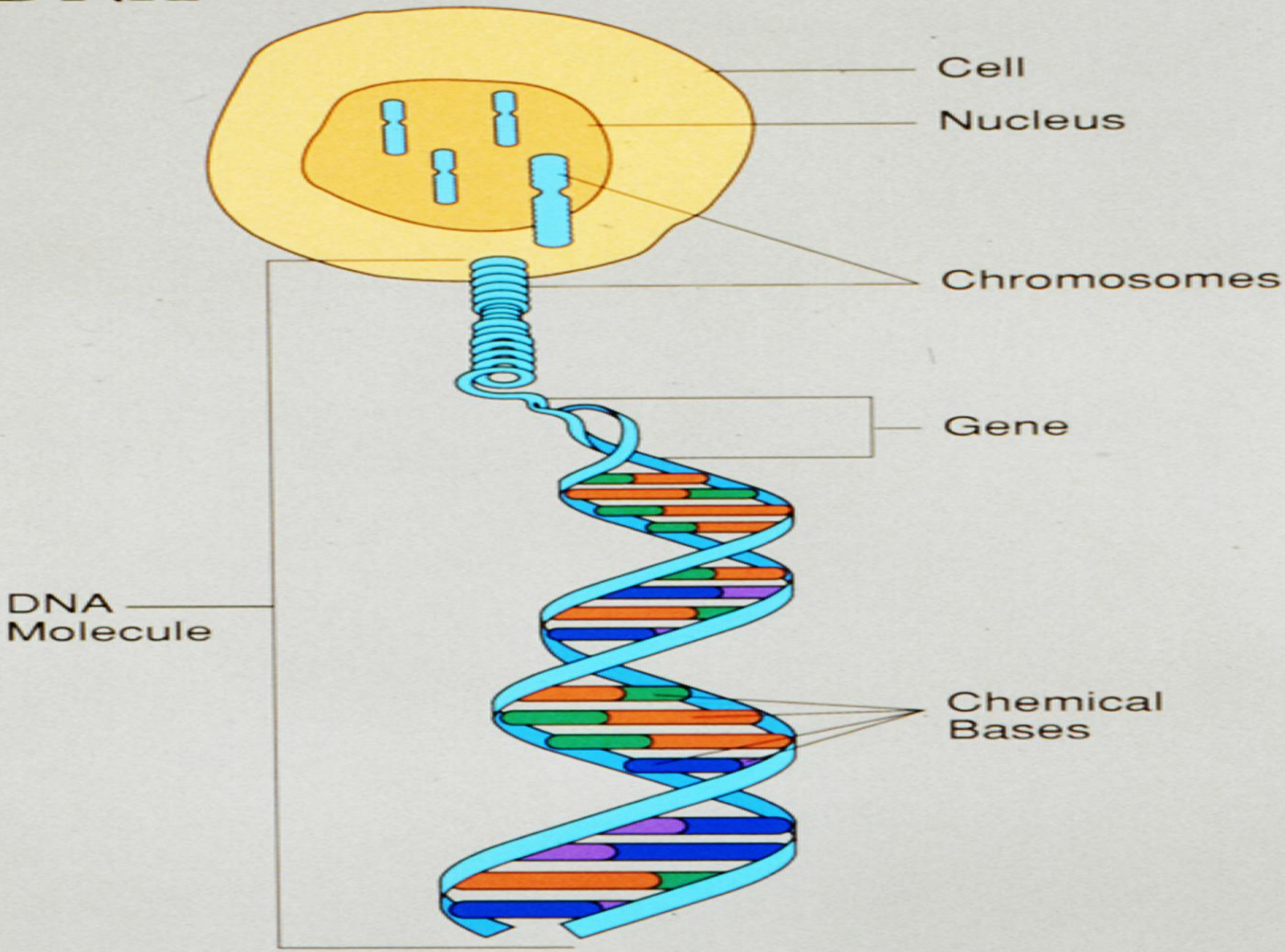
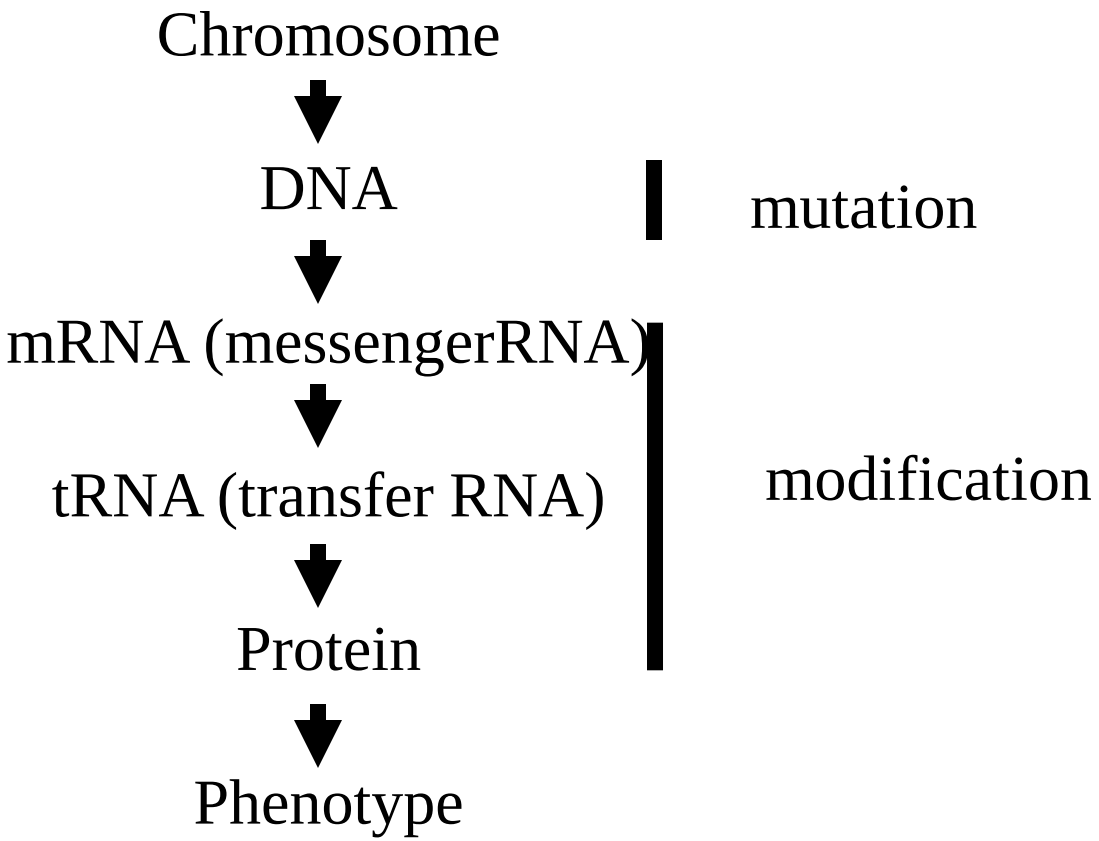
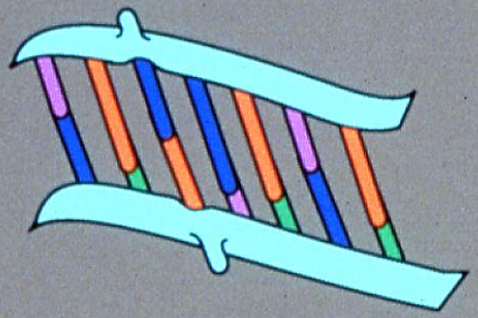
DNA


Cell
Nucleus
Chromosomes
Gene
DNA
Molecule
Chemical
Bases

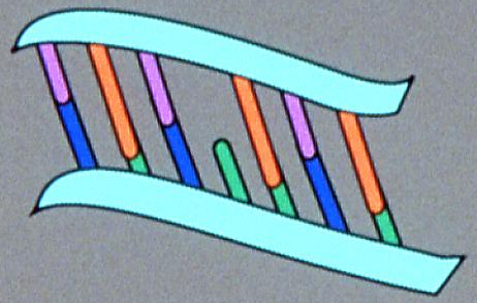
From Genotype to Phenotype-----
Flow of genetic information („classical“ order)



...ene Mutations



Mismatch



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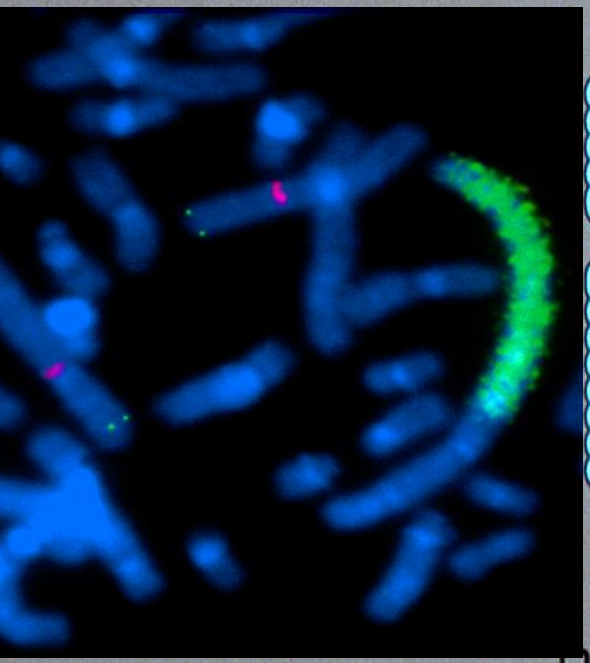
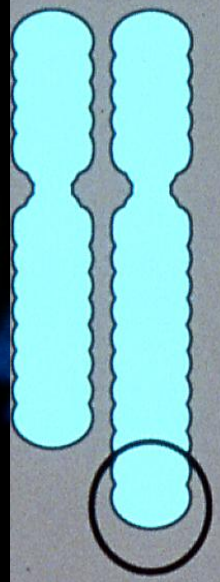
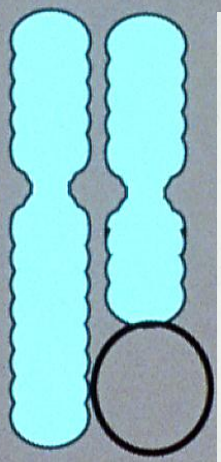




Repetition



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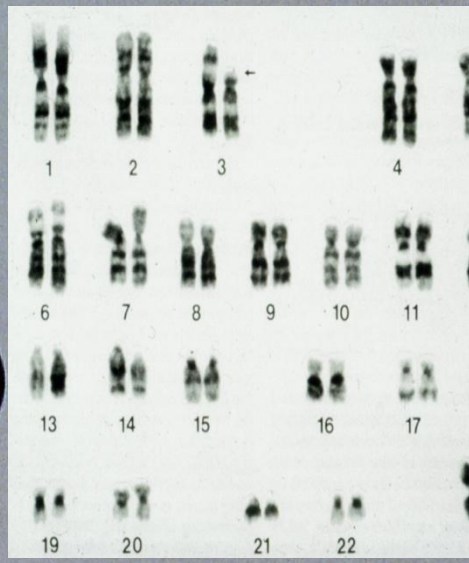
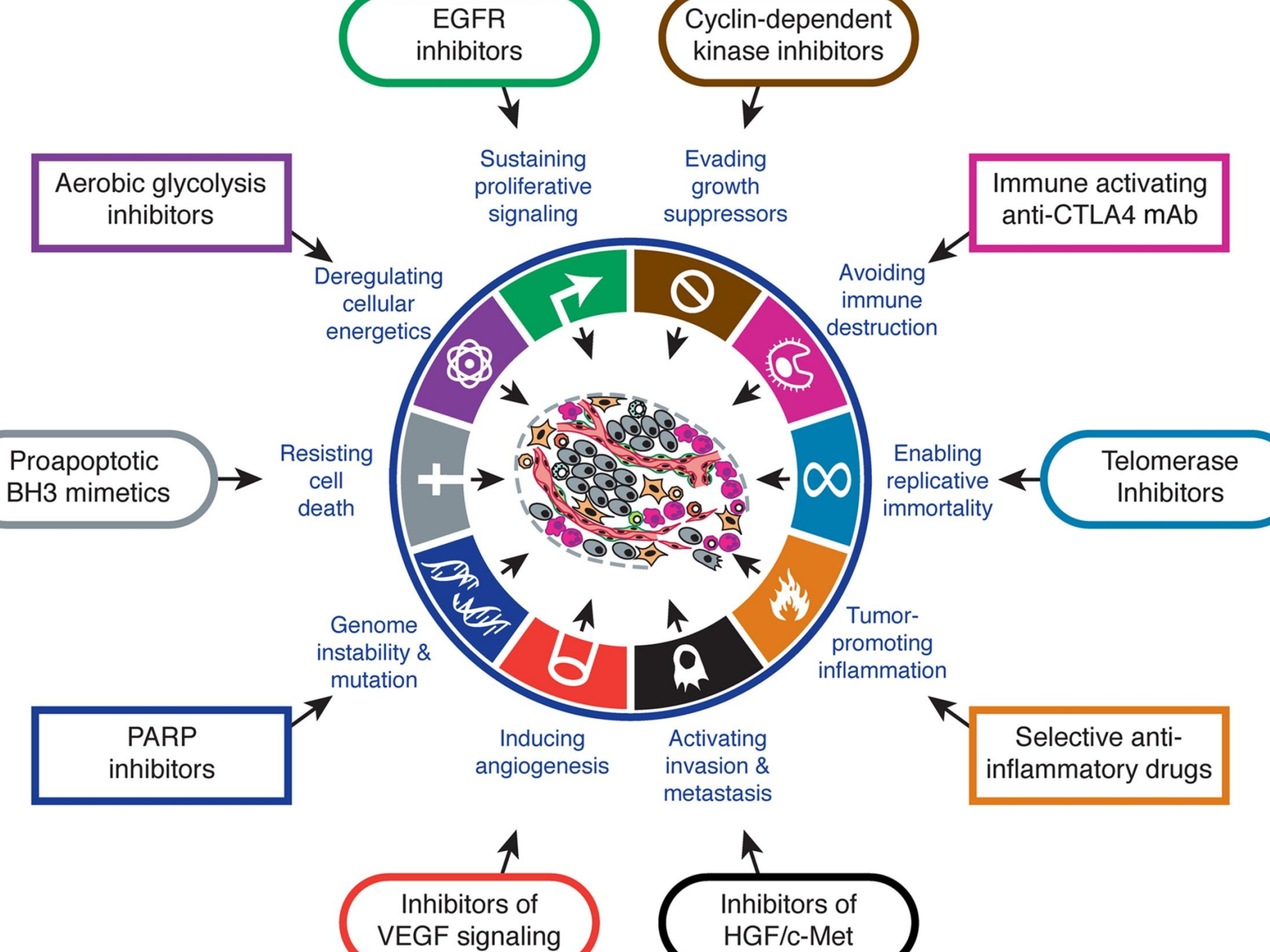
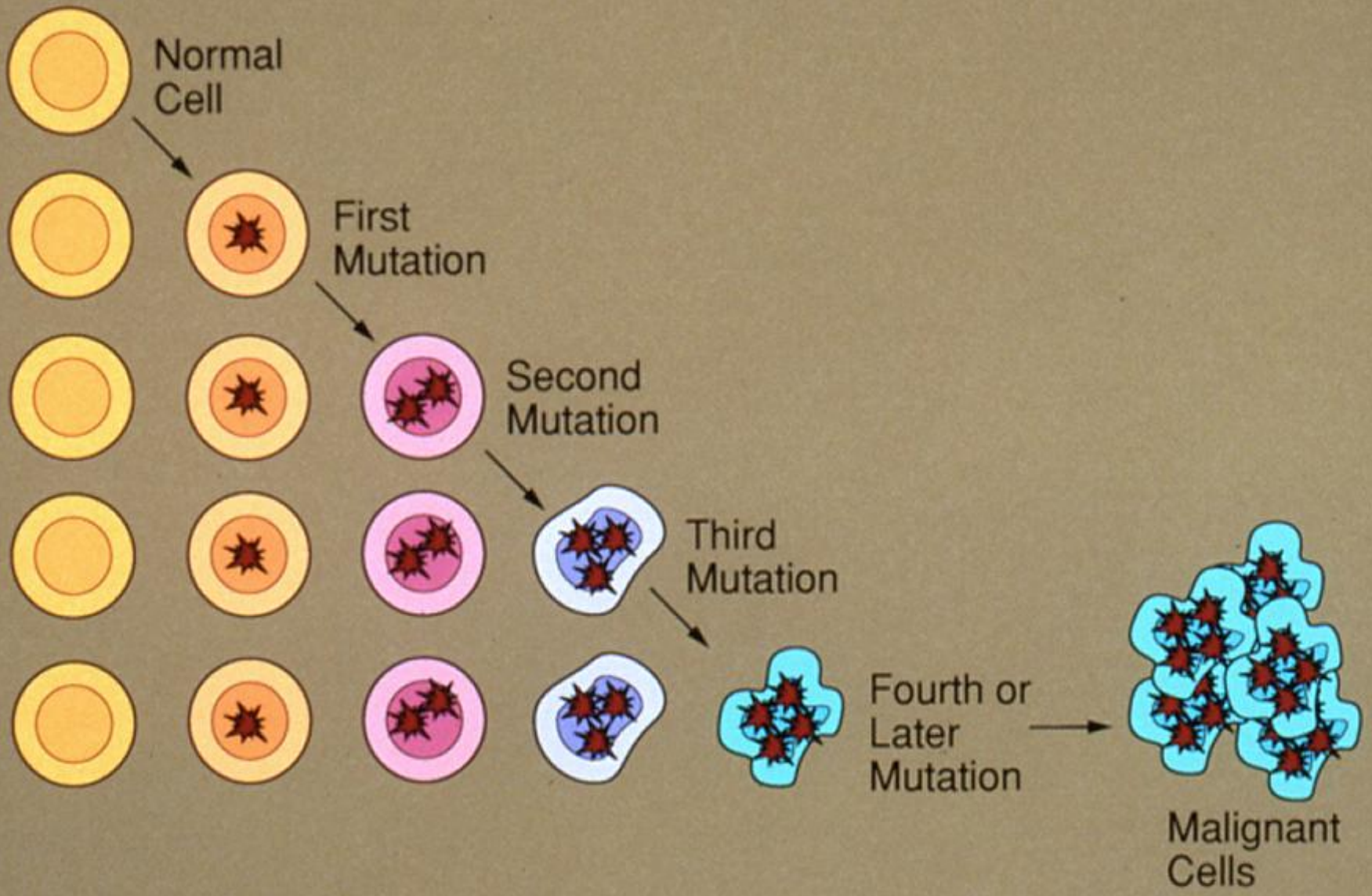
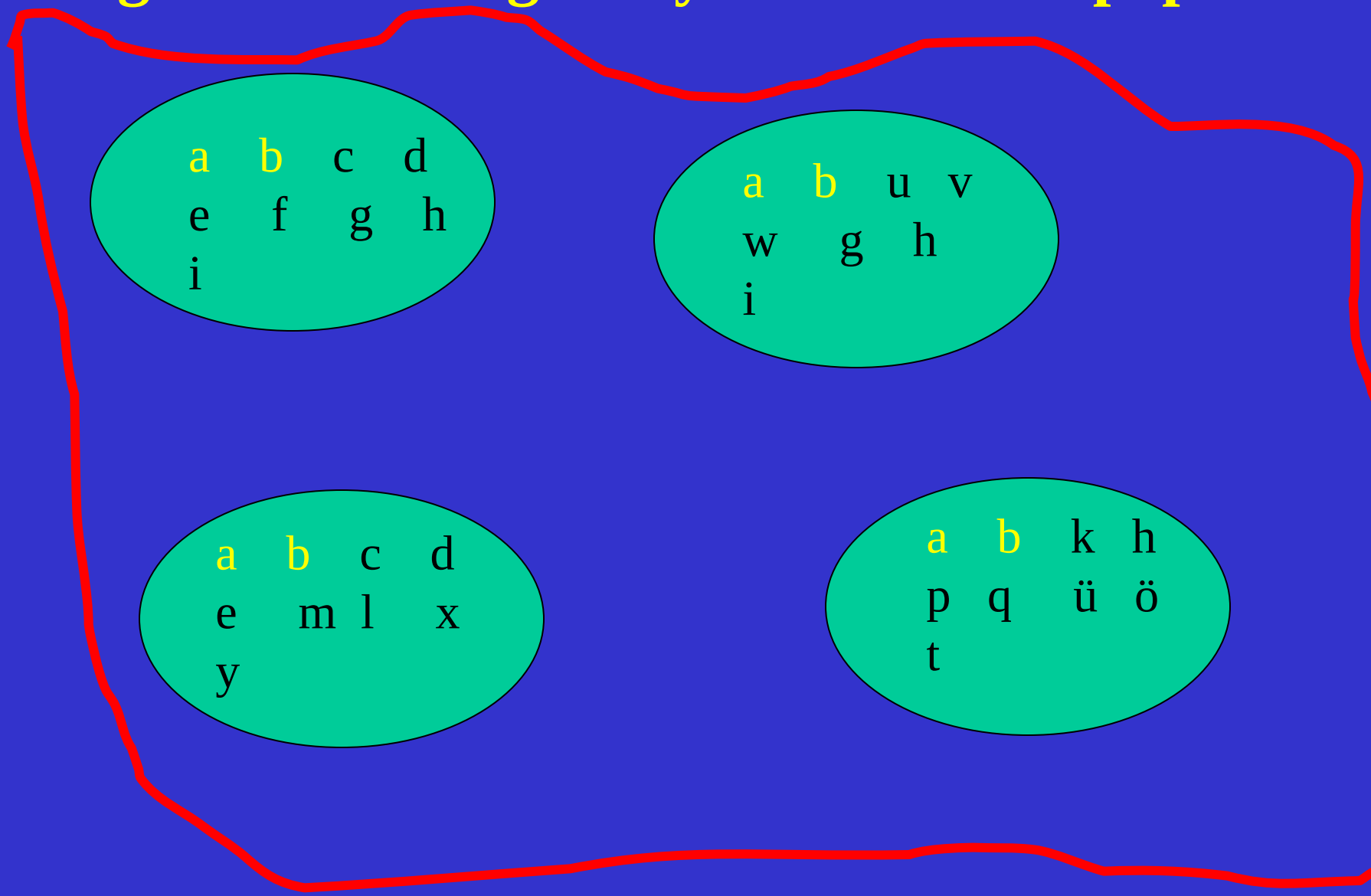


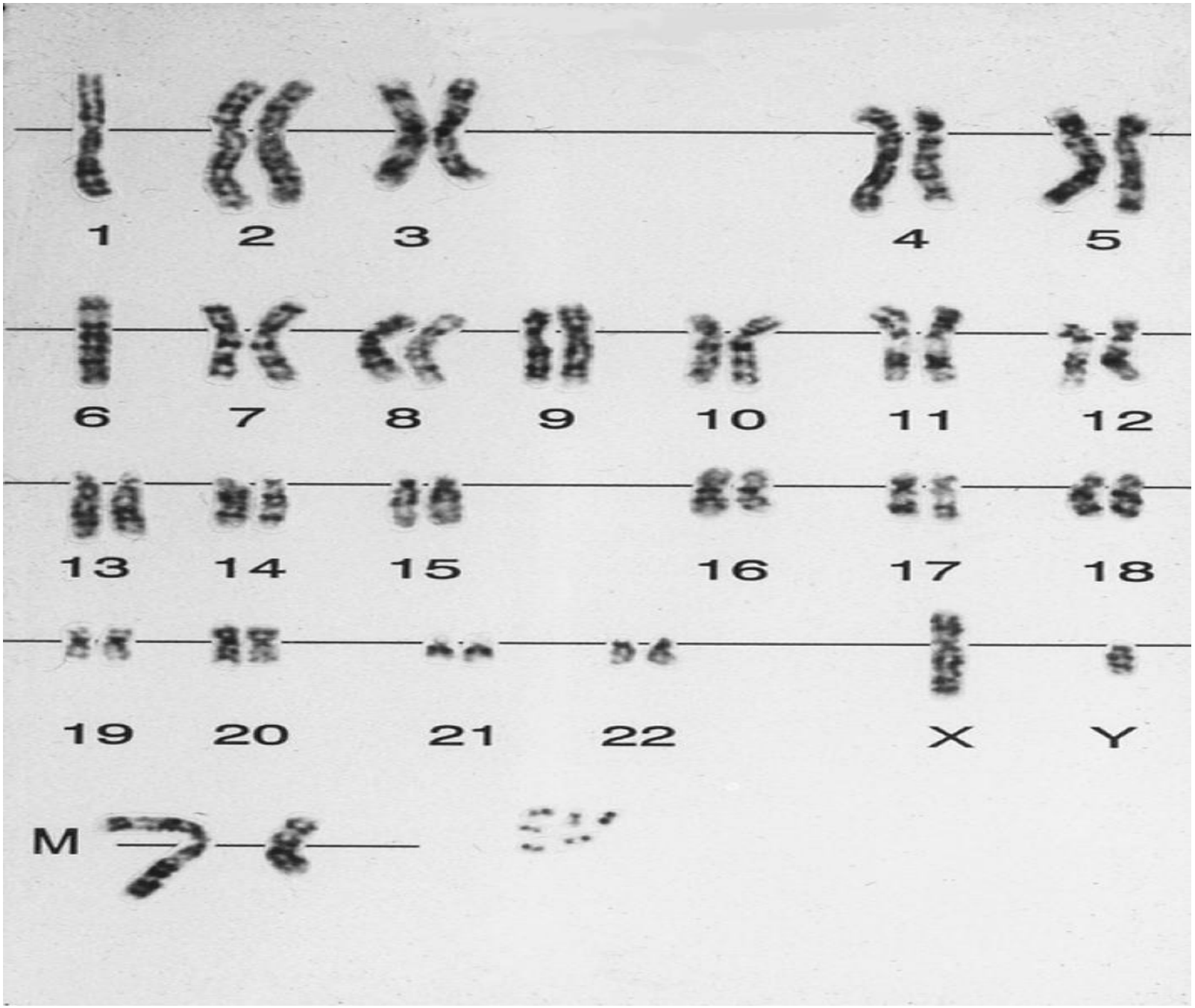

EGFR inhibitors
Cyclin-dependent kinase inhibitors
Aerobic glycolysis inhibitors
Sustaining proliferative signaling
Evading growth suppressors
Immune activating anti-CTLA4 mAb
Deregulating cellular energetics
Avoiding immune destruction
Proapoptotic BH3 mimetics
Resisting cell death
Enabling replicative immortality
Telomerase Inhibitors
Genome instability & mutation
Tumor-promoting inflammation
PARP inhibitors
Inducing angiogenesis
Activating invasion & metastasis
Selective anti-inflammatory drugs
Inhibitors of VEGF signaling
Inhibitors of HGF/c-Met

Many Mutations Lead to Cancer



Genomic instability leads to genetic heterogeneity of tumor cell populations

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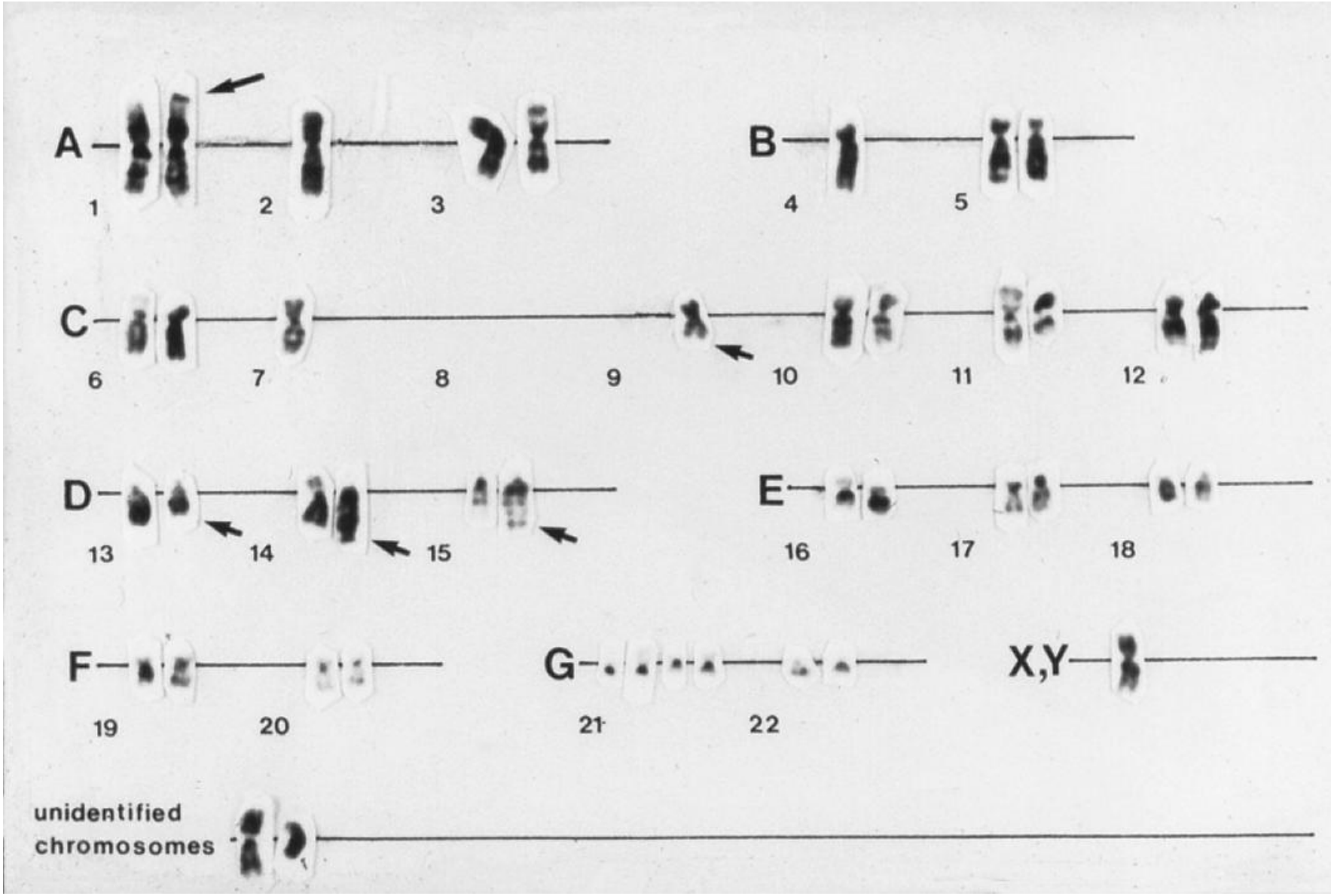
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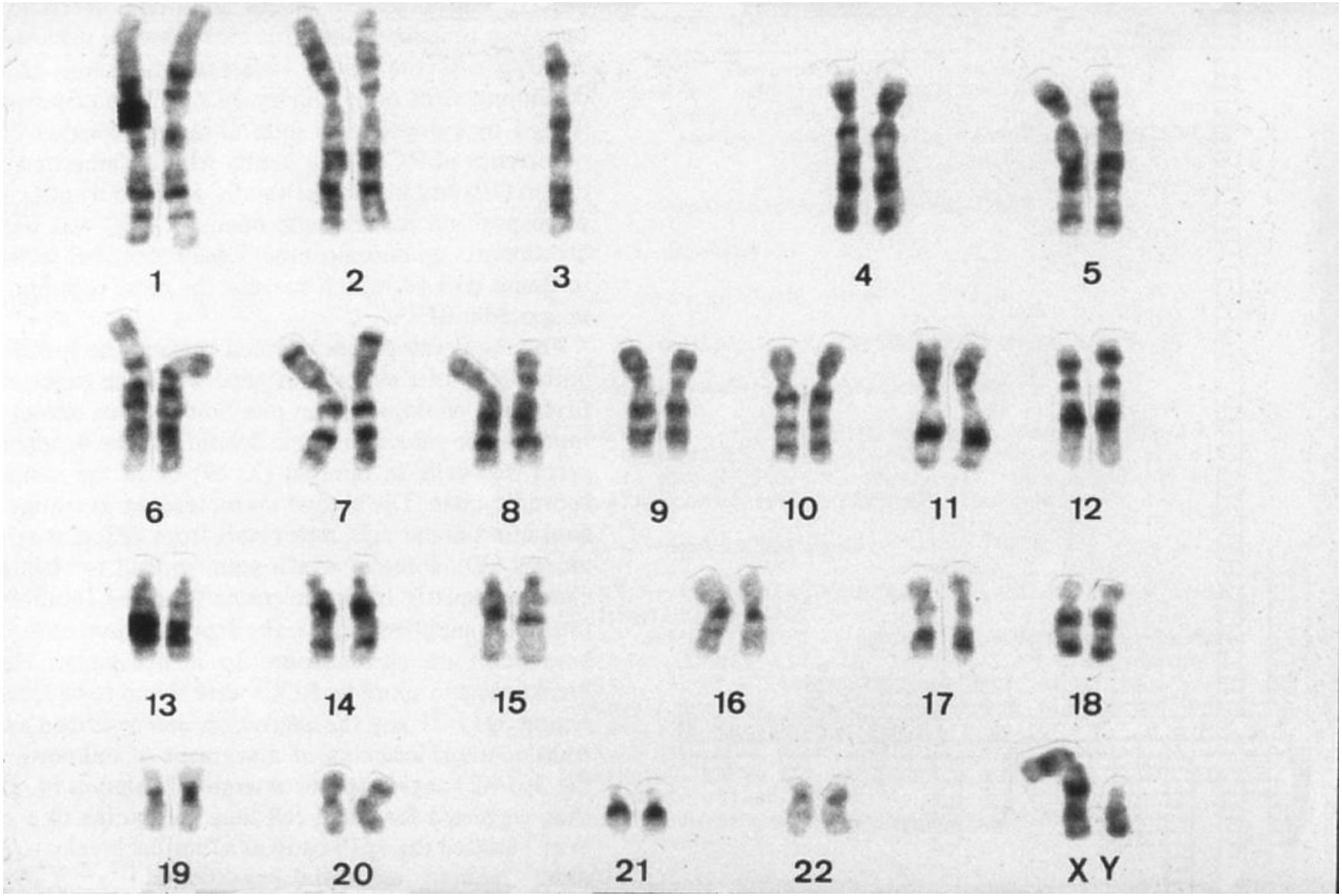
chromosomes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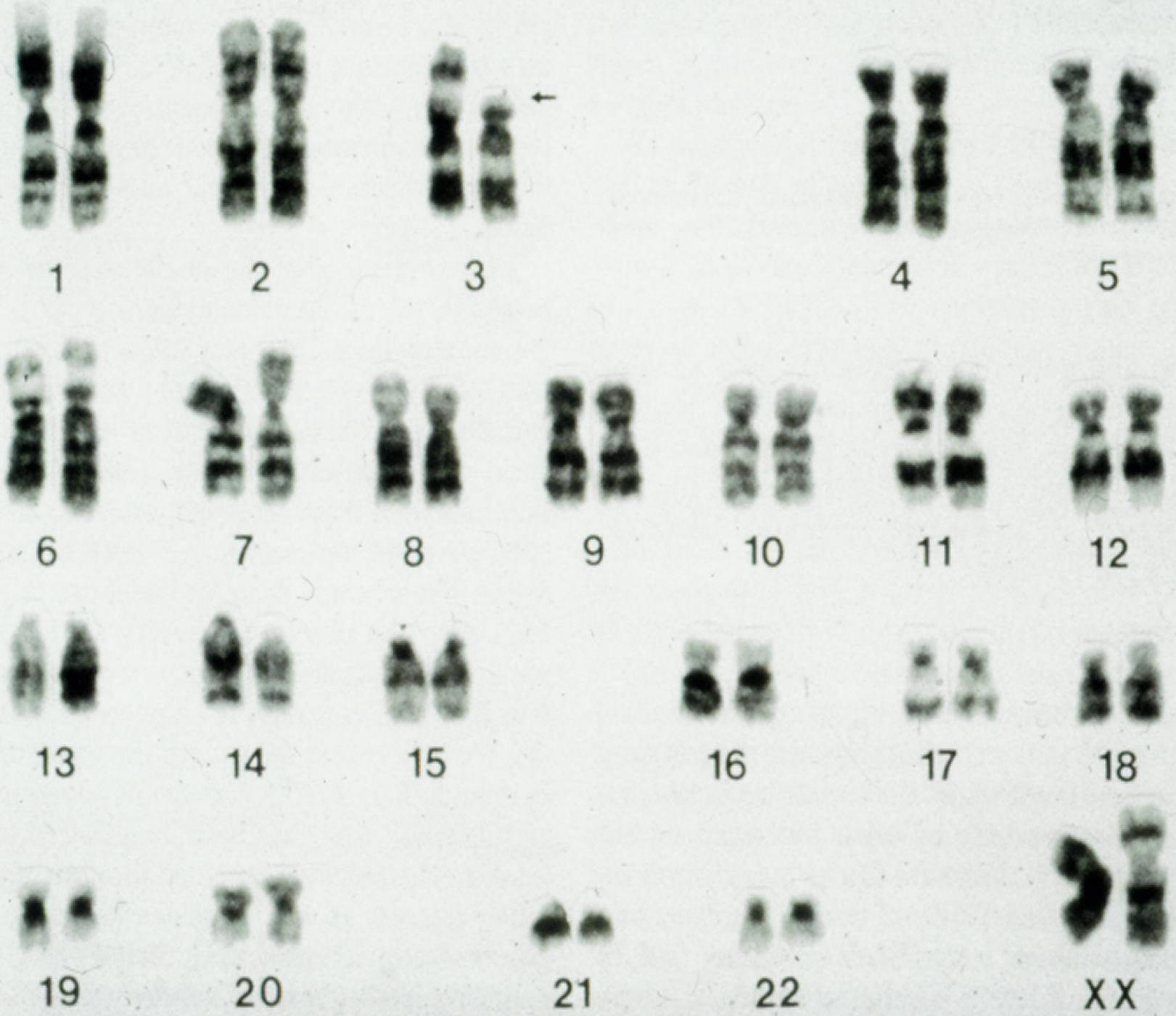
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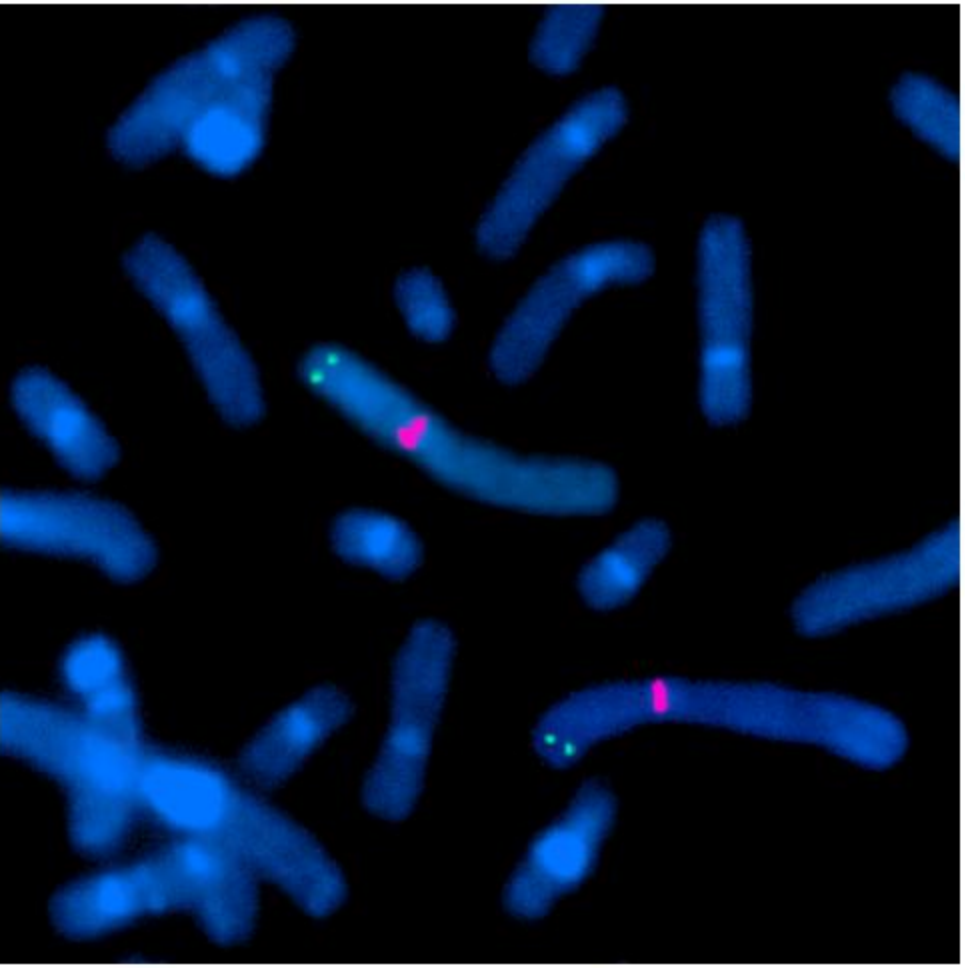
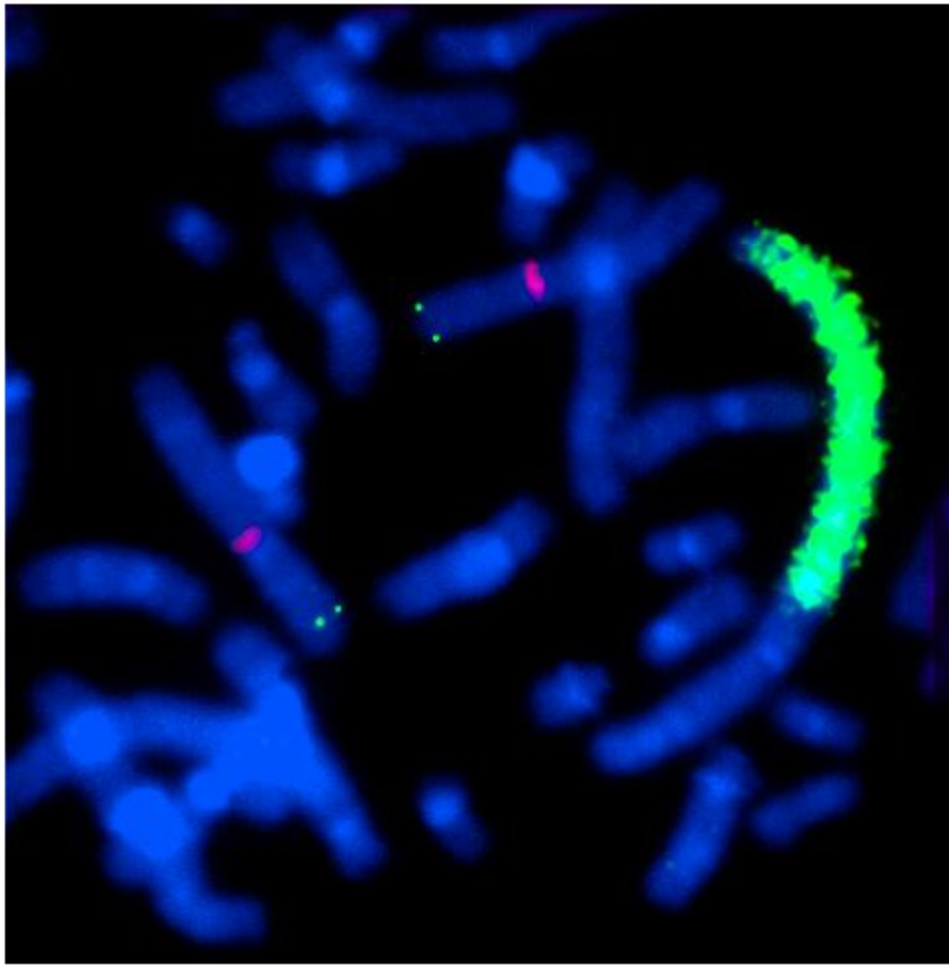


Normale Zelle



Tumorzelle

The role of genes during cancer development

1. **Strong inherited influence,**
   Mendelian-Genetics of inherited risk with high degree of penetrance;
   individual cancer risk can be well determined by a genetic test because the likelihood of gene-mutation carriers to develop cancer is close to 100%

Cancer predisposition genes

1. *Tumour suppressor genes*

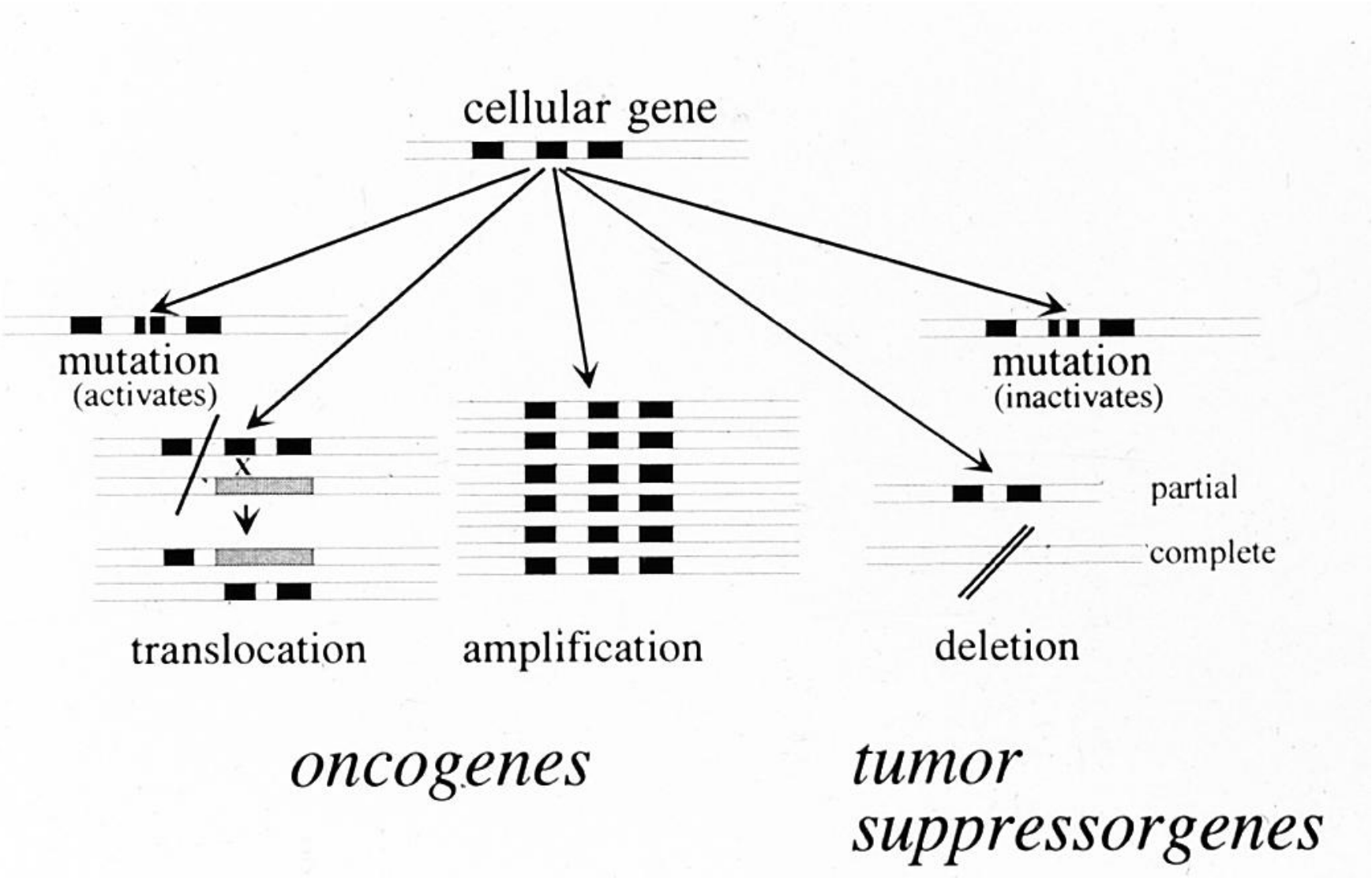
- **gatekeeper genes** (the classic tumour suppressors) limit cell growth by regulating basic cell functions and controlling cell cycling, proliferation, differentiation and apoptosis
- **caretaker genes** correct errors in and repair DNA

both alleles must be inactivated

2. *Oncogenes*

- encode proteins such as growth factors, growth factors receptors, membrane associated signalling proteins or transcription factors; they are activated during cell growth in response to growth promoter stimulation
- oncogenes are abnormally derived from proto-oncogenes; transformation to cancer involves retroviral action, point mutation, chromosome rearrangmenets (translocation) or amplification

mutation of one allele is sufficient to produce uncontrolled cell growth


cellular gene
mutation
(activates)
mutation
(inactivates)
partial
complete
translocation
amplification
deletion
oncogenes
tumor
suppressorgenes

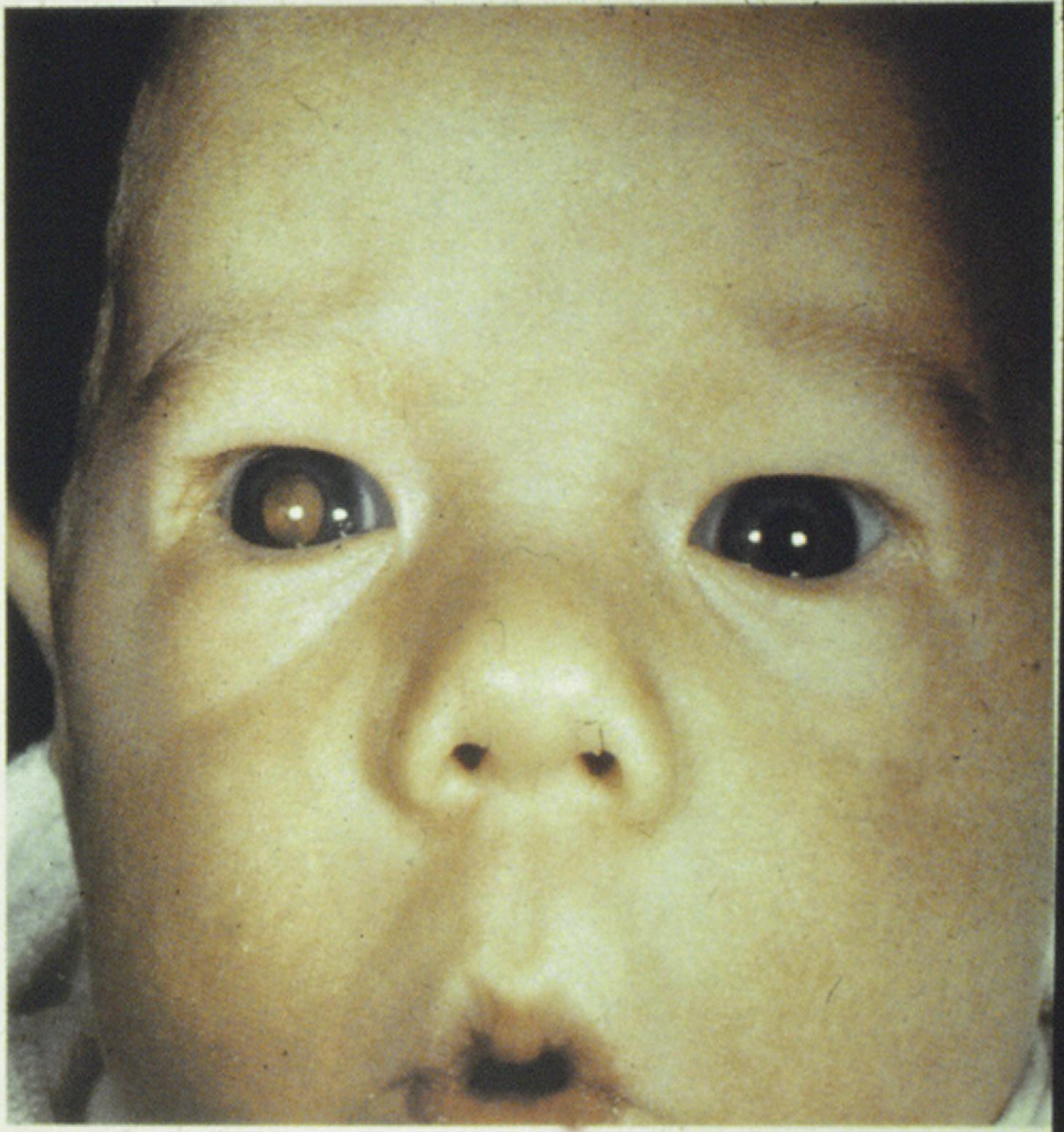
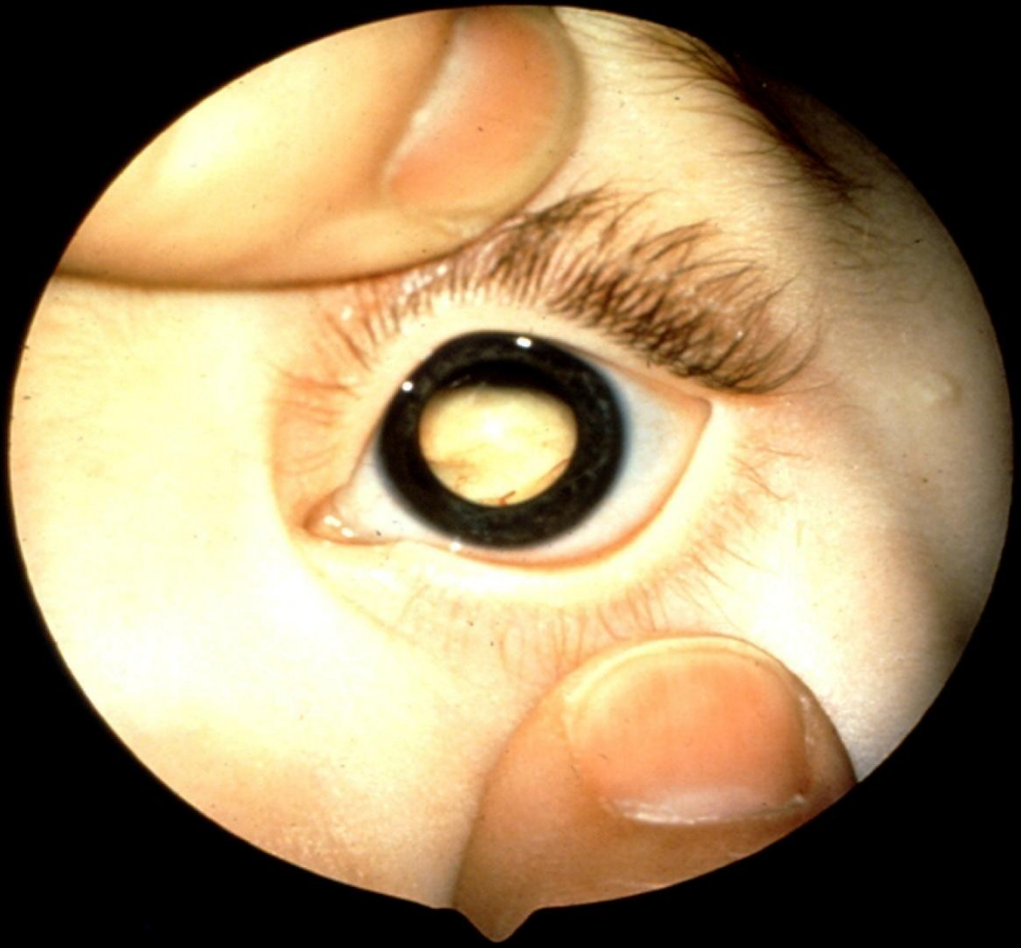


Fig. 9-2. Leukocoria as a presenting sign of retinoblastoma

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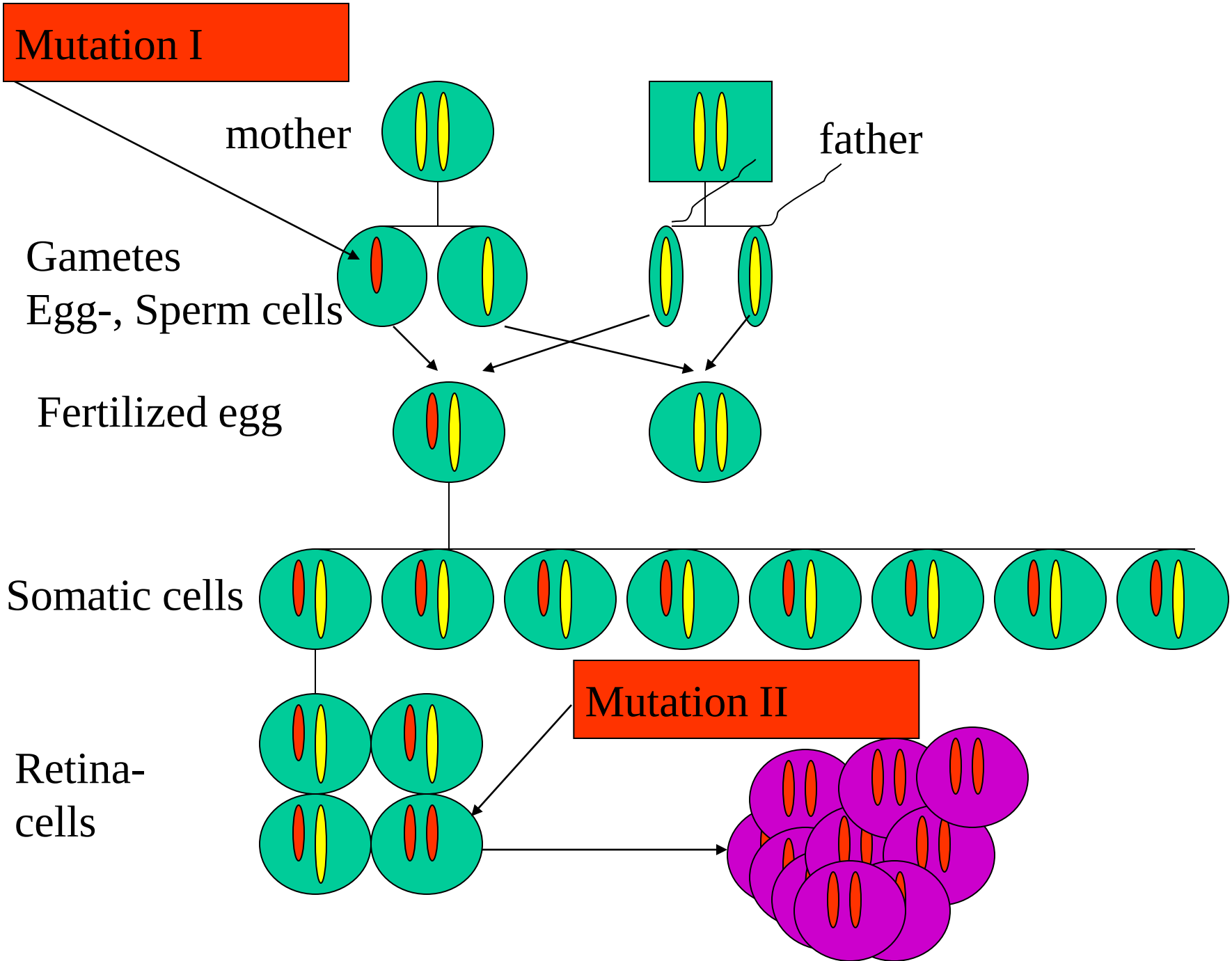

Mutation I
mother
father
Gametes
Egg-, Sperm cells
Fertilized egg
Somatic cells
Mutation II
Retina-
cells

Table 1 | **Hereditary cancer syndromes**

Syndrome	Associated genes	Predominant tumour types or abnormalities
Hereditary breast and ovarian cancer	*BRCA1* *BRCA2*	Breast carcinomas, ovarian carcinomas
Carney complex	*PRKAR1A*	Skin pigment abnormalities, endocrine tumours, schwannomas
Cowden	*PTEN*	Breast carcinomas, thyroid carcinomas, endometrial carcinomas
Familial adenomatous polyposis	*APC*	Adenomatous polyps of the colon/rectum, gastrointestinal cancers, papillary thyroid carcinomas
Familial melanoma	*CDKN2A* *CDK4*	Cutaneous malignant melanoma, pancreatic cancers
Hereditary papillary renal carcinoma	*MET*	Papillary renal-cell carcinomas
Hereditary non-polyposis colorectal cancer	*MSH2* *MSH6* *MLH1* *PMS1* *PMS2*	Colorectal and endometrial adenocarcinomas
Hereditary diffuse gastric cancer	*CDH1*	Diffuse adenocarcinomas of the stomach wall
Juvenile polyposis coli	*MADH4*	Multiple juvenile polyps in the gastrointestinal tract, colorectal and gastrointestinal malignancies
Li–Fraumeni brain	*TP53*	Breast cancers, soft-tissue sarcomas, tumours, adrenocortical tumours, leukaemia
Multiple endocrine neoplasia type 1	*MEN1*	Primary hyperparathyroidism, pancreatic islet-cell tumours, anterior pituitary tumours
Multiple endocrine neoplasia type 2	*RET*	Medullary thyroid carcinomas, phaeochromocytomas, mucosal neuromas
Nevoid basal-cell carcinoma	*PTCH*	Basal-cell carcinomas
Neurofibromatosis type 1	*NF1*	Neurofibrosarcomas, astrocytomas, melanomas, rhabdomyosarcomas, chronic myeloid leukaemia
Neurofibromatosis type 2	*NF2*	Bilateral vestibular schwannomas, meningiomas, spinal tumours, skin tumours
Peutz–Jeghers	*STK11*	Gastrointestinal-tract carcinomas, breast carcinomas, testicular cancers, gynaecological malignancies
Phaeochromocytoma	*SDHB*, *SDHC*, *SDHD*	Phaeochromocytomas, glomus tumours
Retinoblastoma	*RB*	Paediatric retinal tumours
Tuberous sclerosis complex	*TSC1* *TSC2*	Multiple hamartomas, renal-cell carcinoma, astrocytomas
von Hippel–Lindau	*VHL*	Renal-cell carcinomas, retinal and central nervous system haemangioblastomas, phaeochromocytomas

BRCA1, *BRCA2* – breast and ovarian carcinoma

APC – familial adenomatous polyposis (APC)

MET – hereditary papillary renal carcinoma

MSH2, MSH6, MLH1, PMS1, PMS2 – hereditary non-polyposis colorectal cancer (HNPCC)

TP53 – Li-Fraumeni syndrome

RET – multiple endocrine neoplasia type 2

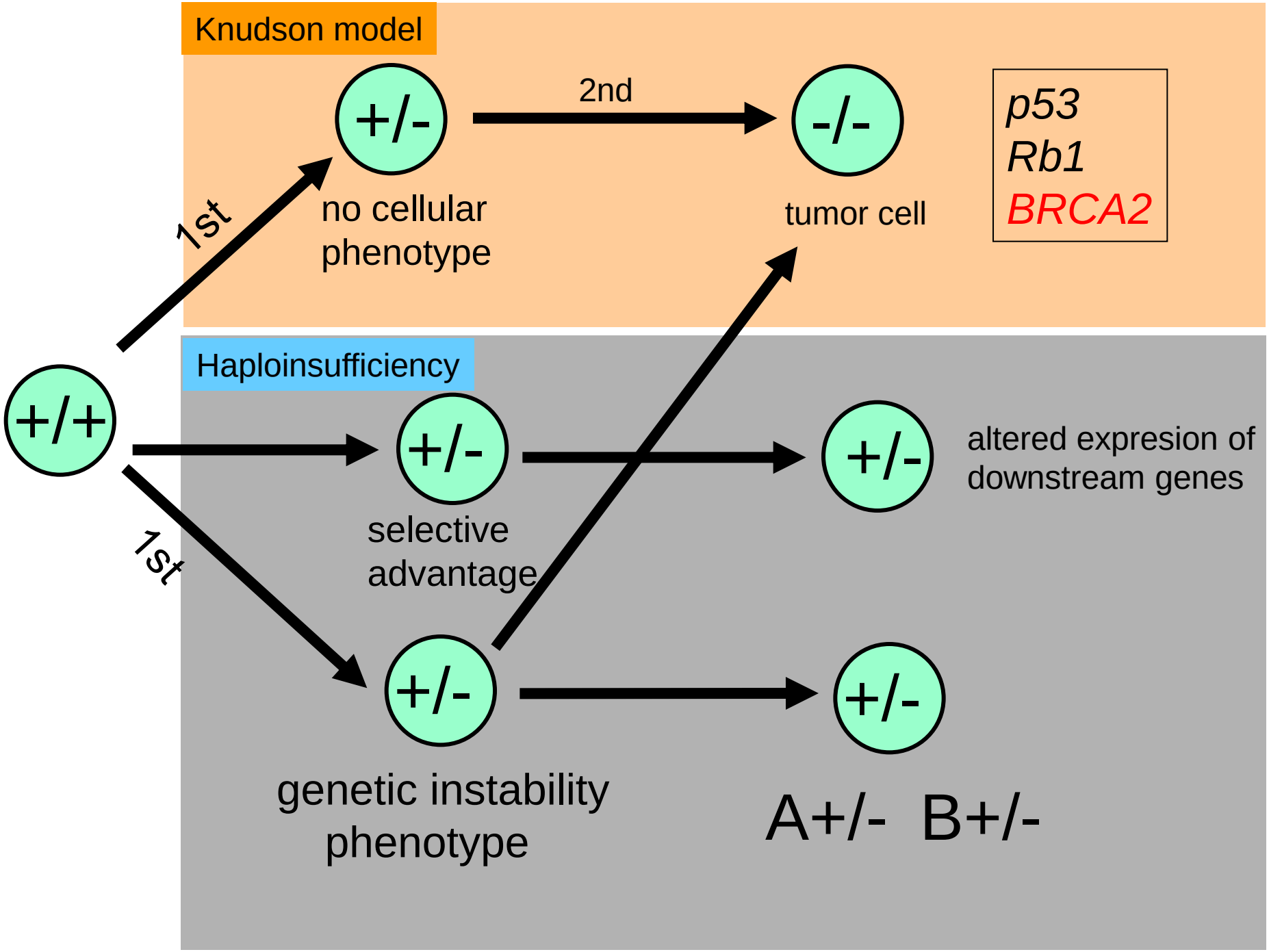
NF1, NF2 – neurofibromatosis type1 /type2

RB – retinoblastoma

Oncogene

Tumor-suppressor genes

Stability genes


Knudson model
+/-
2nd
-/-
p53
Rb1
BRCA2
1st
no cellular
phenotype
tumor cell
Haploinsufficiency
+/+
+/-
+/-
altered expresion of
downstream genes
1st
selective
advantage
+/-
+/-
genetic instability
phenotype
A+/- B+/-

The role of genes in cancer development

2. **Medium inherited influence,**
   Penetrance limited; individual risk hard to evaluate;
   gene carriers can develop cancer unpredictably

"All the News That's Fit to Print"

The

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Research Links One Gene To Most Breast Cancers

New Hope for Predicting and Treating Disease

By GINA KOLATA

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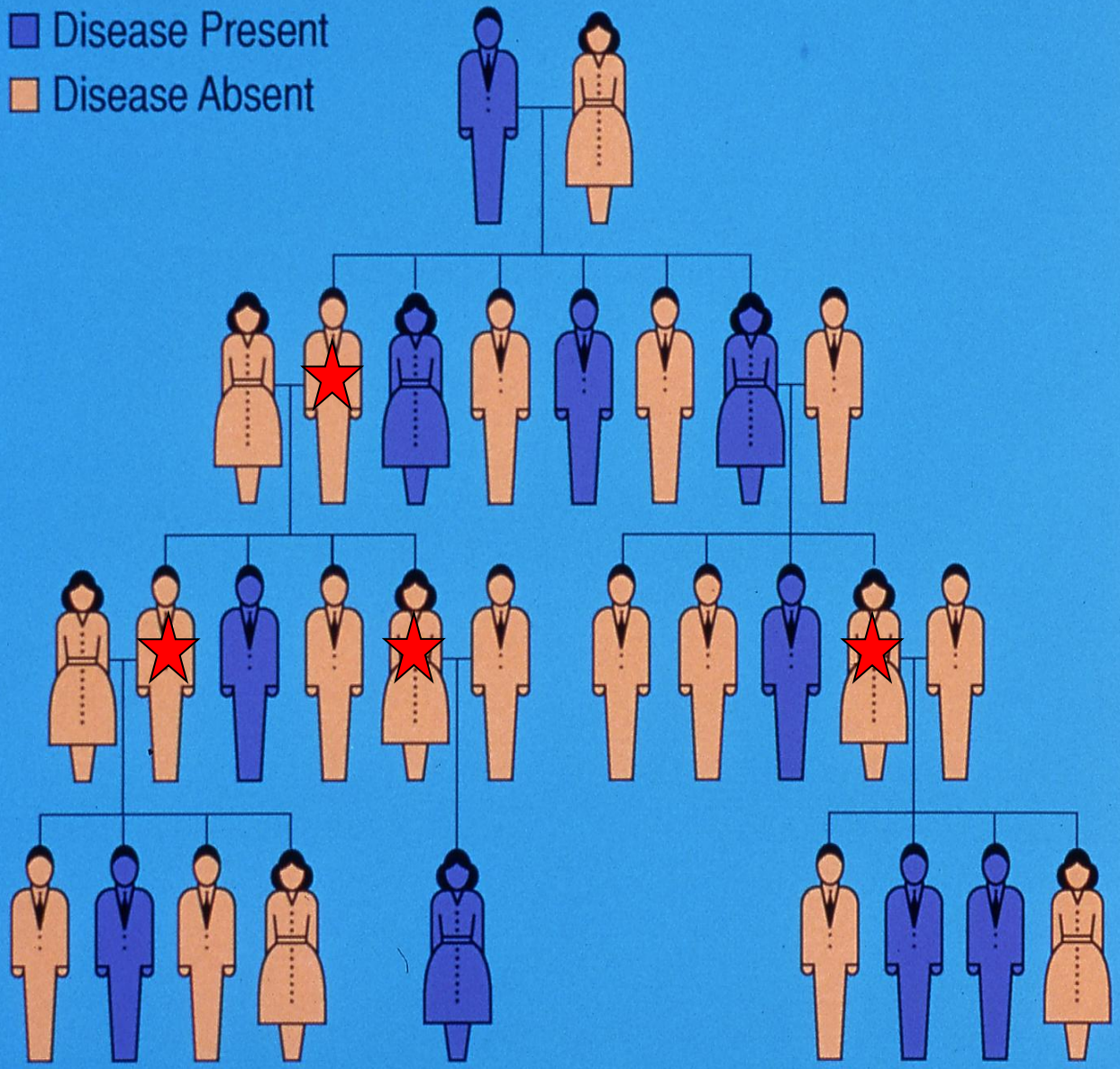
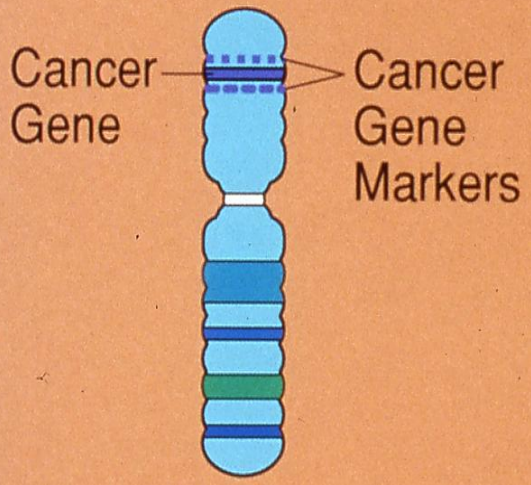
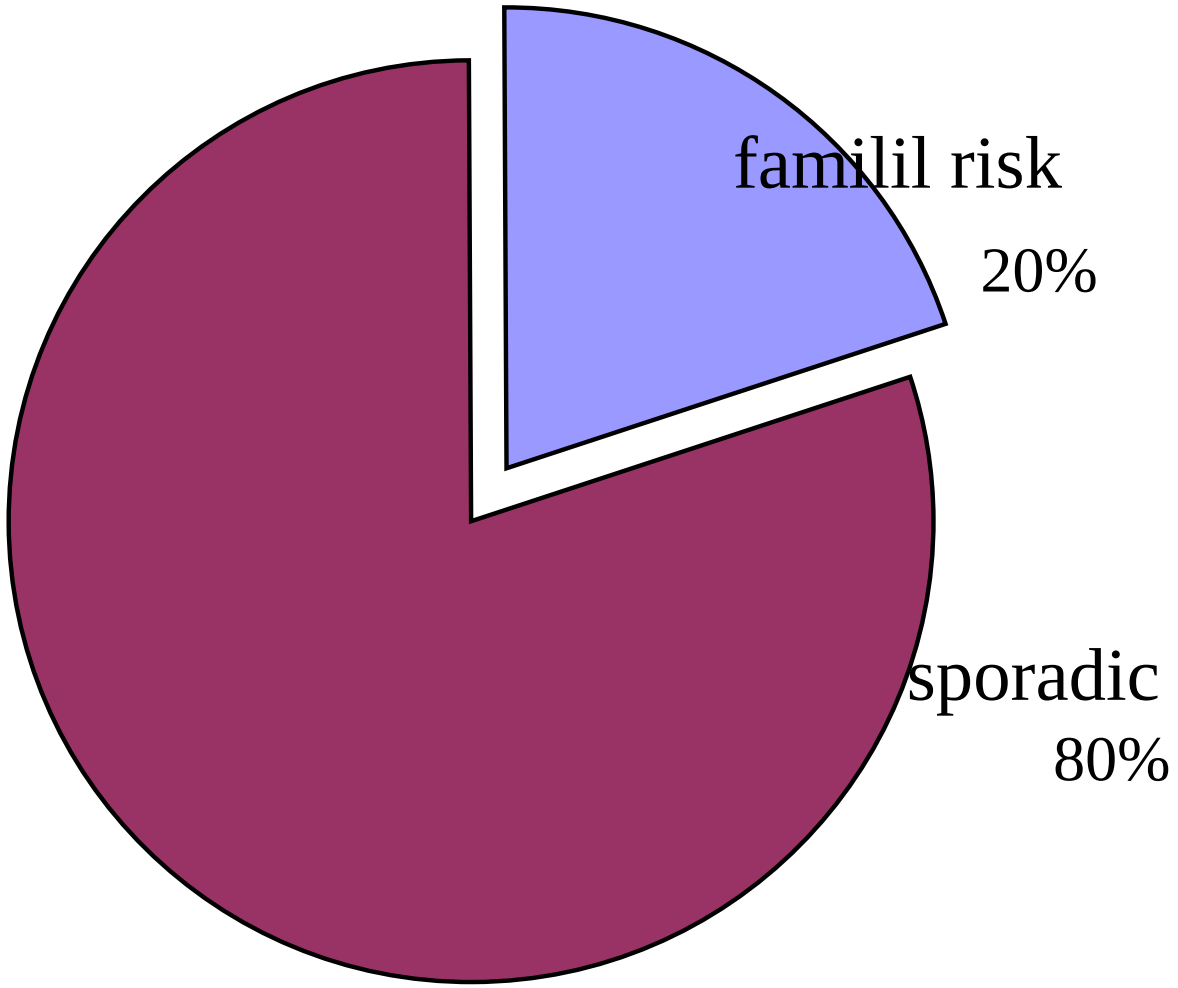
But women with familial breast cancers constitute just 5 percent of all women with the disease, so the importance of the finding seemed of minor importance for the vast majority of women who might contract

Searching Disease Families

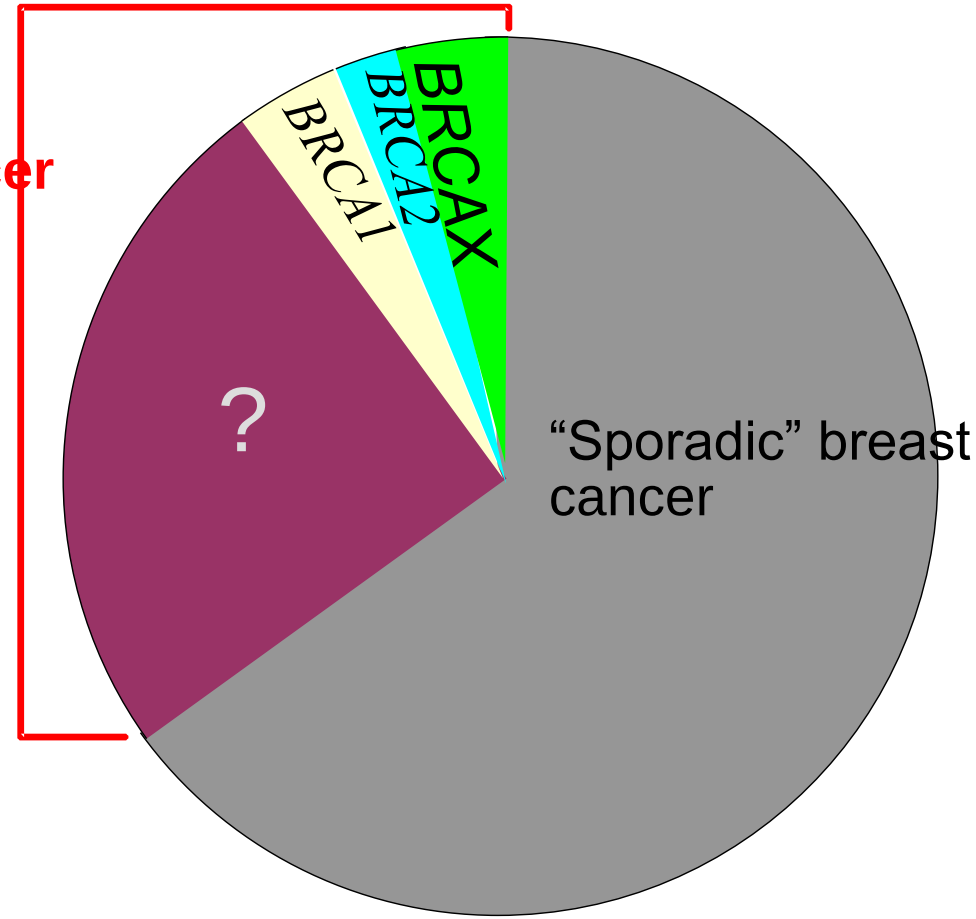




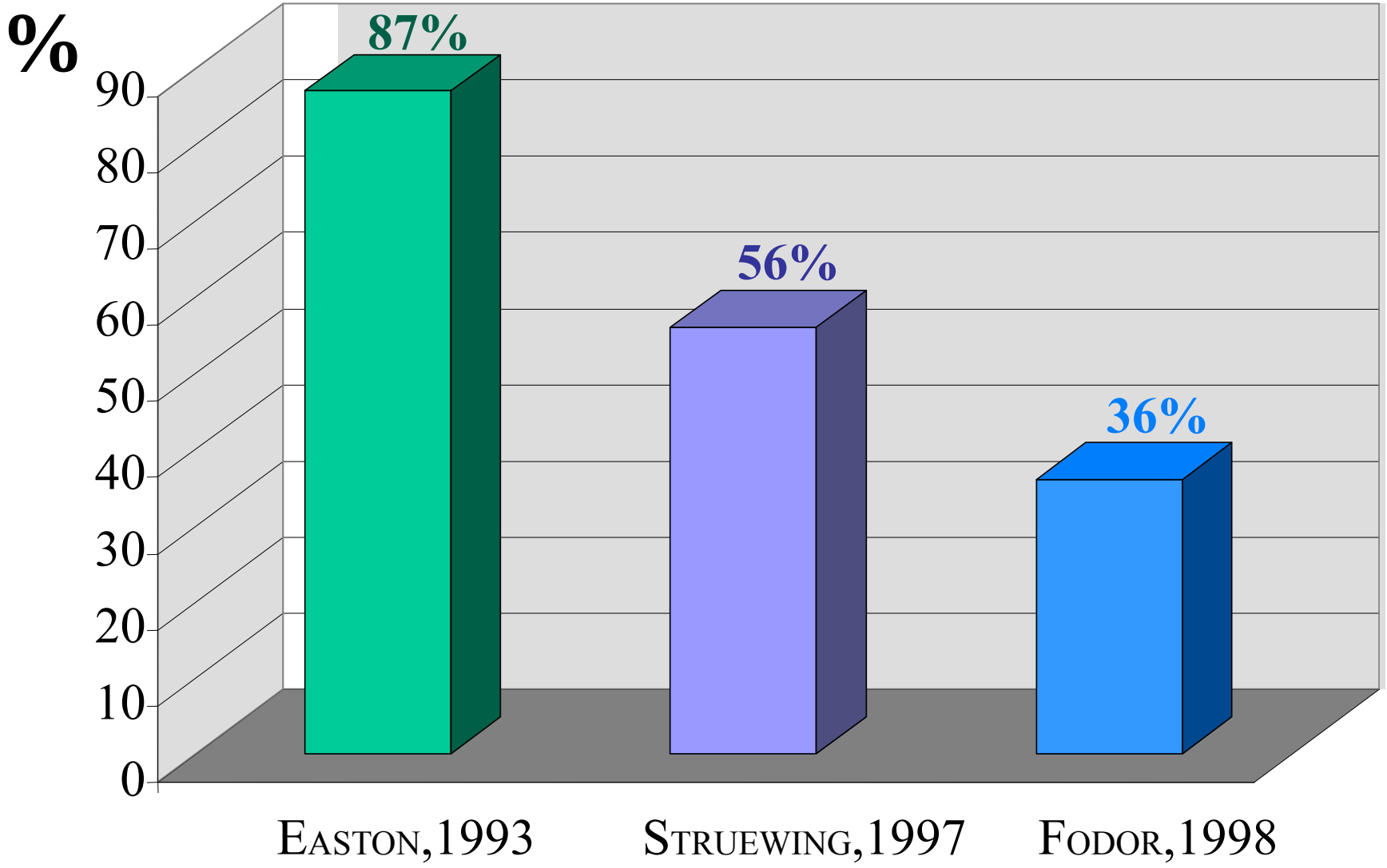
Contribution of inherited factors to breast cancer



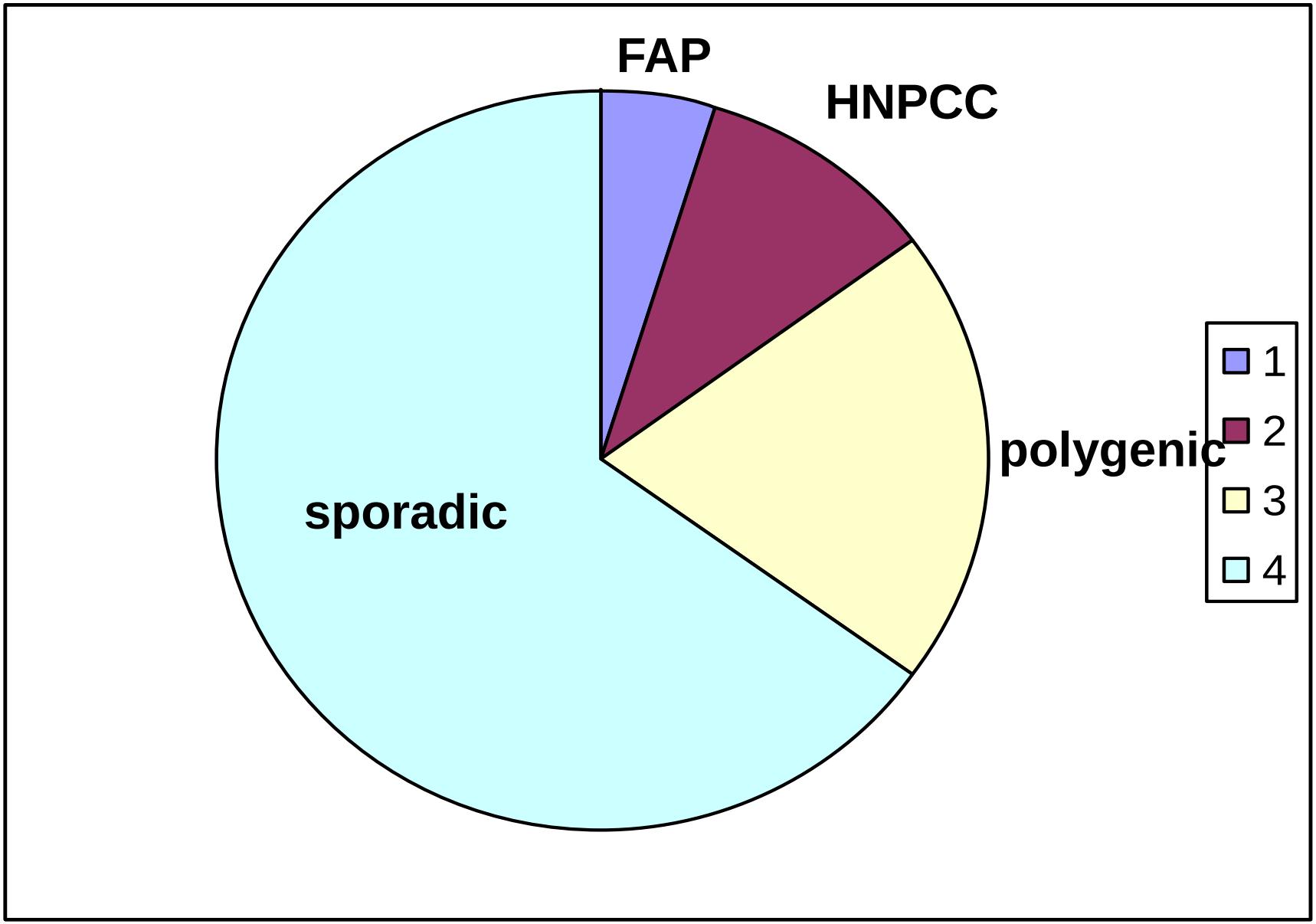
Genes in breast cancer



Lifetime risk for breast cancer - BRCA mutation carriers(>75 years)



Genetics and colorectal cancer



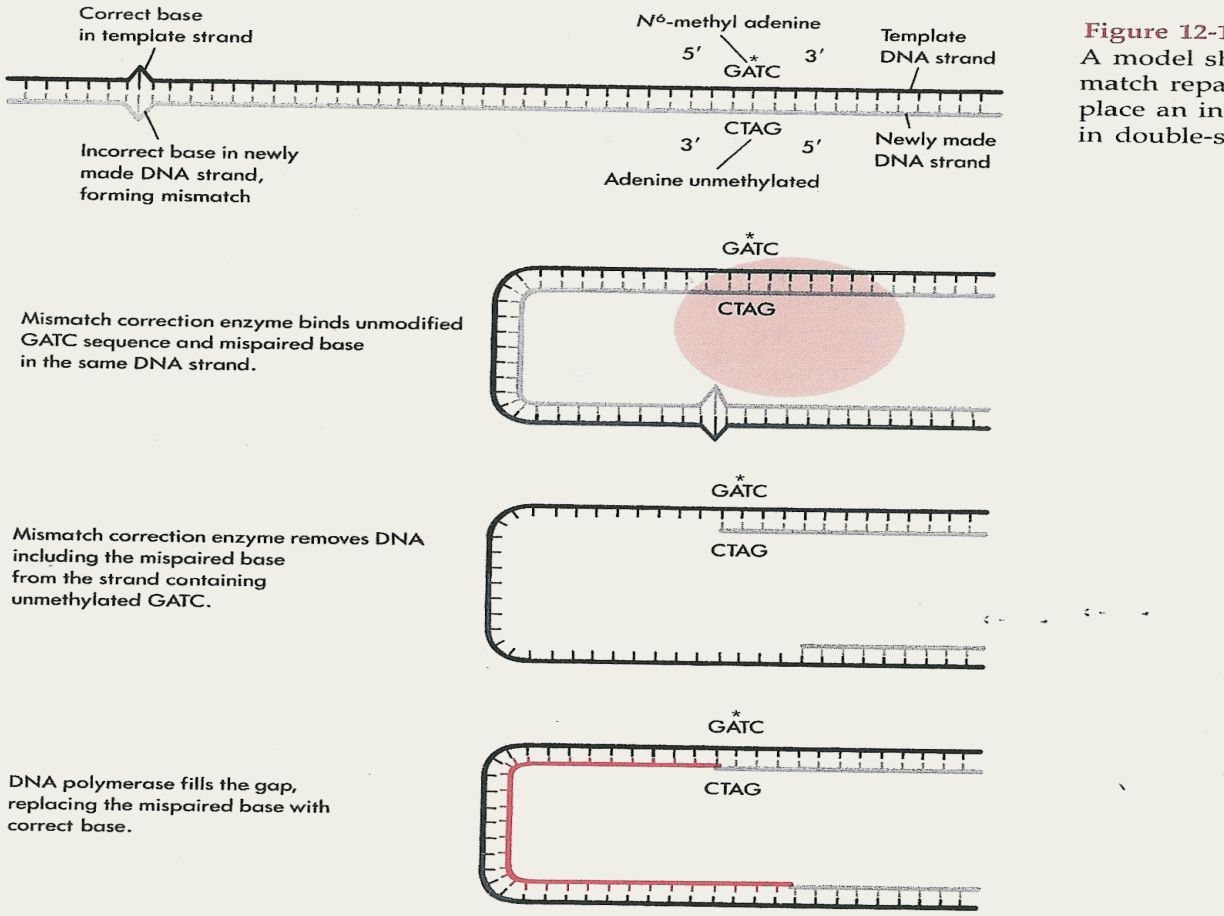


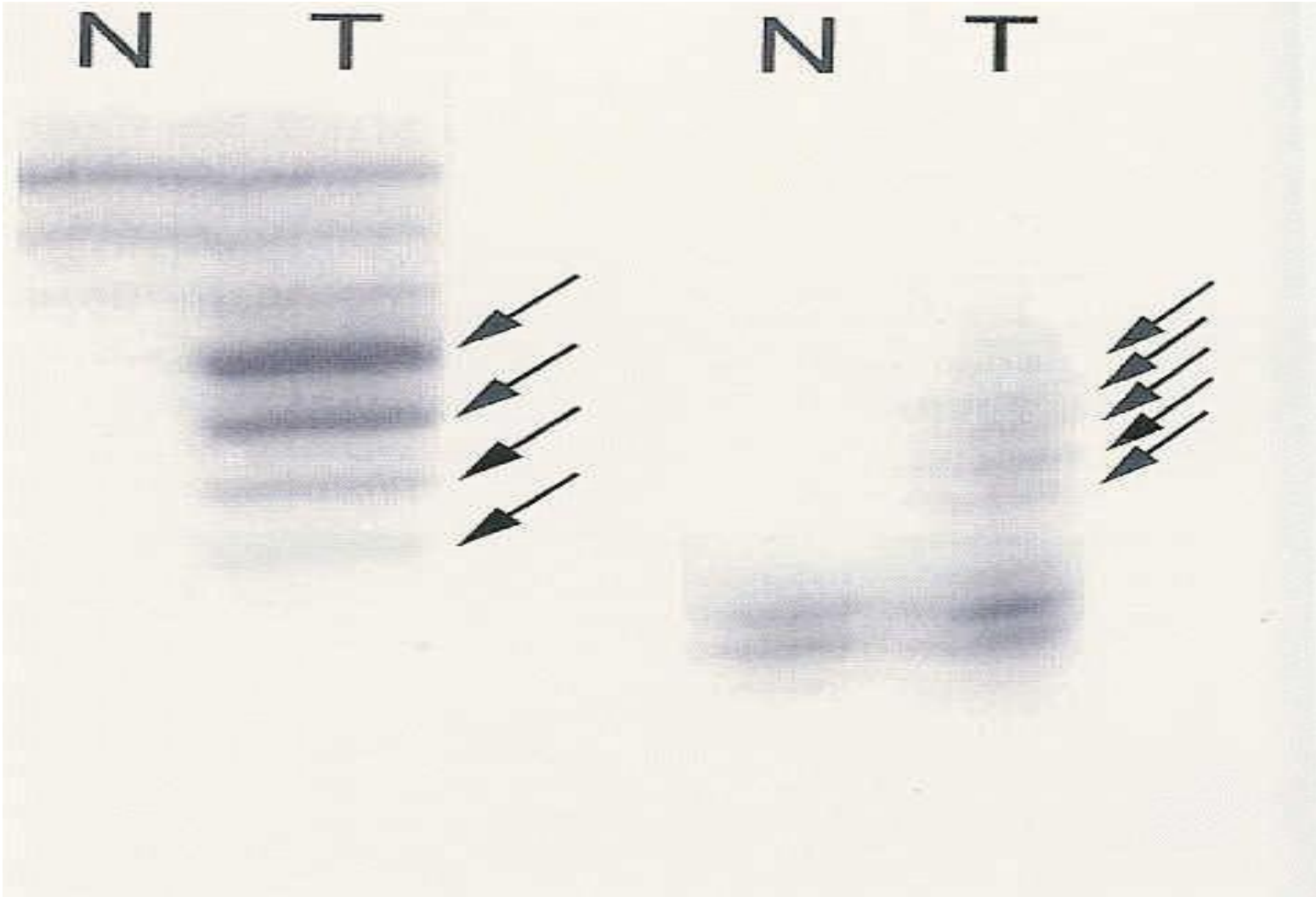
Figure 12-11
A model showing how the *E. coli* mismatch repair system could act to replace an incorrect and mispaired base in double-stranded DNA.

that DNA polymerase leaves about one mistake per 10^8 replicated base pairs. However, not even these usually appear as mutations, since the measured mutation rate can be as low as one mistake per 10^{10} or 10^{11} nucleotides. In *E. coli*, the final degree of accuracy is the responsibility of a **mismatch correction enzyme** encoded by genes *mutH*, *mutL*, and *mutS*. The enzyme scans newly replicated DNA for mismatched base pairs and removes a single-stranded segment containing the wrong nucleotide, thereby allowing a DNA polymerase to insert the correct base when it fills the resulting gap. The obvious problem that this entails is that of distinguishing which base of a mismatched pair is wrong, because both are natural components of

Mikrosatellites

Are present in high copy numbers in the human genome

Single copy		Repeat		Single copy
Mononucleotide	---GGTAGCC	AAAAAA	(A)n	CGATCCA--------
Dinucleotide	---TCGCATG	CA CA CA	(CA)n	ATTCGCA---
Trinucleotide	---TTAGCAT	CAG CAG	(CAG)n	CCAGTGA---
Tetranucleotide	---AATGGTA	CCGG	(CCGG)n	GTCACGT-----
Pentanucleotide	---CGATGAT	CCAAG	(CCAAG)n	TTACGTA---
Hexanucleotide	---GCTAAGG	CCATTG	(CCATTG)n	ACTGTCA---


N
T
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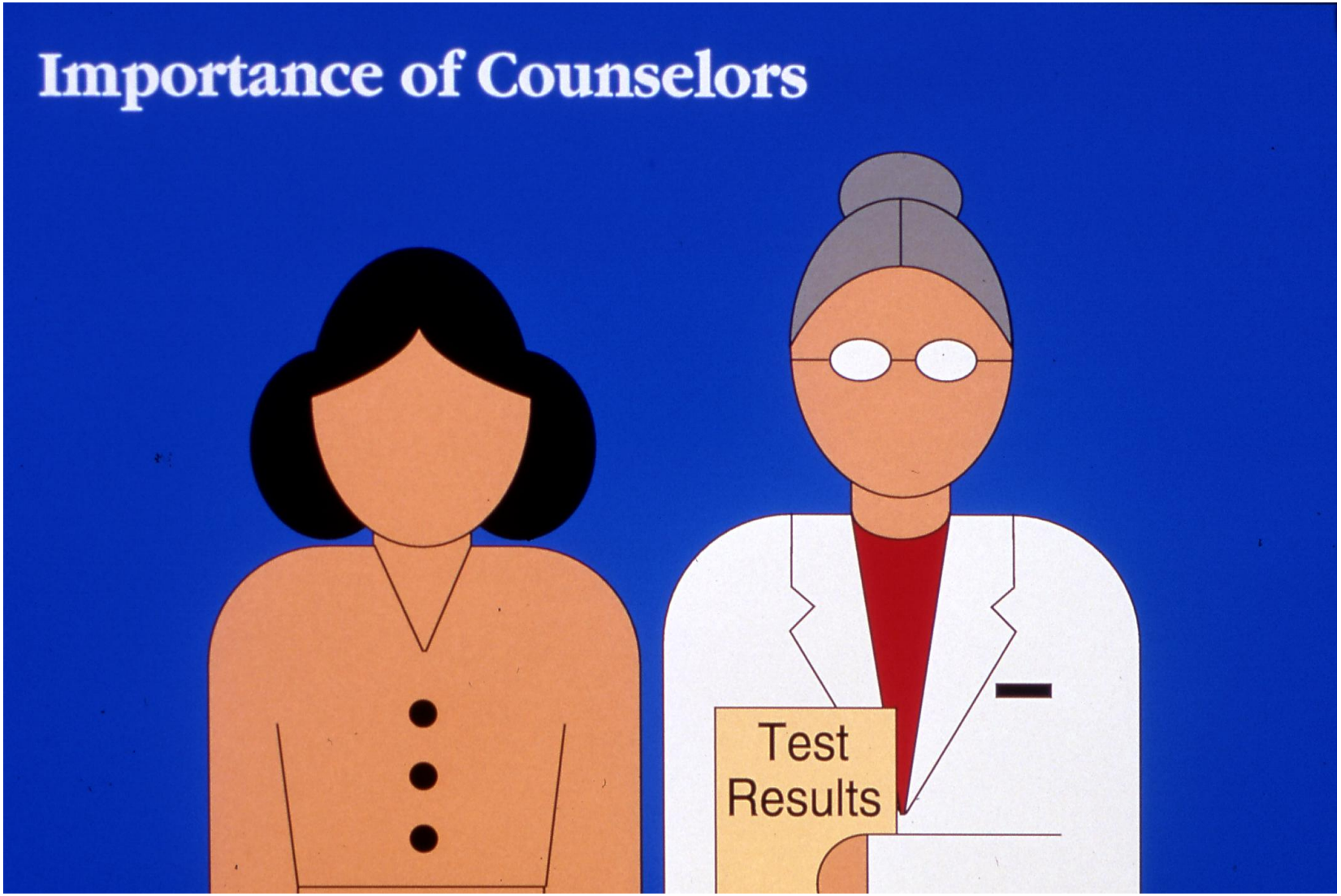
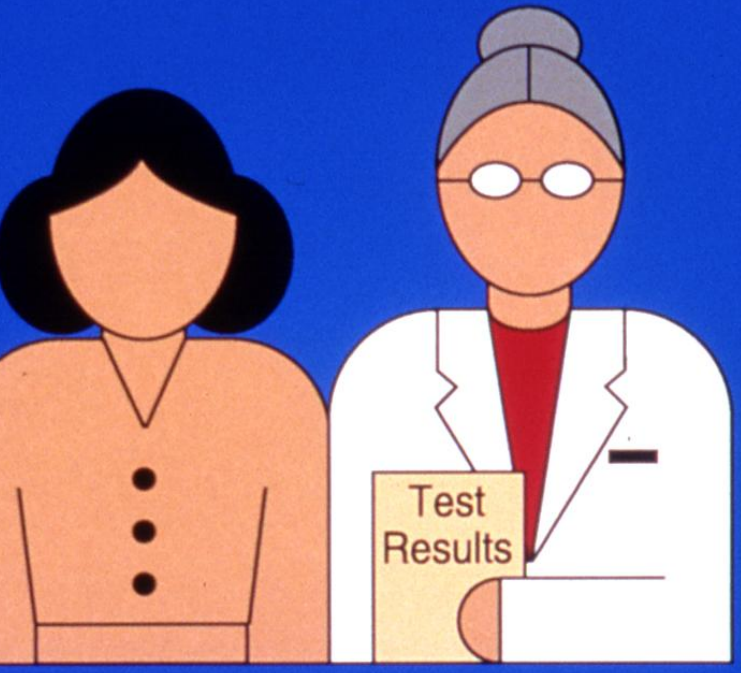
Mikrosatellite Instability results in frameshift mutations in coding regions of cancer risk genes

BAX	--AATGGGGGGGGAGG-- ↓ + 1 base --AATGGGGGGGGGAGG—	(G)8
MSH6	--ATACCCCCCCCTTC-- ↓ - 1 base --ATACCCCCCCTTC—	(C)8
TCF4	--GAGAAAAAAAAAGTG-- ↓ - 1 base --GAGAAAAAAAAGTG—	(A)9
TGFβRII	--AGGAAAAAAAAAAGCC-- ↓ - 1 base --AGGAAAAAAAAAGCC--	(A)10

Importance of Counselors





Benefits of Gene Testi

- Relief
- Fewer Checkups
- Informed Decisions
- Intervention

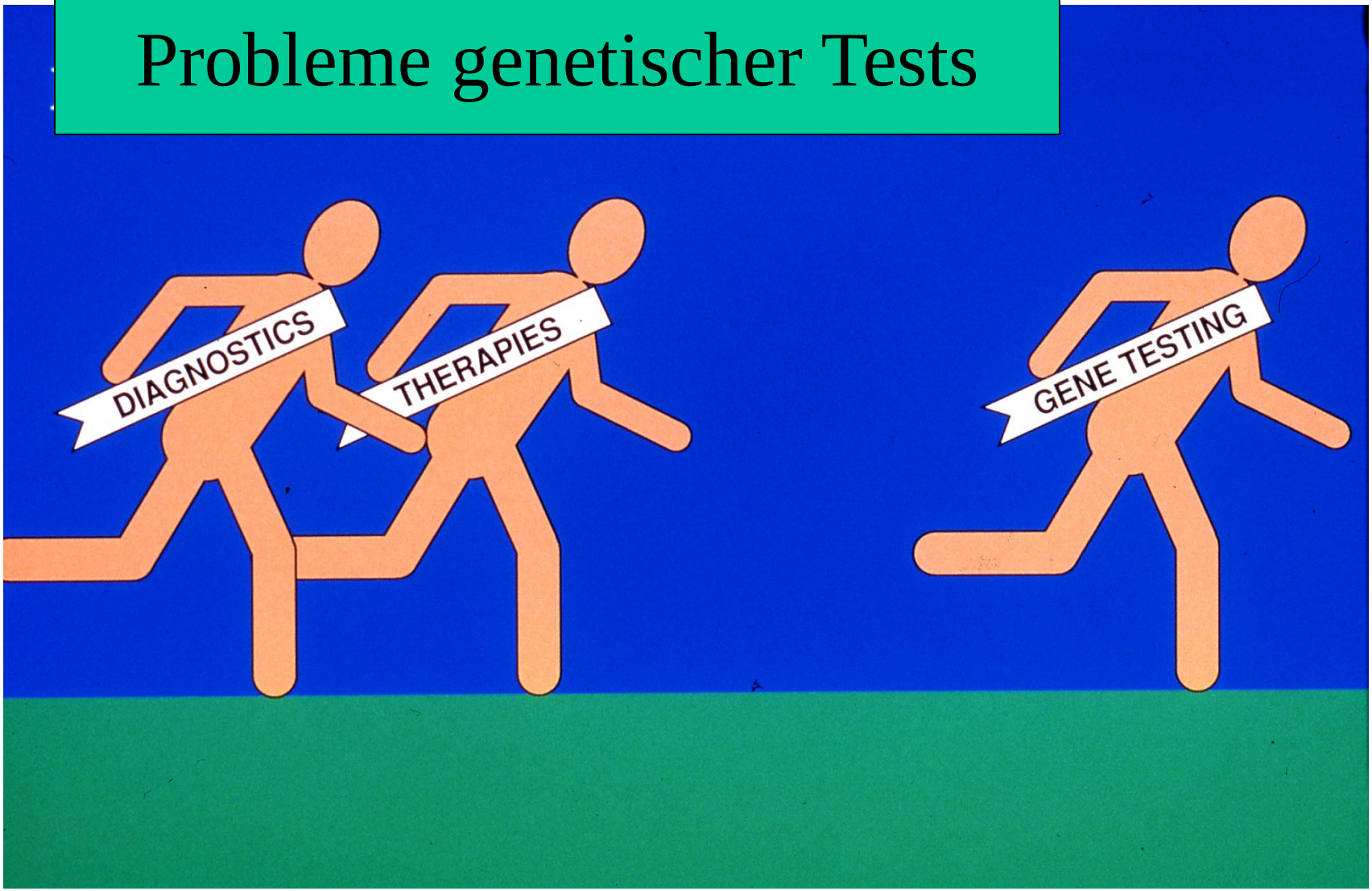
Limitations of Gene Testing

Mutation Present But:

- May Be Acquired, Not Inherited
- May Never Lead to Disease
- May Go Undetected

Difficult Decision

Probleme genetischer Tests

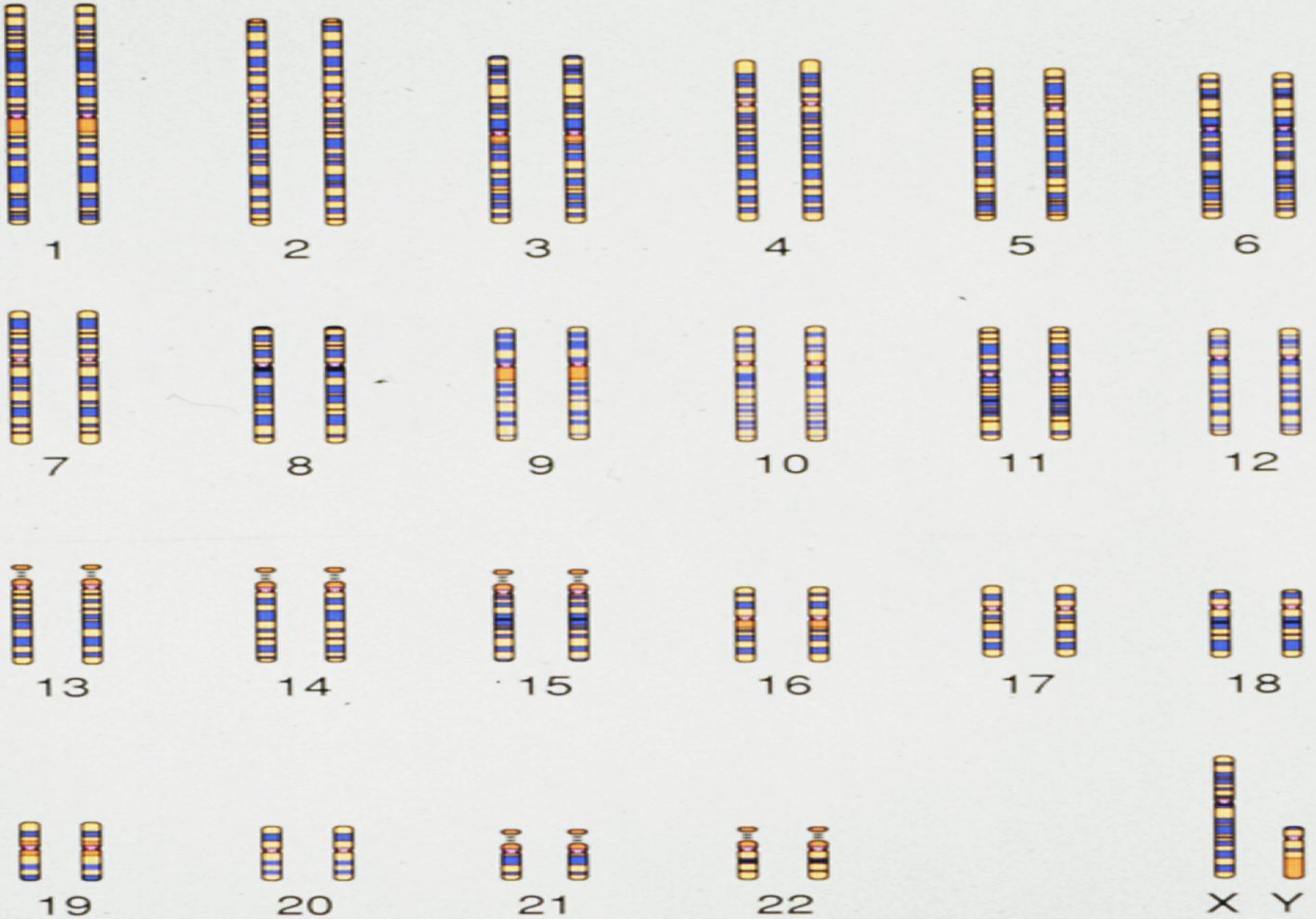


Die Rolle von Genen bei der Krebsentstehung

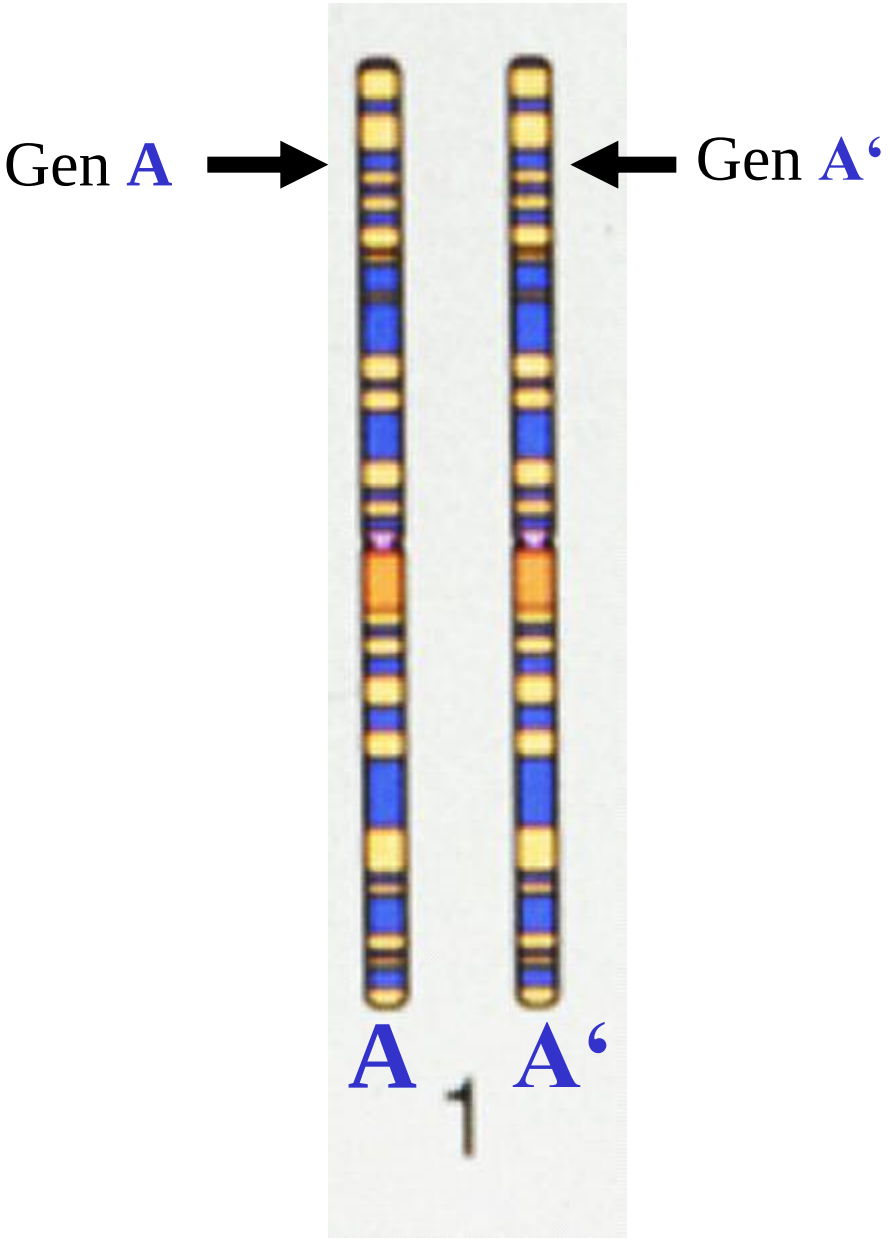
3. **Schwacher erblicher Einfluß, schwer nachweisbar**

   Hinweise kommen aus der Erkrankung multipler Organe in demselben Patienten, ohne erkennbaren erblichen Hintergrund

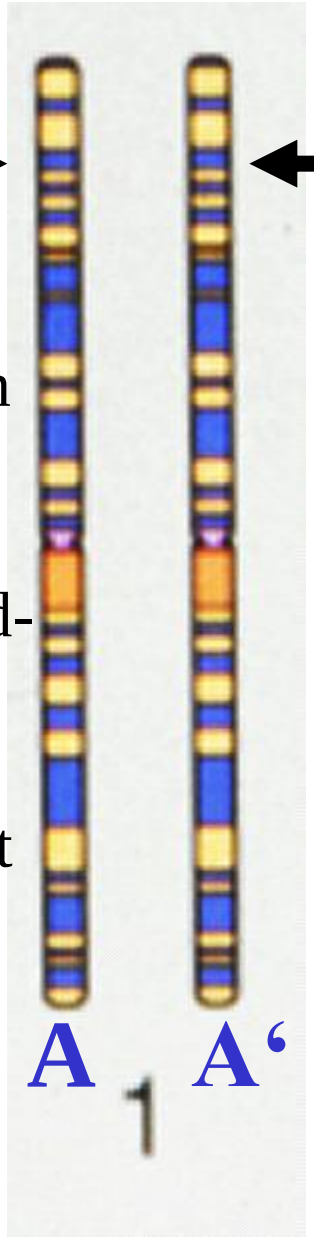
   vermutete Basis: „ungünstige“Allel-Kombinationen


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
X
Y

Ist die DNA Sequenz der Gene A und A‘ identisch??



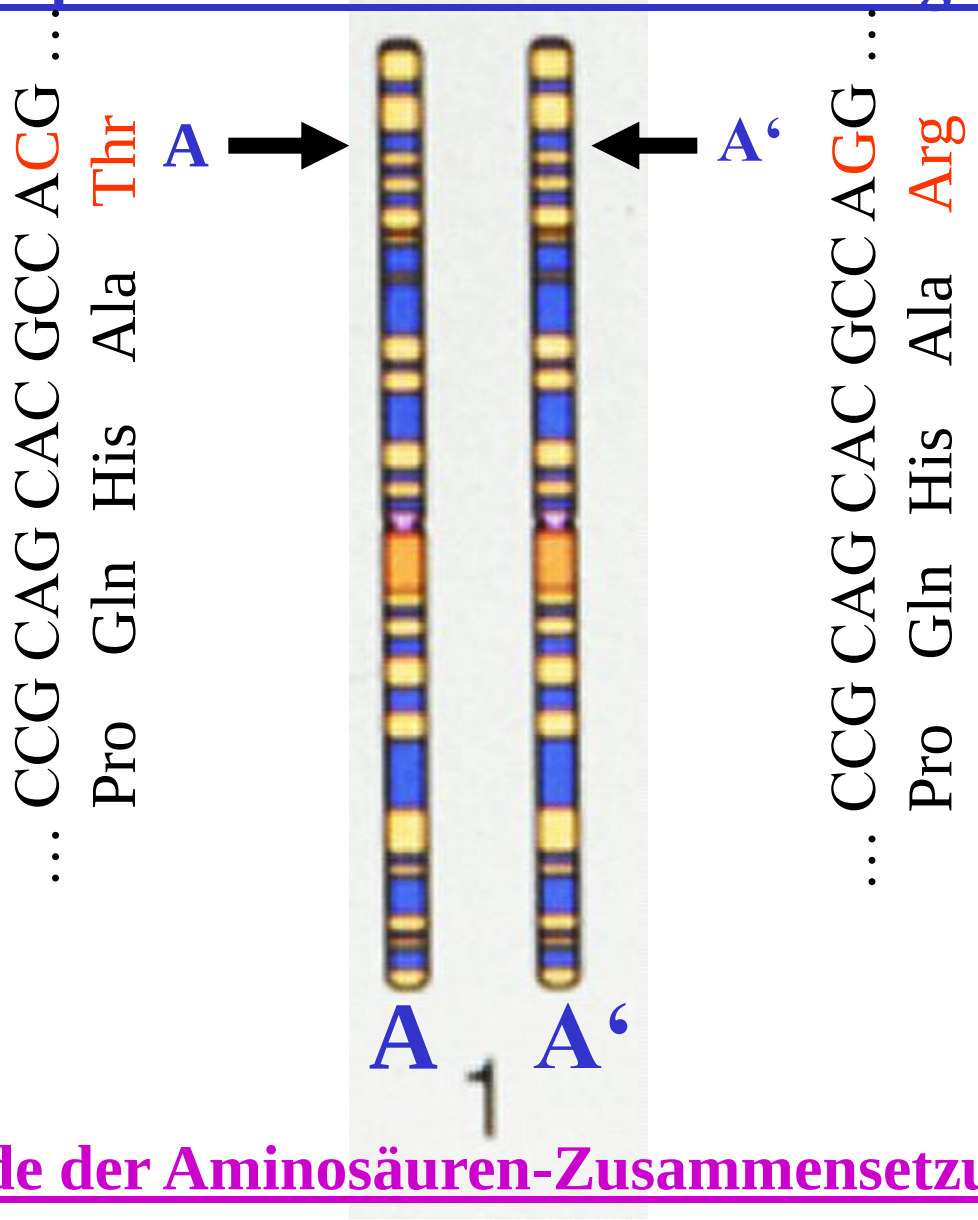
Ist die DNA Sequenz der Gene A und A‘ identisch??



Unwahrscheinlich

Die Mitglieder der humanen Spezies besitzen zwar die gleichen Gene. Diese Gene kommen aber in unterschiedlichen DNA Sequenzvarianten vor, die als Polymorphismen bezeichnet werden.

Polymorphismen kommen in unterschiedlichen humanen Populationen in bestimmten Häufigkeiten vor



Unterschiede der Aminosäuren-Zusammensetzung eines Proteins beeinflussen die Stärke seiner Funktion.

Polymorphismen und Krebsrisiko : Ein Modell-Beispiel

Allel A: starker Schutz, z.B. gegen bestimmte Agenzien
Allel A‘: schwacher Schutz
Allel-Häufigkeit jeweils 50%

Mutter: A A‘
Vater: A A‘

Erbschema

	A	A‘
A	AA	AA‘
A‘	AA‘	A‘A‘

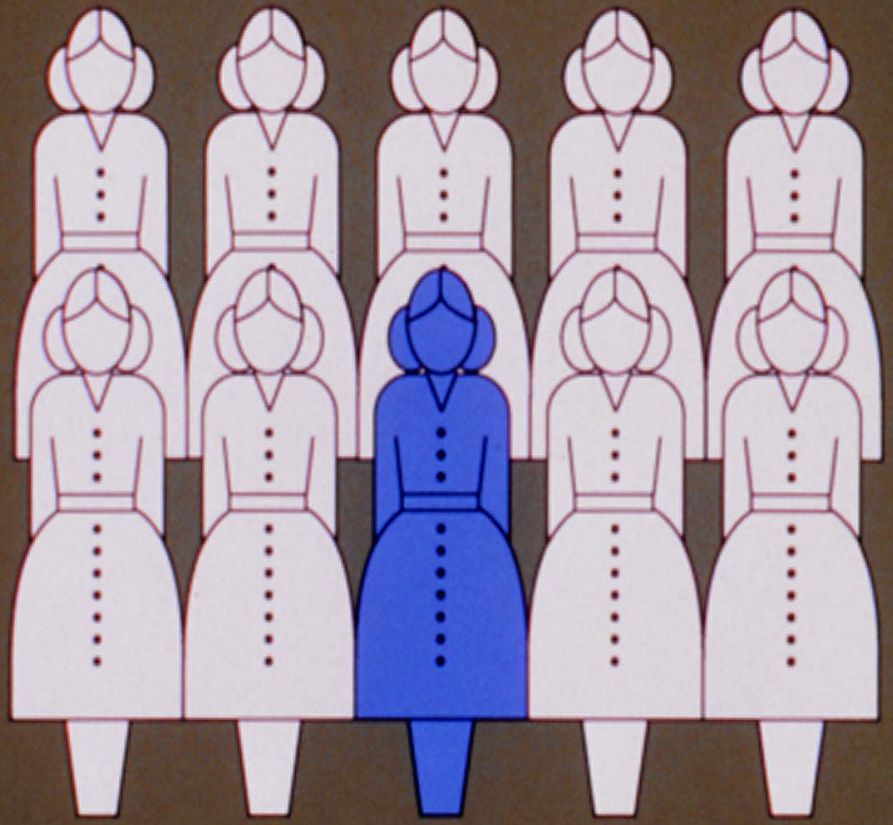
Erhöhtes Risiko gegenüber AA

Die Rolle von Genen bei der Krebsentstehung

4. **Somatische Genveränderungen ohne erkennbare erbliche Basis**

Die überwiegende Anzahl von Krebserkrankungen basiert nicht auf einem erblichen Risiko

Summe aller Patienten mit Brustkrebs



- Erbliche Risiko-Faktoren bekannt
- Grund für Krebsentstehung unbekannt

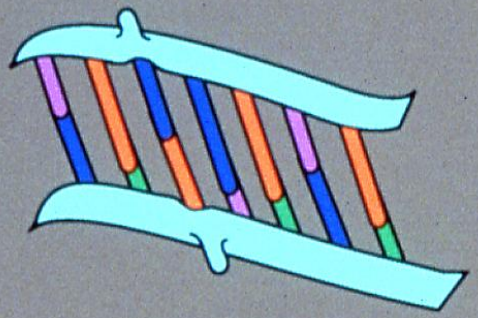
Jedes Gen hat eine spontane Mutationsrate, die in der Größenordnung von 10^{-7} bis 10^{-9} Veränderungen pro Zellteilung liegt.

Das humane Genom besteht aus etwa 3 Milliarden Einzelbausteinen, die im Verlaufe jeder Zellteilung exakt kopiert werden müssen.

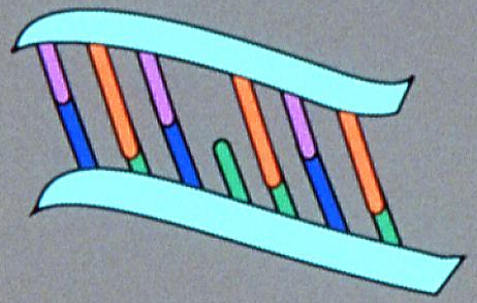
Kopierfehler werden in der Regel durch spezielle Proteinsysteme Korrigiert. Bleibende Fehler führen zur Mutation.
Konsequenz kann sein:

- kein Effekt; in Zusammenhang mit Mutationen anderer Gene kann in Abkömmlingen der Zelle ein Effekt auftreten
- Zelltod
- Veränderung des Zellwachstums

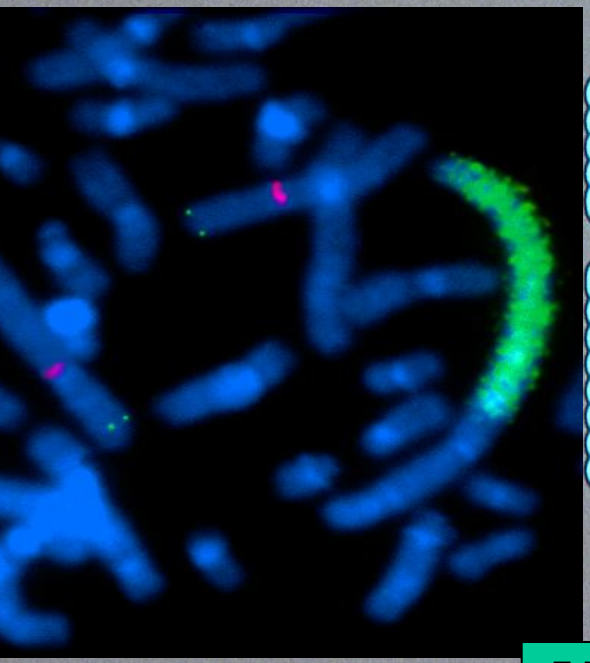
Haupt-Typen von Mutationen

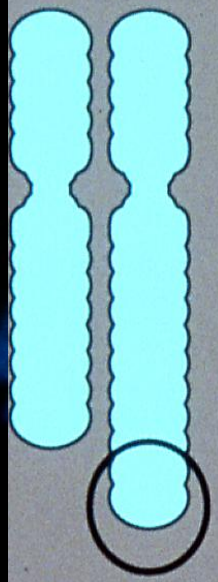


Fehl-Paarung

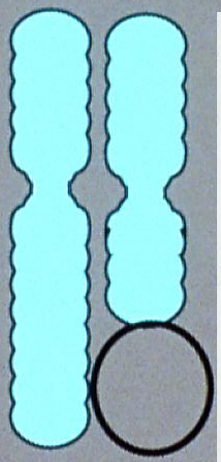


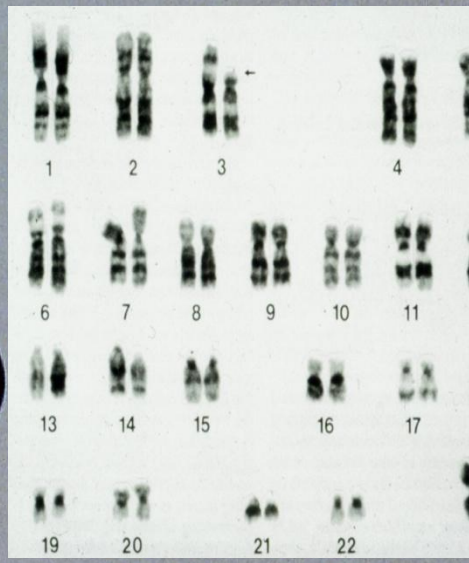
Verlust





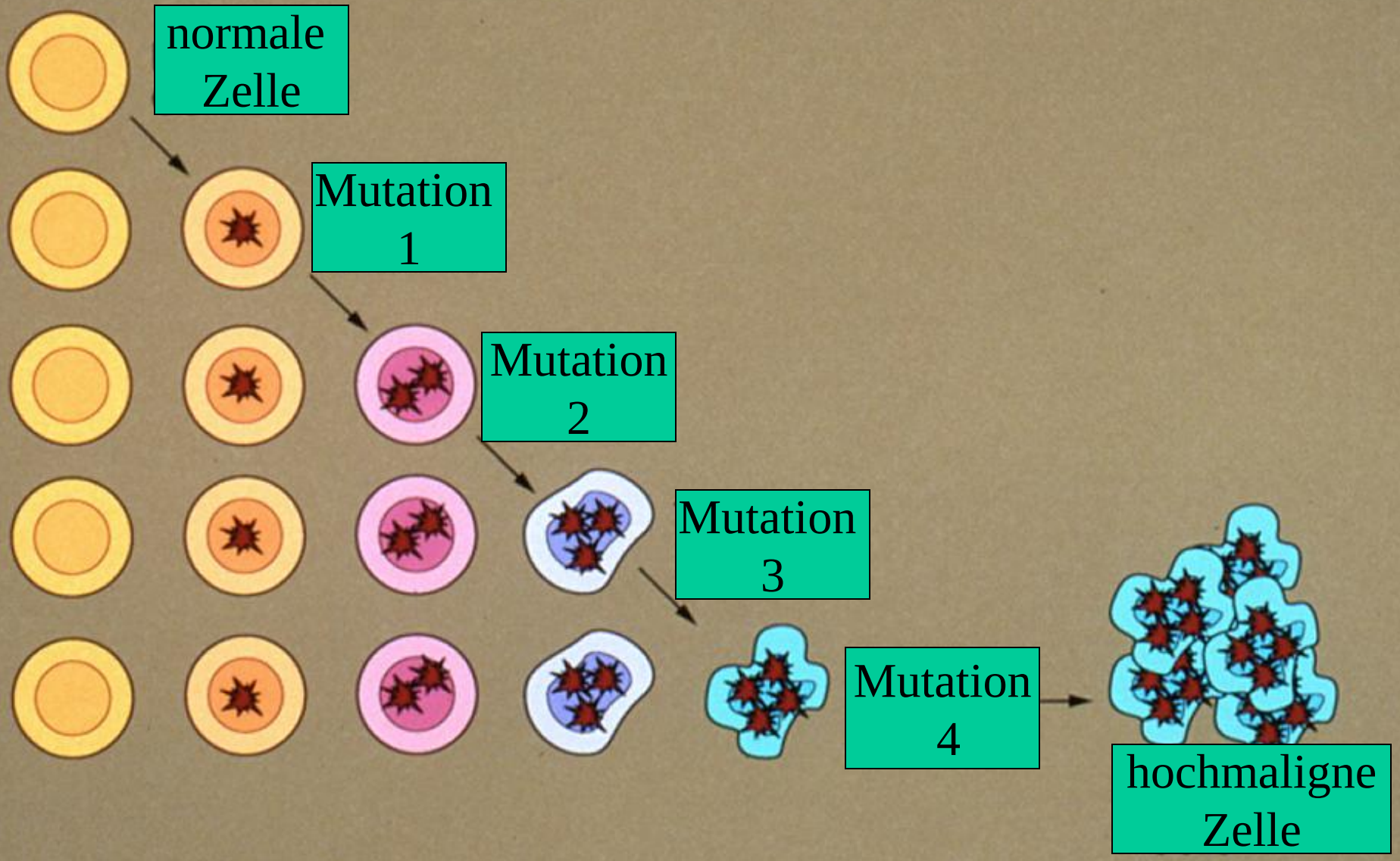
Vervielfachung



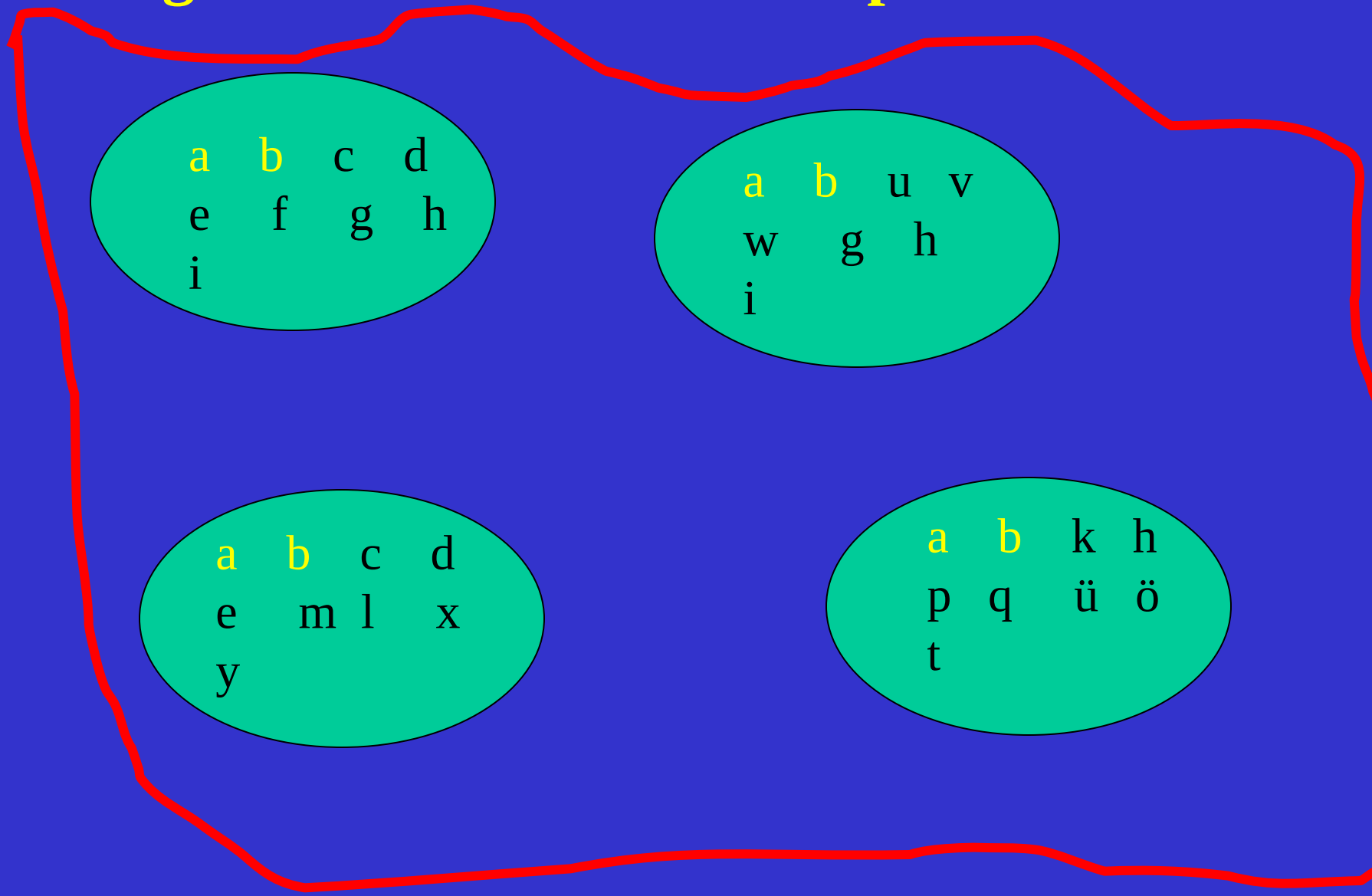


Verlust

Krebs ist das Resultat einer Vielzahl von Mutationen



Genetische Instabilität führt zur genetischen Heterogenität von Tumorzell-Populationen

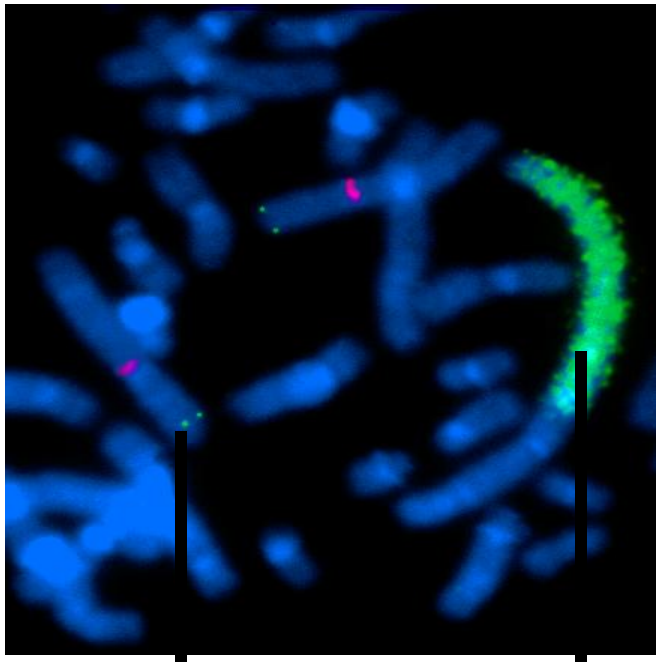


Die Rolle von Genen bei der Krebsentstehung

5. „**Epigenetische“ Veränderungen der Genexpression**

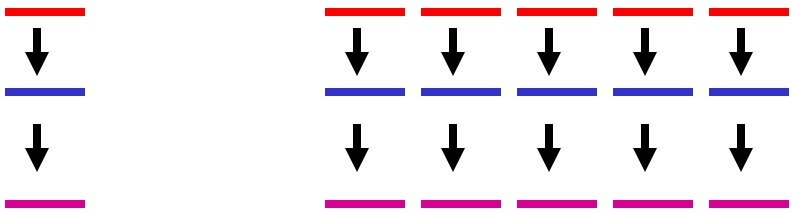
Wahrscheinlich, aber im Einzelfall schwer nachweisbar,
da eine genetische Veränderung in einem der ca. 30.000 Gene des Menschen nicht auszuschließen ist.

Der Phänotyp einer Zelle wird durch die regulierte Stärke von Genen bestimmt. „Induzierte“ Veränderungen der Genexpression können den Phänotyp, also die Zell-Vermehrung, verändern!



normales Gen

vermehrtes Gen



(bis zu 1000 Genkopien)

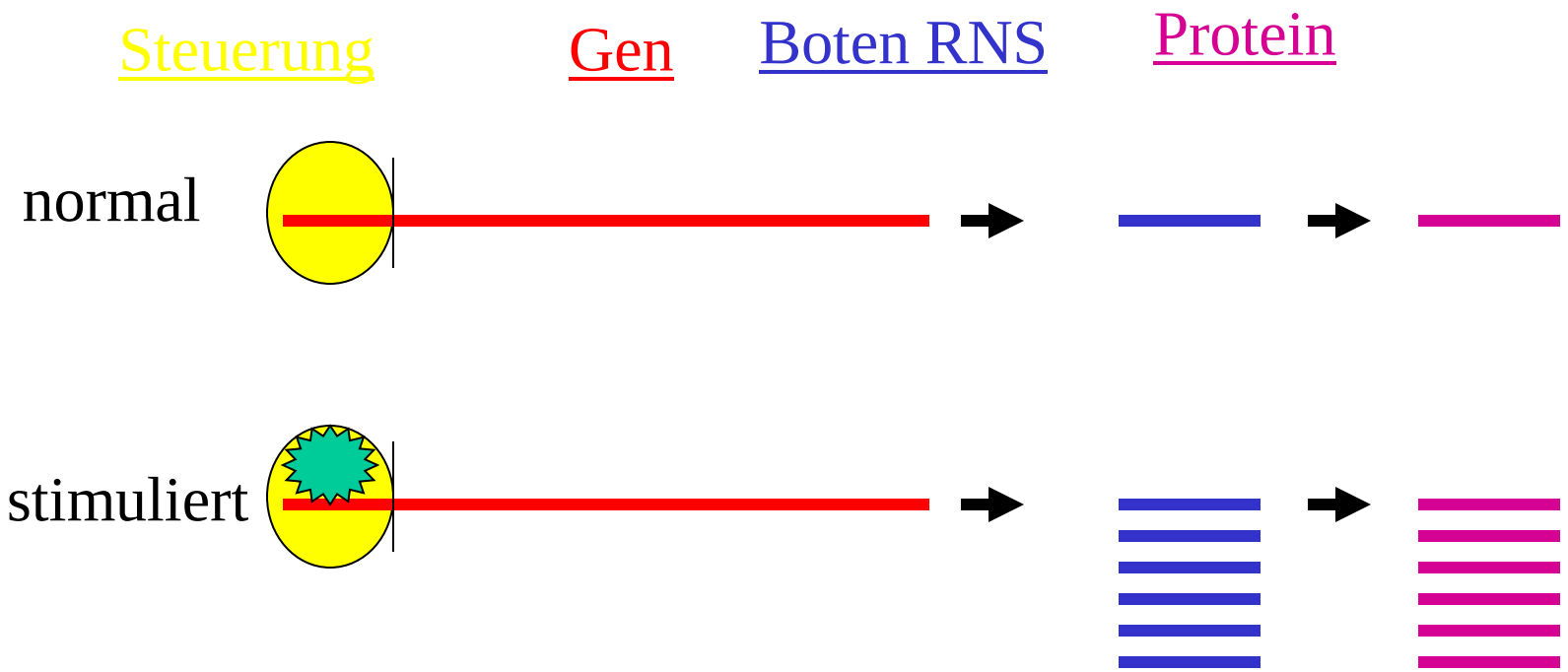
Boten RNS

Protein

Beispiel: Genvermehrung führt zur abnormal erhöhten Expression und ist häufig an Krebsentstehung beteiligt

Die Expression von Genen kann durch äußere Einflüsse abnormal Verändert werden. Abnormale innere Einfüsse können ebenfalls Eine Rolle spielen. Als Folge kann sich der Phänotyp der Zelle verändern.

Modell: Stimulation der Genexpression durch eine chemische Substanz



Die Rolle von Genen bei der Krebsentstehung

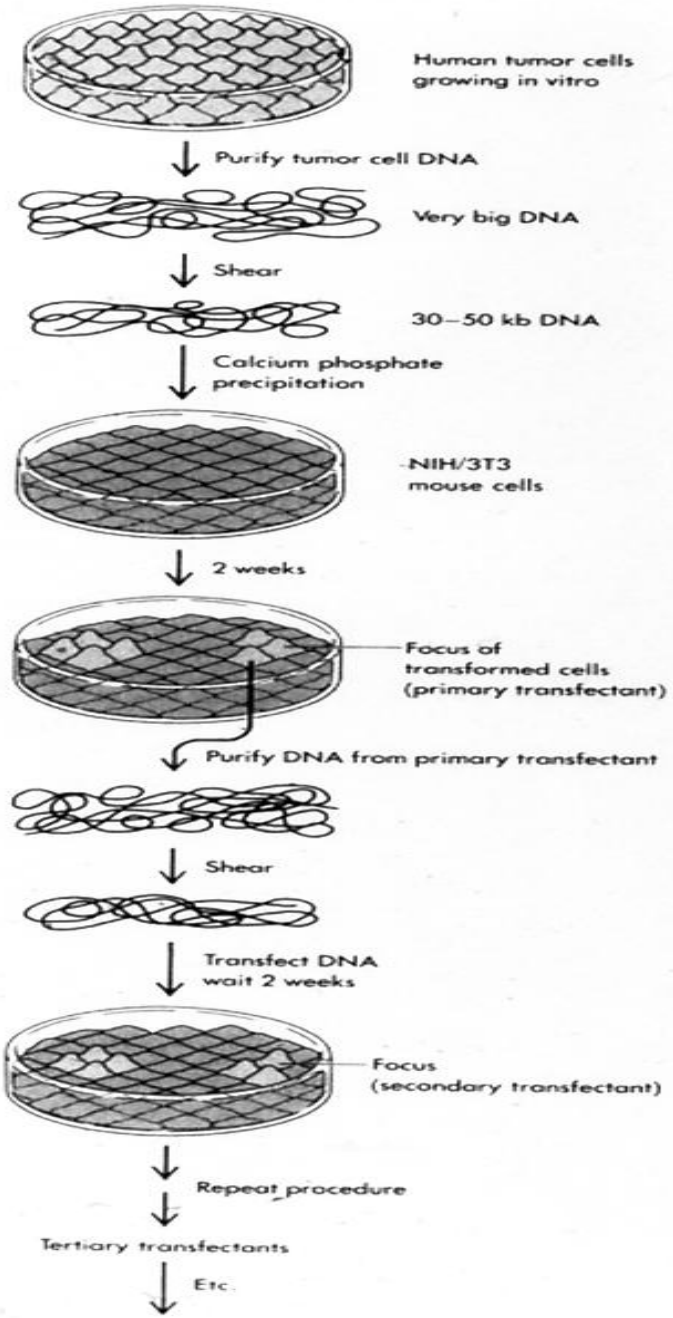
1. Starker erblich-genetischer Einfluß, Mendel-Genetik der Vererbung des Risikos mit hohem Ausprägungsgrad

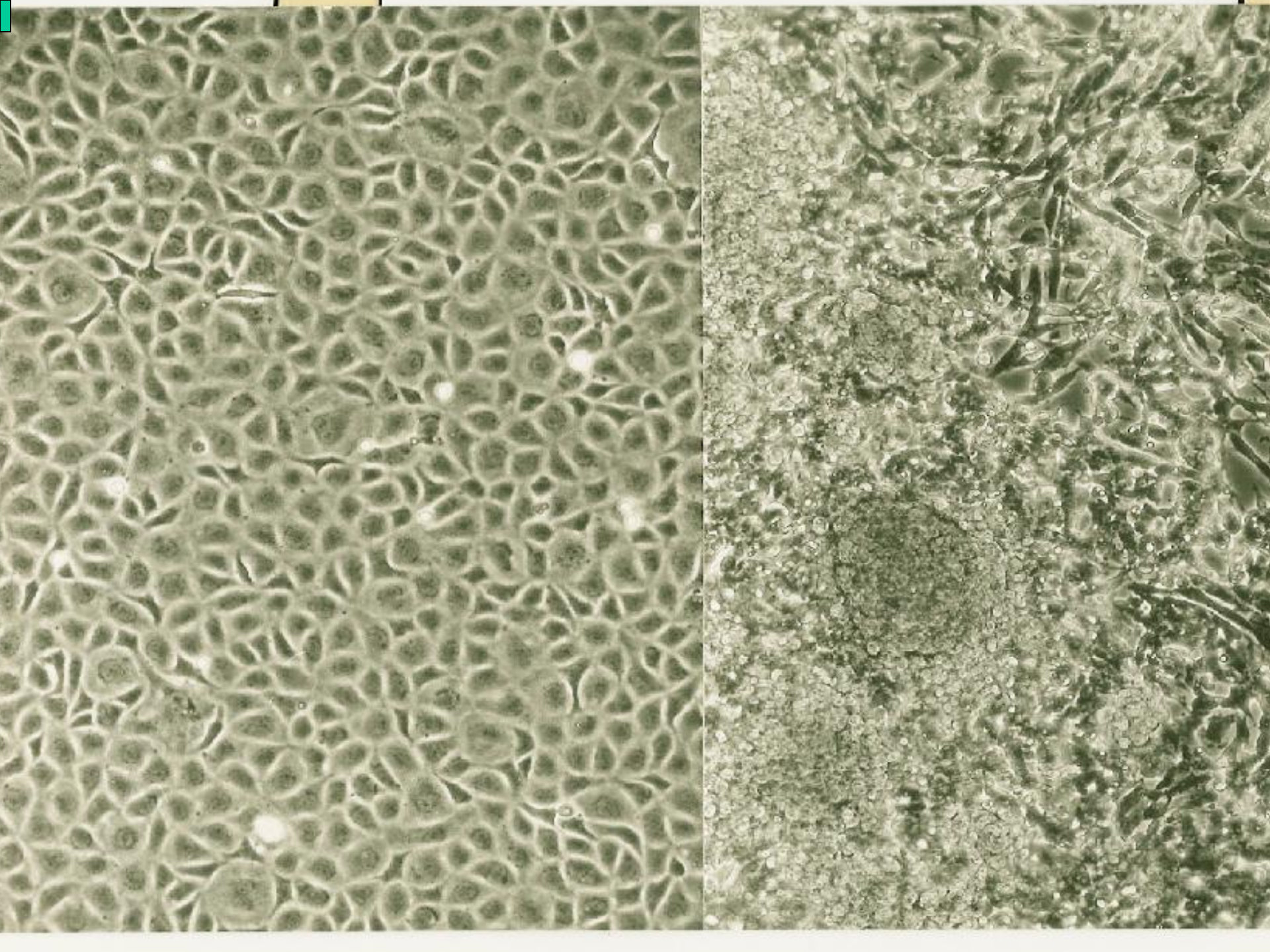
2. Mittlerer erblich-genetischer Einfluß, Ausprägungsgrad begrenzt

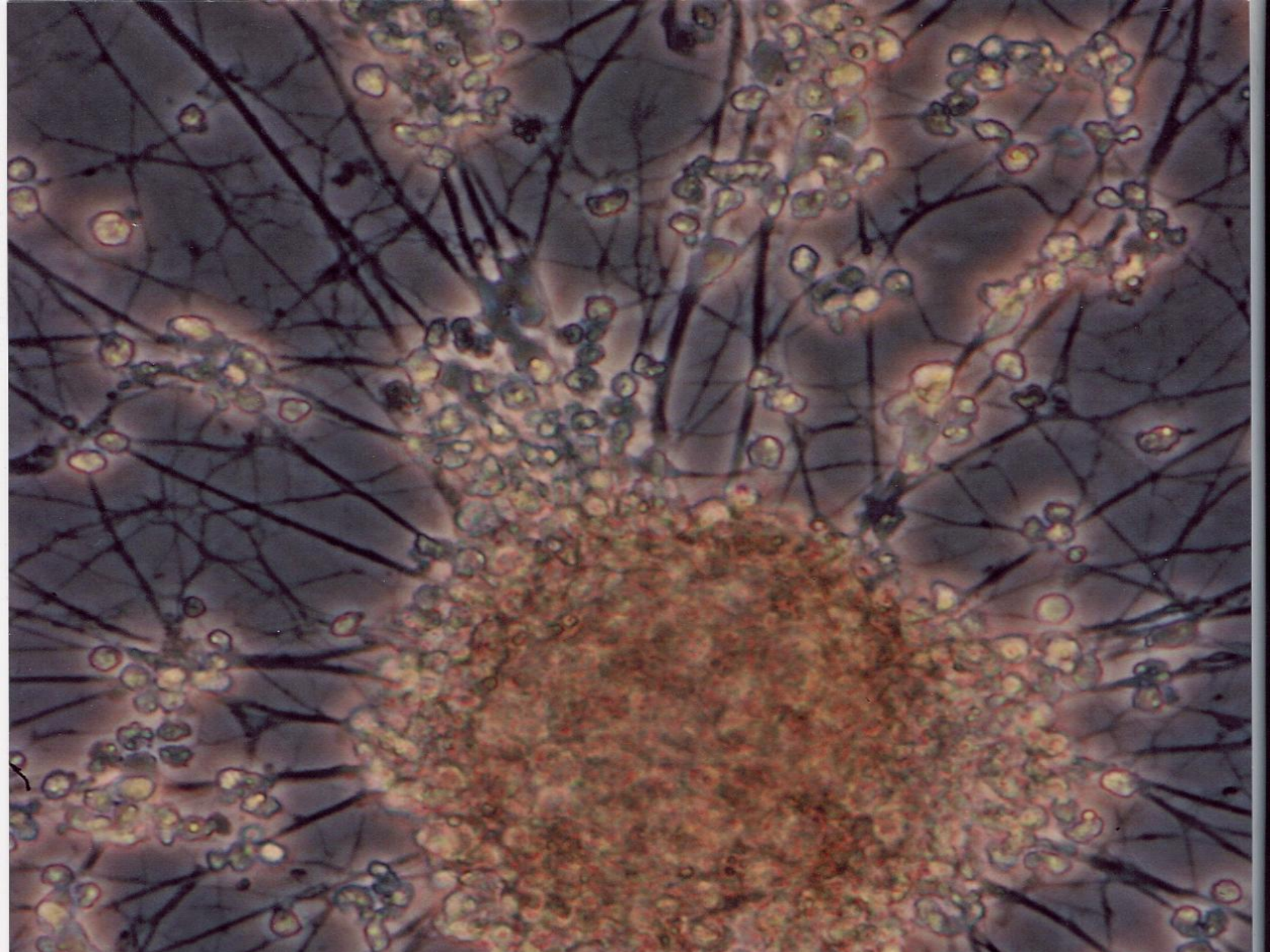
3. Schwacher erblicher Einfluß, häufig nur diffus ableitbar

4. Somatische Genveränderungen ohne erkennbare erbliche Basis

5. „Epigenetische“ Veränderungen der Genexpression


Human tumor cells growing in vitro
Purify tumor cell DNA
Very big DNA
Shear
30–50 kb DNA
Calcium phosphate precipitation
NIH/3T3 mouse cells
2 weeks
Focus of transformed cells (primary transfectant)
Purify DNA from primary transfectant
Shear
Transfect DNA wait 2 weeks
Focus (secondary transfectant)
Repeat procedure
Tertiary transfectants
Etc.

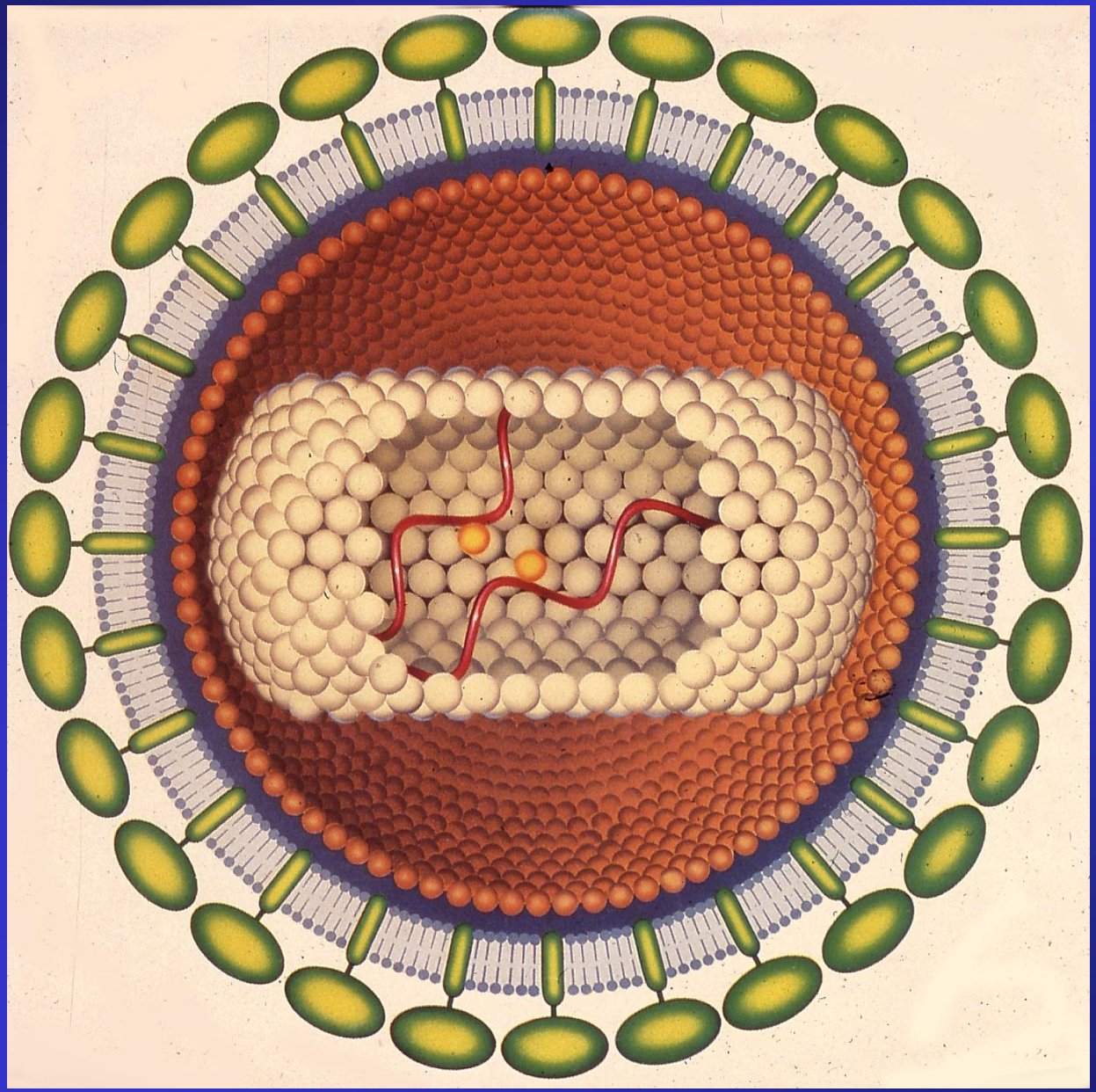


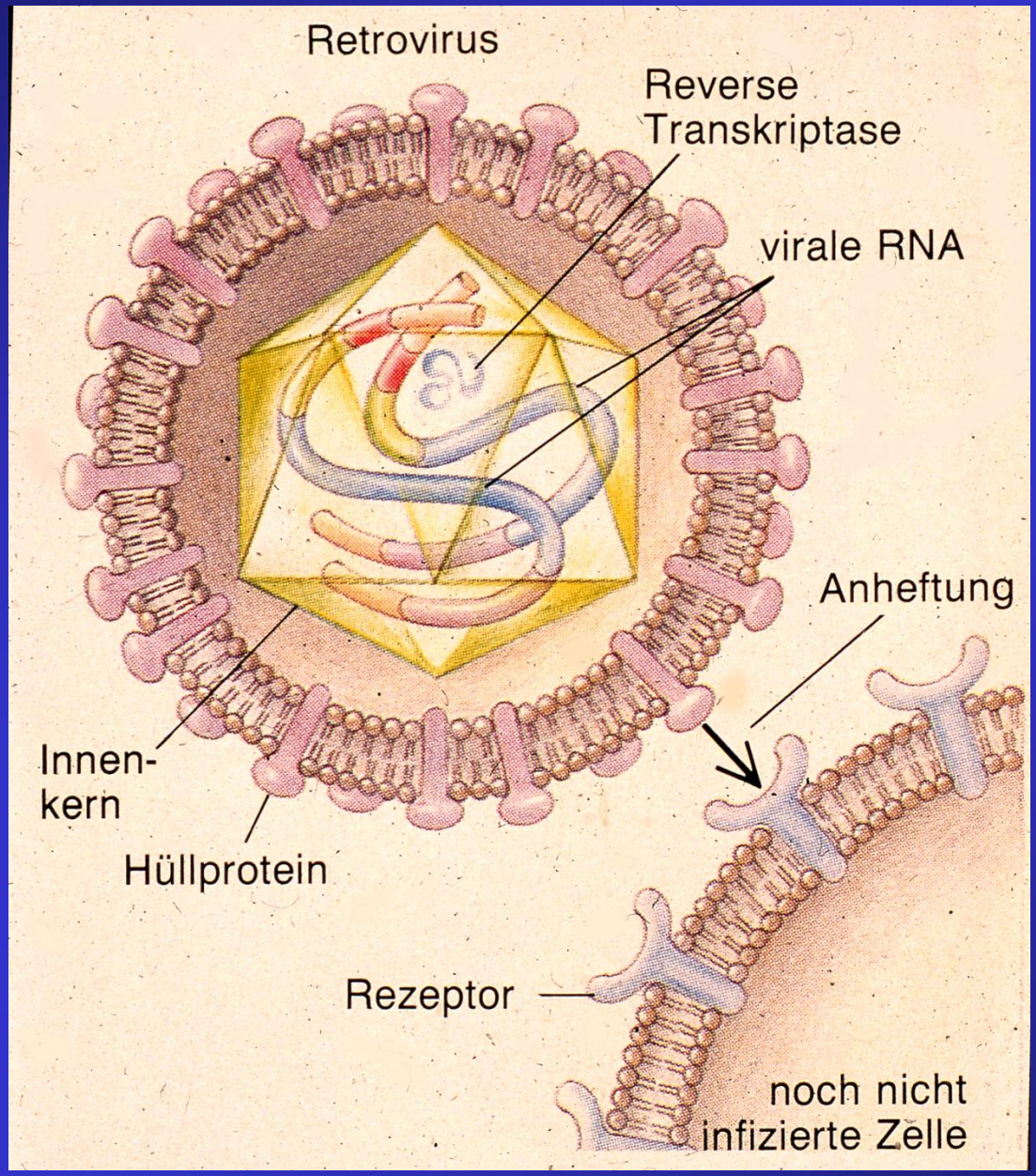


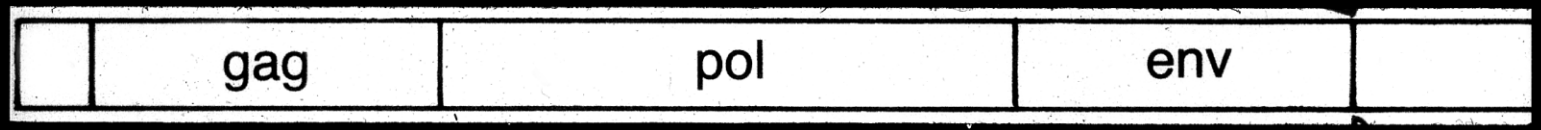
RNA

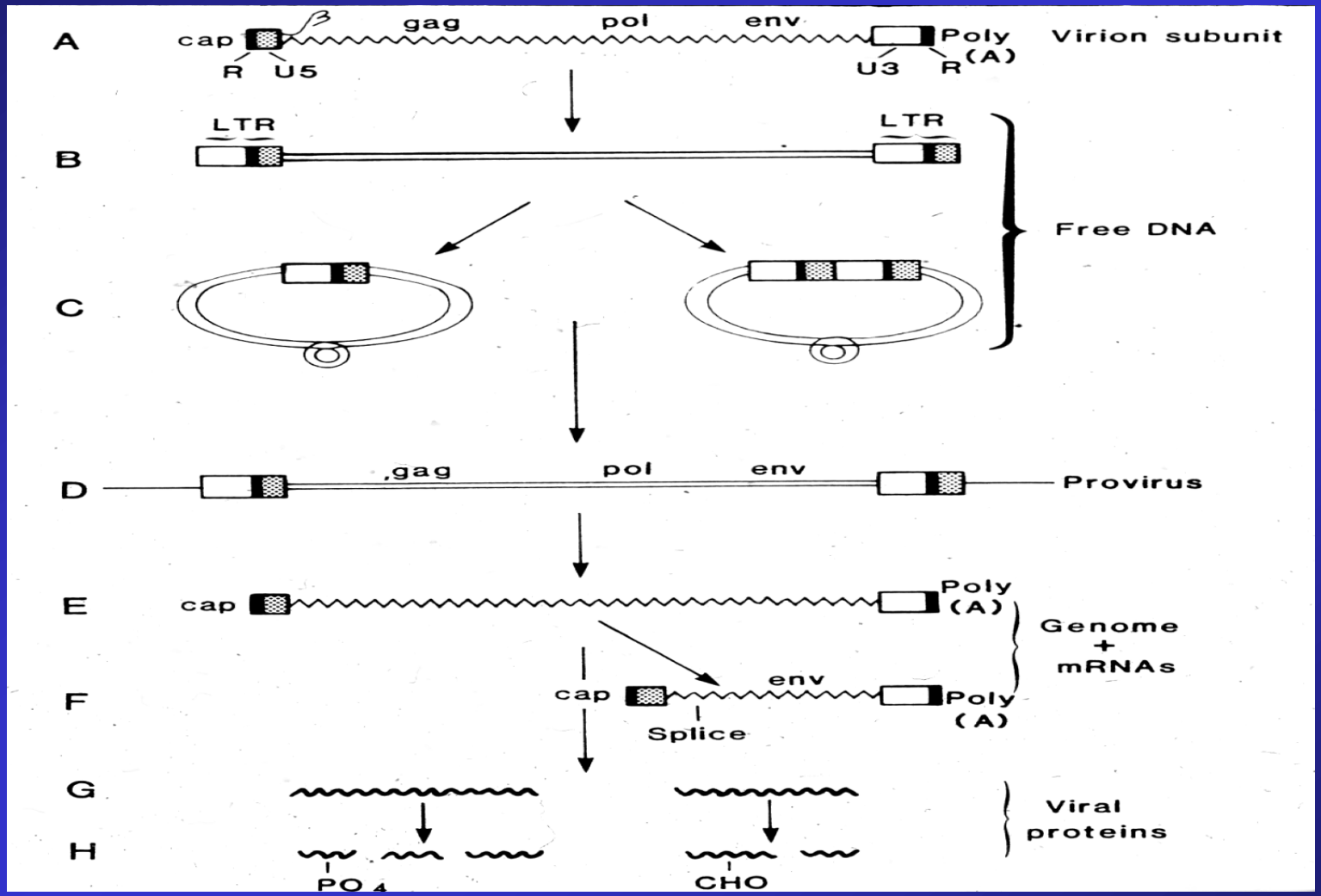
Kapsid

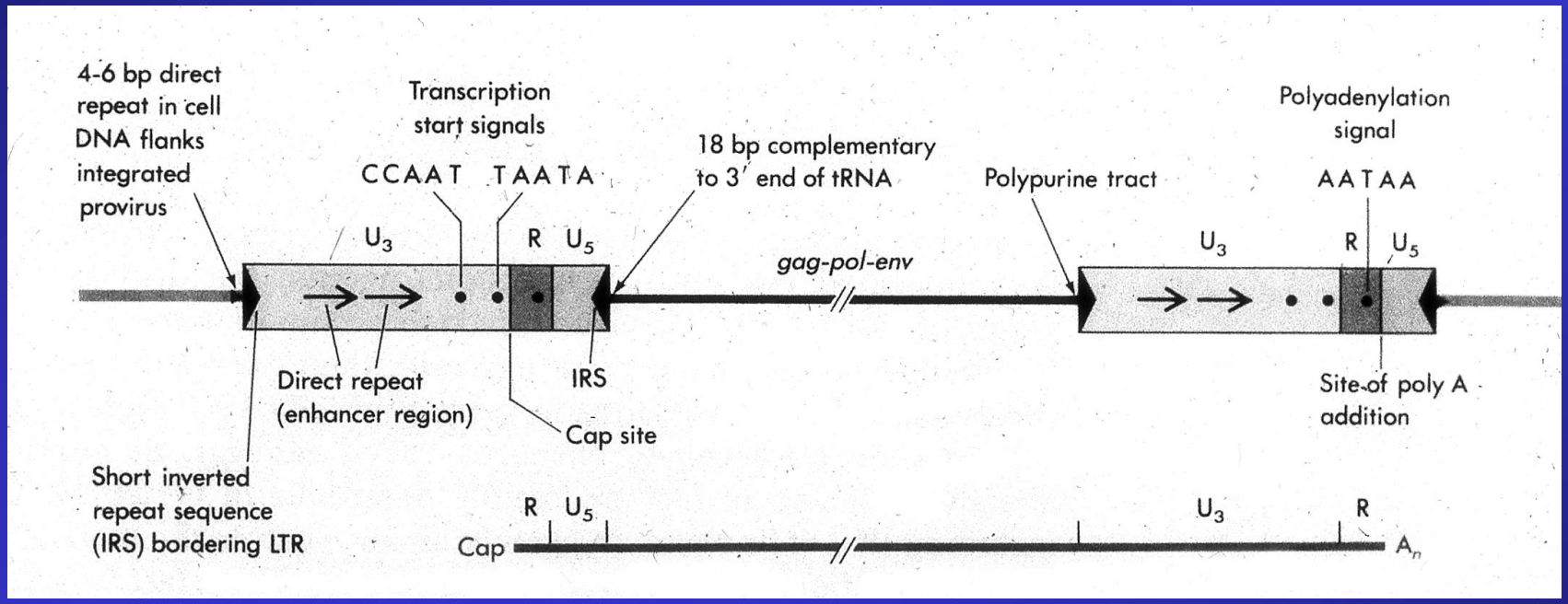
äußere Hülle
mit Stacheln

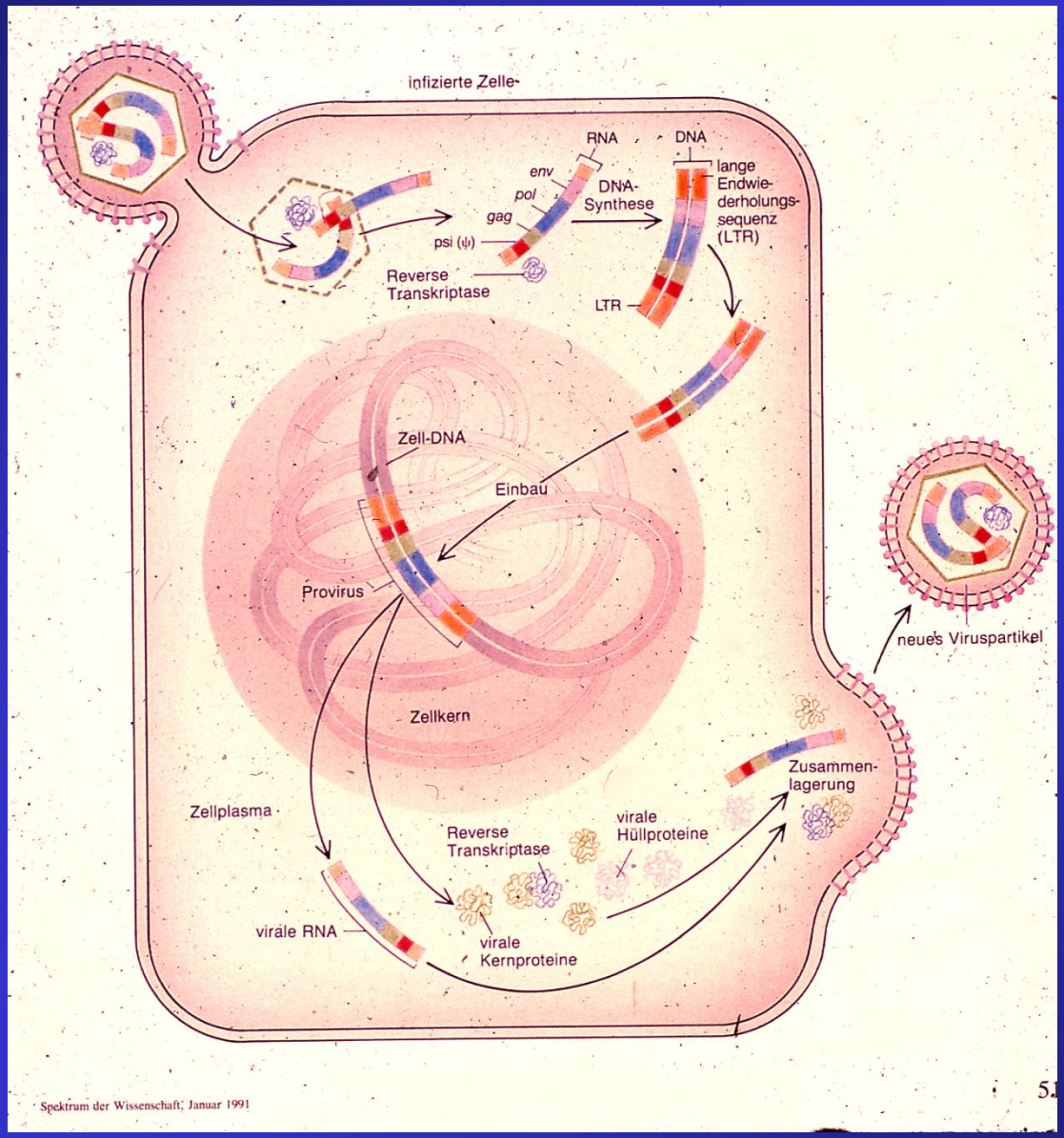


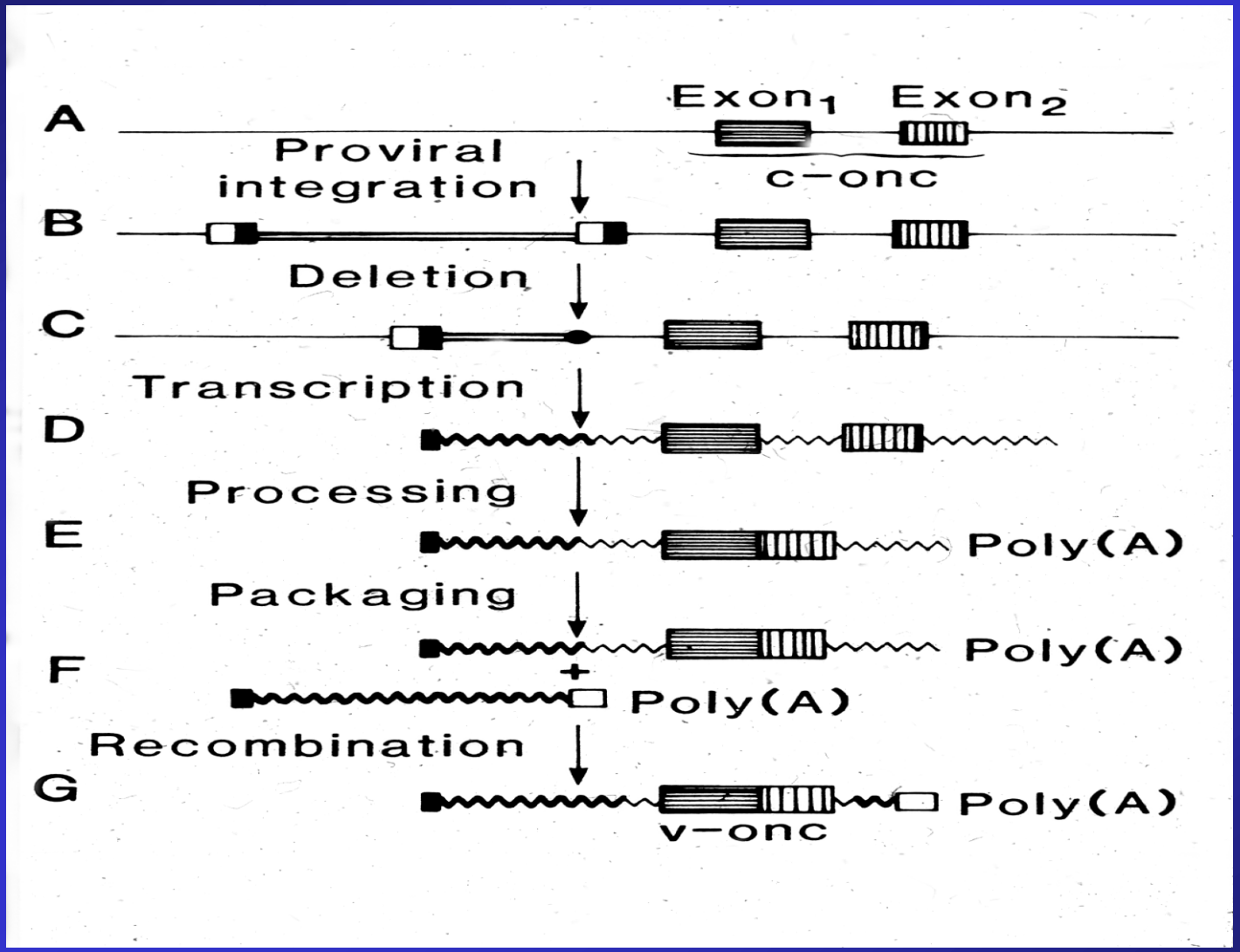

Retrovirus
Reverse Transkriptase
virale RNA
Anheftung
Innen-kern
Hüllprotein
Rezeptor
noch nicht infizierte Zelle

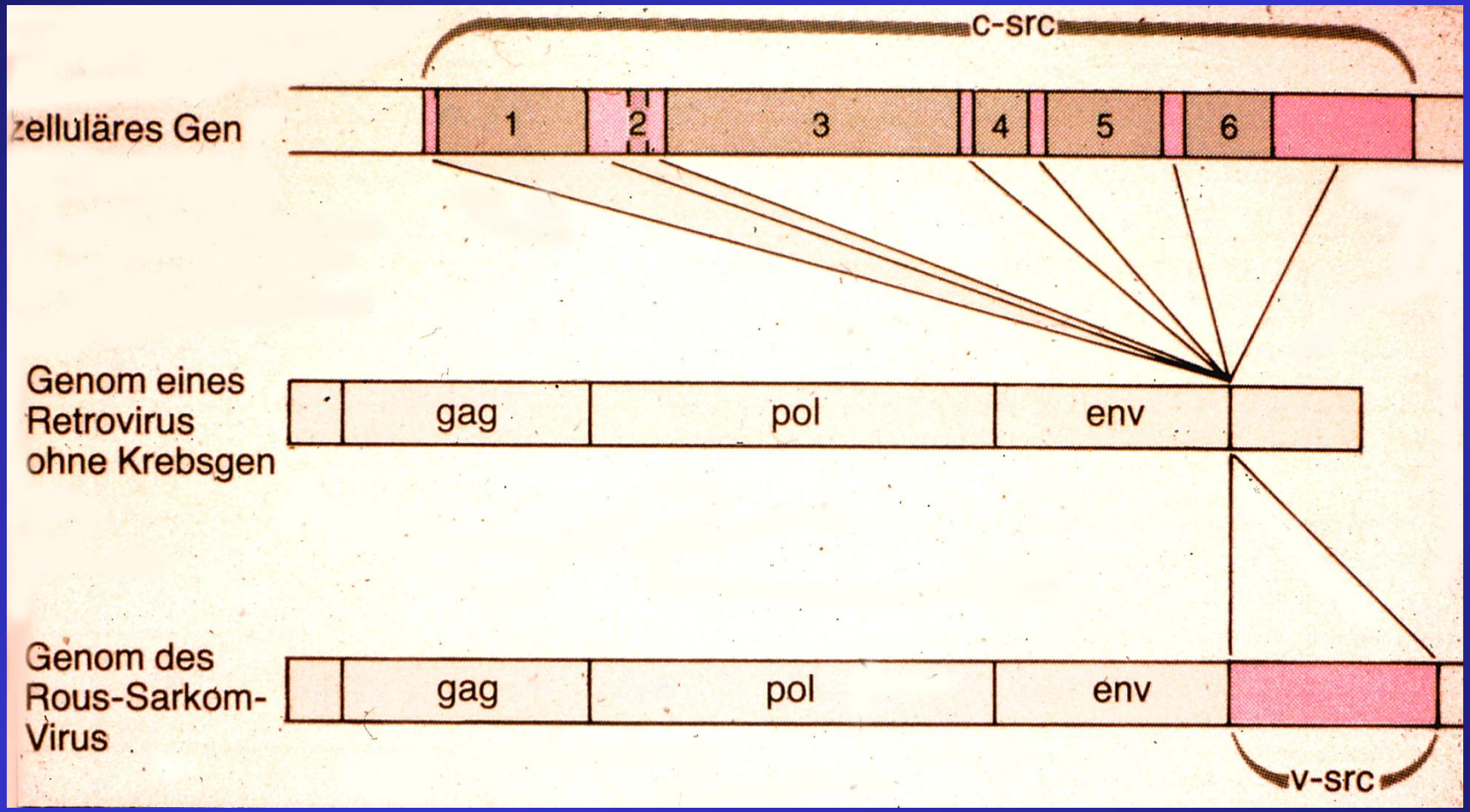

gag
pol
env

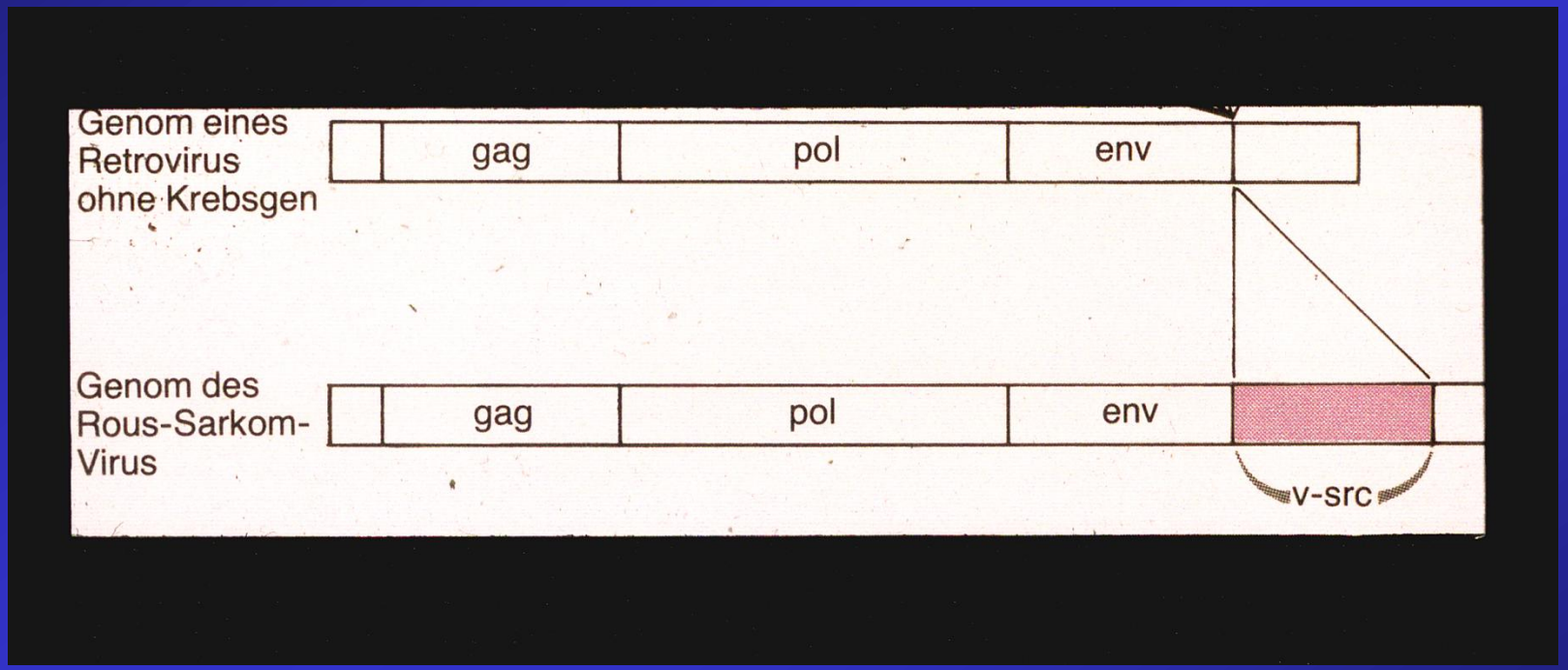

A
cap
gag
pol
env
Poly (A)
Virion subunit
R
U5
U3
R
B
LTR
LTR
Free DNA
C
D
gag
pol
env
Provirus
E
cap
Poly (A)
Genome + mRNAs
F
cap
env
Poly (A)
Splice
G
Viral proteins
H
PO4
CHO


4-6 bp direct repeat in cell DNA flanks integrated provirus
Transcription start signals
CCAAT
TAATA
18 bp complementary to 3′ end of tRNA
Polypurine tract
Polyadenylation signal
AATAA
U3
R
U5
gag-pol-env
U3
R
U5
Direct repeat (enhancer region)
IRS
Cap site
Site of poly A addition
Short inverted repeat sequence (IRS) bordering LTR
R
U5
U3
R
Cap
An


infizierte Zelle
RNA
DNA
env
pol
gag
psi (ψ)
DNA-Synthese
lange Endwiederholungssequenz (LTR)
Reverse Transkriptase
LTR
Zell-DNA
Einbau
Provirus
Zellkern
neues Viruspartikel
Zusammenlagerung
Zellplasma
Reverse Transkriptase
virale Hüllproteine
virale RNA
virale Kernproteine


A
Exon1
Exon2
Proviral
integration
c-onc
B
Deletion
C
Transcription
D
Processing
E
Poly(A)
Packaging
F
Poly(A)
+
Poly(A)
Recombination
G
Poly(A)
v-onc

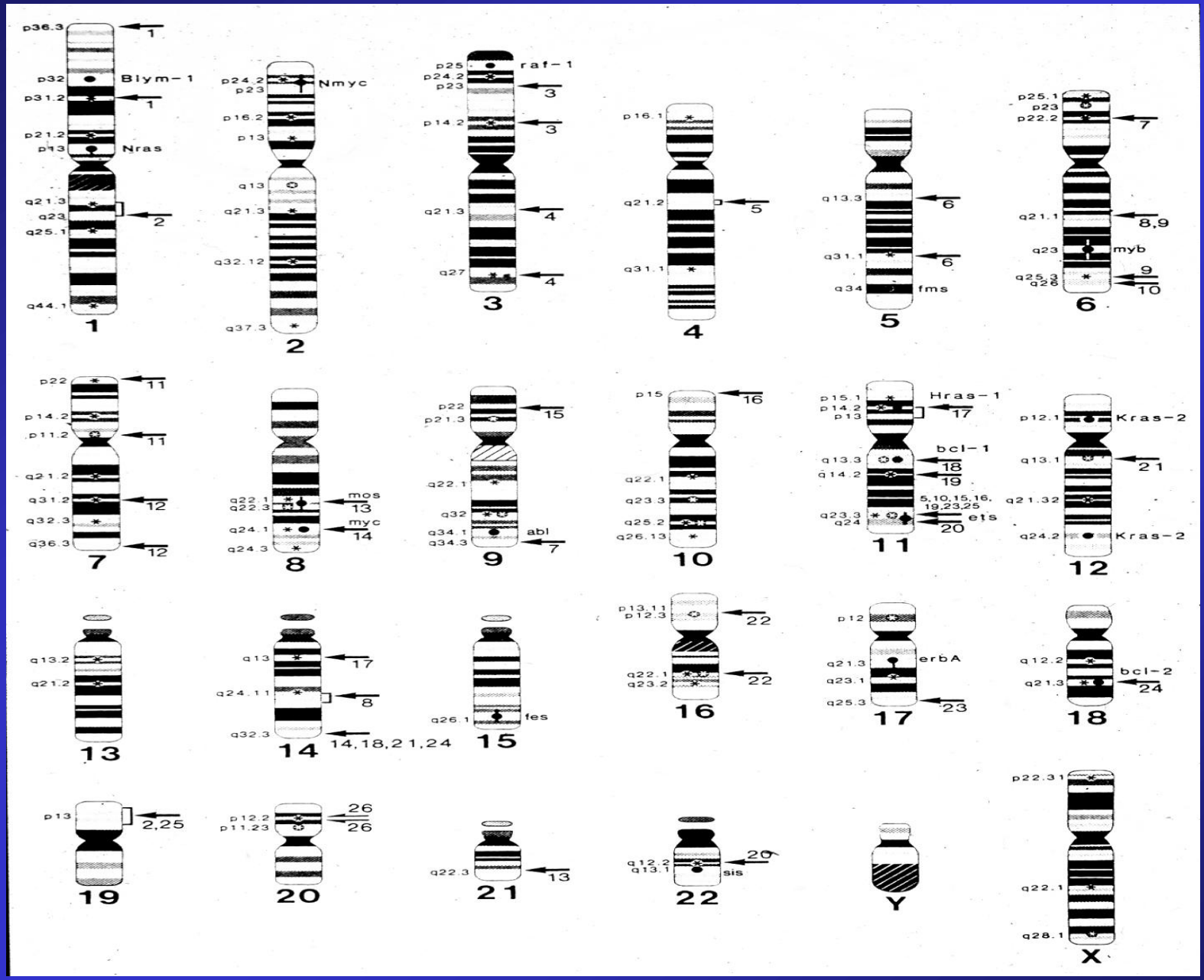

c-src
zelluläres Gen
1
2
3
4
5
6
Genom eines Retrovirus ohne Krebsgen
gag
pol
env
Genom des Rous-Sarkom-Virus
gag
pol
env
v-src


Genom eines Retrovirus ohne Krebsgen
gag
pol
env
Genom des Rous-Sarkom-Virus
gag
pol
env
v-src

Virale und zelluläre Onkogene

RNA Tumorvirus	Wirt	virales Onkogen	zelluläres Onkogen
Rous Sarkomvirus	Huhn	v-src	c-src
Erythroblastose Virus	Huhn	v-erb	c-erb
Myelozytomatose Virus	Huhn	v-myc	c-myc
Leukämie Virus	Maus	v-abl	c-abl
Sarkomvirus	Maus	v-mos	c-mos
Sarkomvirus	Katze	v-fes	c-fes
Sarkomvirus	Affe	v-sis	c-sis

onc gene sequence	Virus isolates (No.)	Virus (example)	Animal origin
src	>3	Rous sarcoma, Prague strain	Chicken, quail
fps	>3	Fujinami sarcoma	Chicken
yes	2	Y73 sarcoma	Chicken
ros	1	UR-2	Chicken
myc	4	Avian myelocytomatosis-29	Chicken
erb	1	Avian erythroblastosis	Chicken
myb	2	Avian myeloblastosis	Chicken
rel	1	Reticuloendotheliosis, strain T	Turkey
mos	2	Moloney murine sarcoma	Mouse
abl	1	Abelson murine leukemia	Mouse
bas	1	BALB murine sarcoma	Mouse
ras	>3	Harvey murine sarcoma	Rat, mouse
fes	2	Snyder-Theilin feline sarcoma	Cat
fms	1	McDonough feline sarcoma	Cat
sis	1	Simian sarcoma	Woolly monkey


p36.3
1
p32
Blym-1
p31.2
1
p21.2
p13
Nras
q21.3
q23
2
q25.1
q44.1
1
p24.2
p23
Nmyc
p16.2
p13
q13
q21.3
q32.12
q37.3
2
p25
p24.2
p23
raf-1
3
p14.2
3
q21.3
4
q27
4
3
p16.1
q21.2
5
q31.1
4
q13.3
6
q31.1
6
q34
fms
5
p25.1
p23
p22.2
7
q21.1
8,9
q23
myb
q25.3
q26
9
10
6
p22
11
p14.2
p11.2
11
q21.2
q31.2
12
q32.3
q36.3
12
7
q22.1
q22.3
mos
13
q24.1
myc
14
q24.3
8
p22
p21.3
15
q22.1
q32
q34.1
q34.3
abl
7
9
p15
16
q22.1
q23.3
q25.2
q26.13
10
p15.1
p14.2
p13
Hras-1
17
q13.3
q14.2
bcl-1
18
19
q23.3
q24
5,10,15,16,
19,23,25
ets
20
11
p12.1
Kras-2
q13.1
21
q21.32
q24.2
Kras-2
12
q13.2
q21.2
13
q13
17
q24.11
8
q32.3
14,18,21,24
14
q26.1
fes
15
p13.11
p12.3
22
q22.1
q23.2
22
16
p12
q21.3
erbA
q23.1
q25.3
23
17
q12.2
q21.3
bcl-2
24
18
p13
2,25
19
p12.2
p11.23
26
26
20
q22.3
13
21
q12.2
q13.1
sis
20
22
Y
p22.31
q22.1
q28.1
X

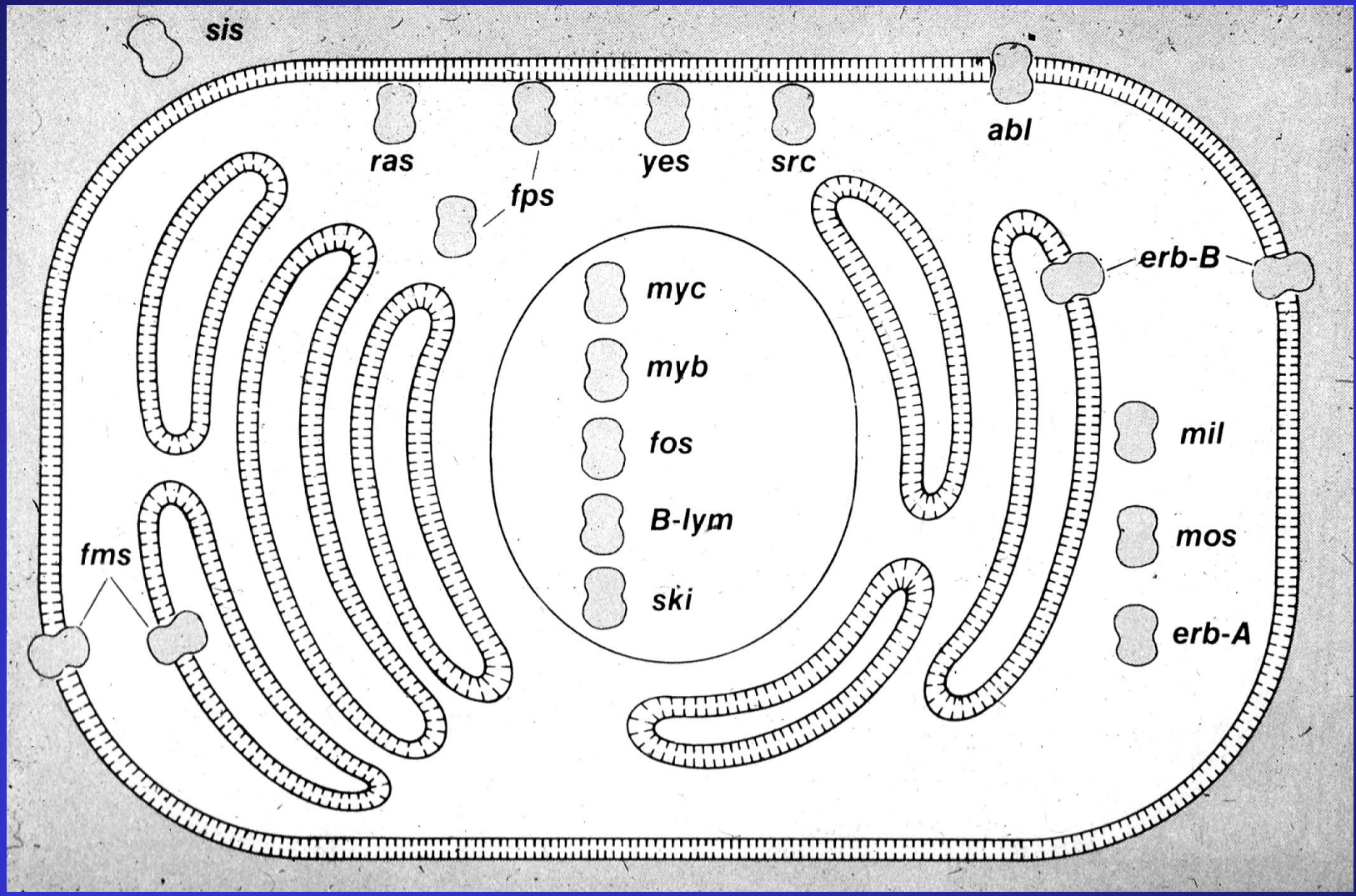
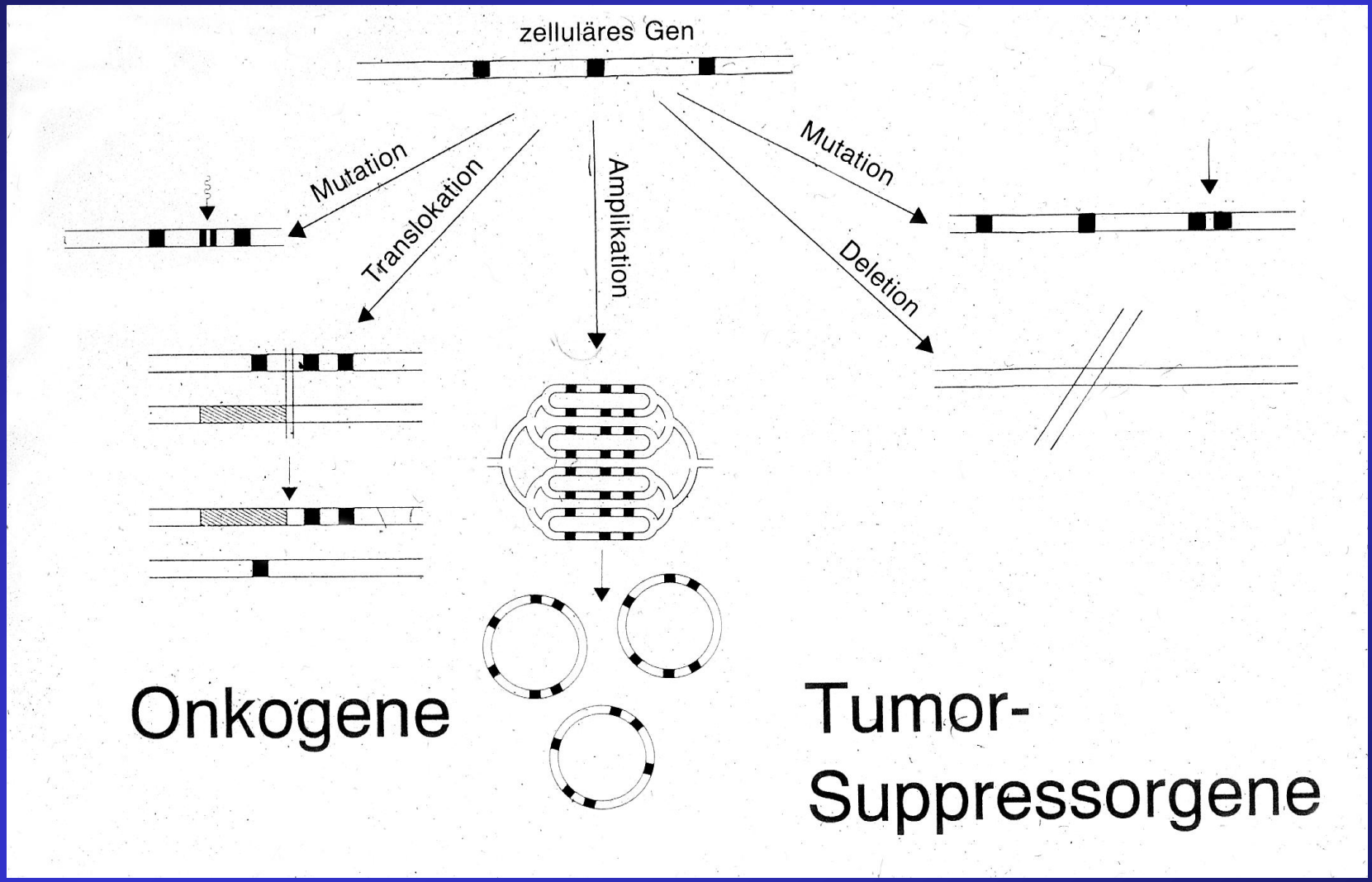

sis
ras
fps
yes
src
abl
erb-B
myc
myb
fos
B-lym
ski
fms
mil
mos
erb-A

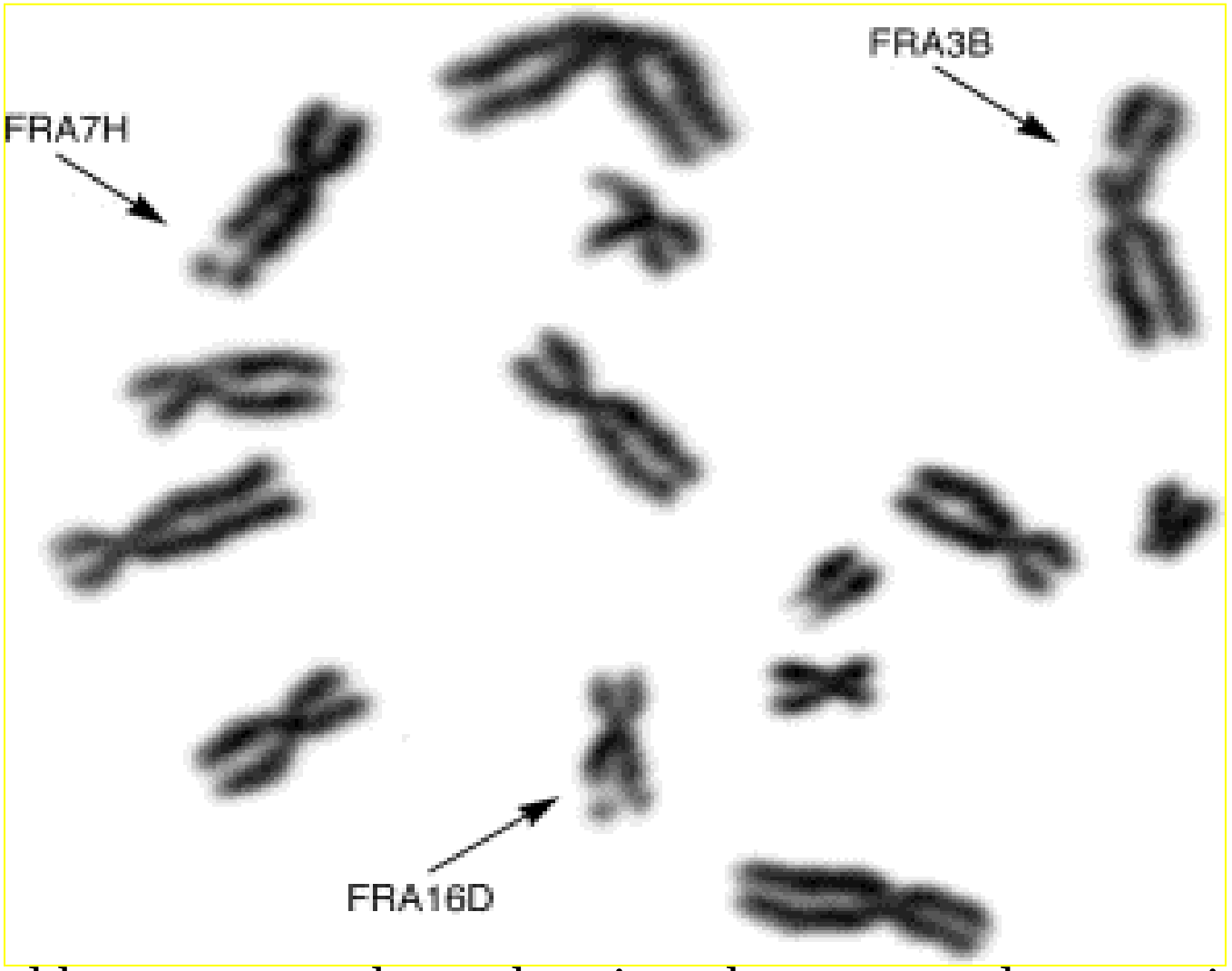
Table 26-3 Oncogene Families

Oncogene	Subcellular location of protein	Properties or normal function of protein
Class I: Protein kinases		
src	Plasma membrane	Tyrosine-specific protein kinase
yes	Plasma membrane	Tyrosine-specific protein kinase
fgr	?	Tyrosine-specific protein kinase
abl	Plasma membrane	Tyrosine-specific protein kinase
fps (*fes*)	Cytoplasm	Tyrosine-specific protein kinase
erbB	Plasma membrane (transmembrane)	EGF receptor/tyrosine-specific protein kinase
fms	Plasma membrane (transmembrane)	CSF-1 receptor/tyrosine-specific protein kinase
ros	Plasma membrane (transmembrane)	Tyrosine-specific protein kinase
kit	Plasma membrane	
mos	Cytoplasm	Serine/threonine protein kinase
raf (*mil*)	?	Serine/threonine protein kinase
Class II: GTP binding proteins		
H-ras	Plasma membrane	Guanine nucleotide binding protein with GTPase activity
K-ras	Plasma membrane	Guanine nucleotide binding protein with GTPase activity
Class III: Growth factors		
sis	Secreted	Derived from a gene that encodes PDGF
Class IV: Nuclear proteins		
myc	Nucleus	
myb	Nucleus	
fos	Nucleus	
ski	Nucleus	
Class V: Hormone receptor		
erbA	Cytoplasm	Thyroid hormone receptor
Unclassified:		
rel	?	
ets	?	


zelluläres Gen
Mutation
Translokation
Amplikation
Mutation
Deletion
Onkogene
Tumor-
Suppressorgene

FRAGILOME

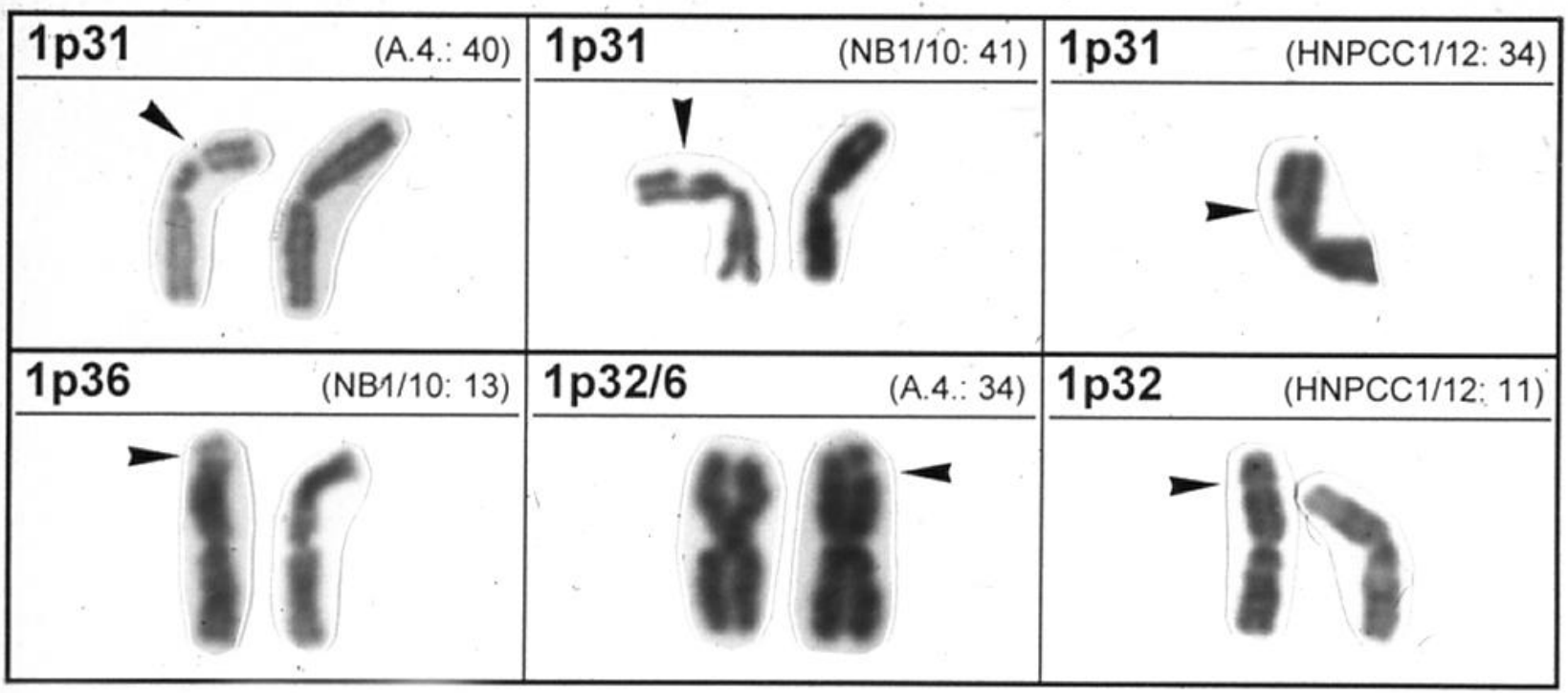
Identifying the repertoire of common fragile sites and determining their role in cancer-associated genomic damage

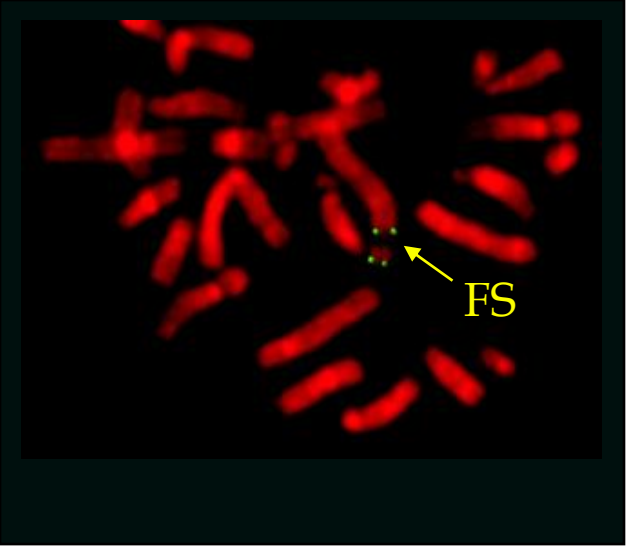


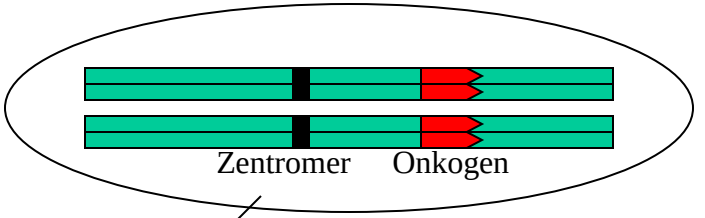
Partial human metaphase showing chromosomal expression of three common fragile sites following exposure to aphidicolin.

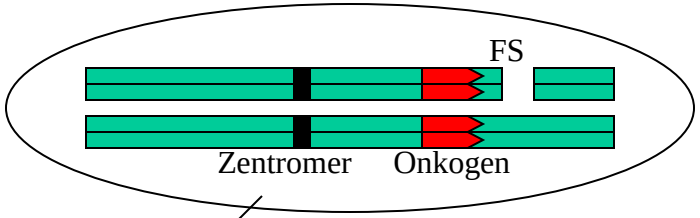
FRAGILE SITES

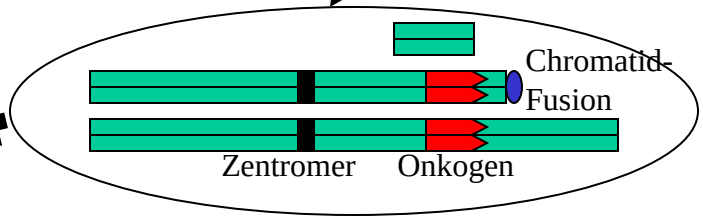
0,2 µM Aphidicolin (APC)

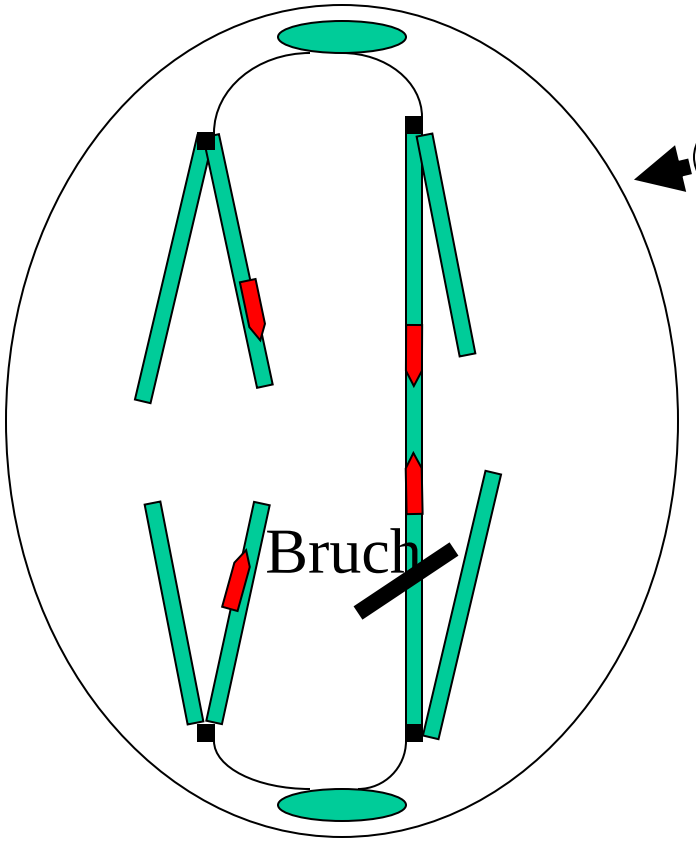


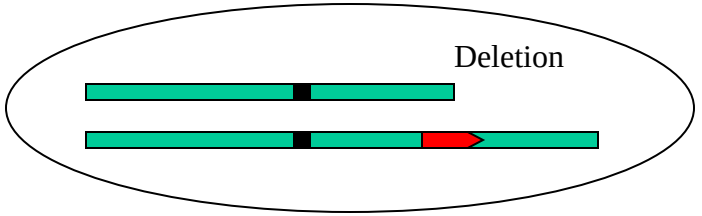

FS

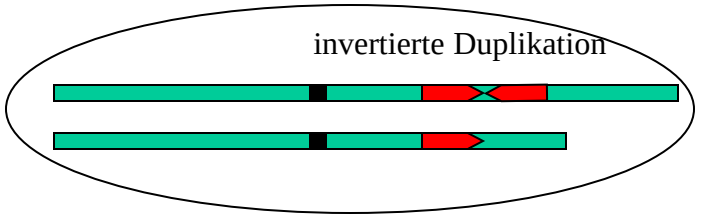

Zentromer
Onkogen

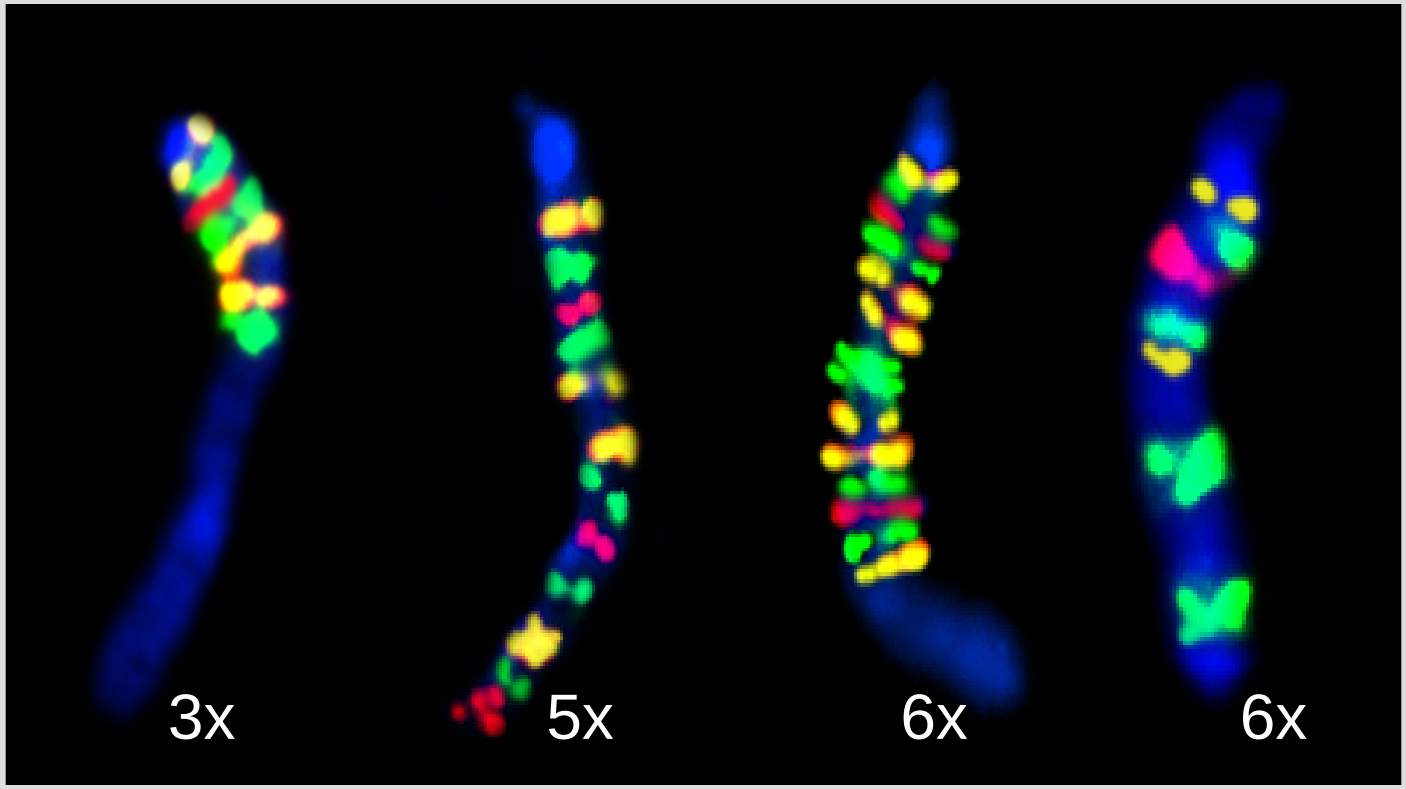

FS
Zentromer
Onkogen

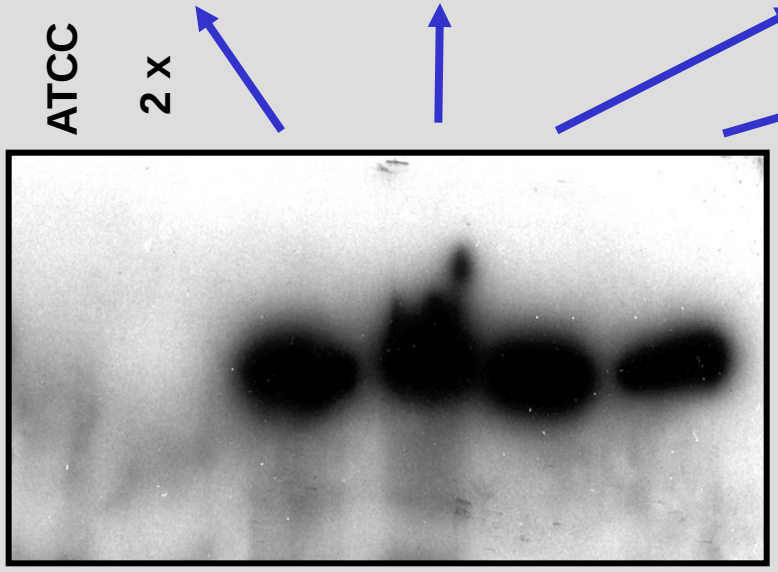

Chromatid-
Fusion
Zentromer
Onkogen

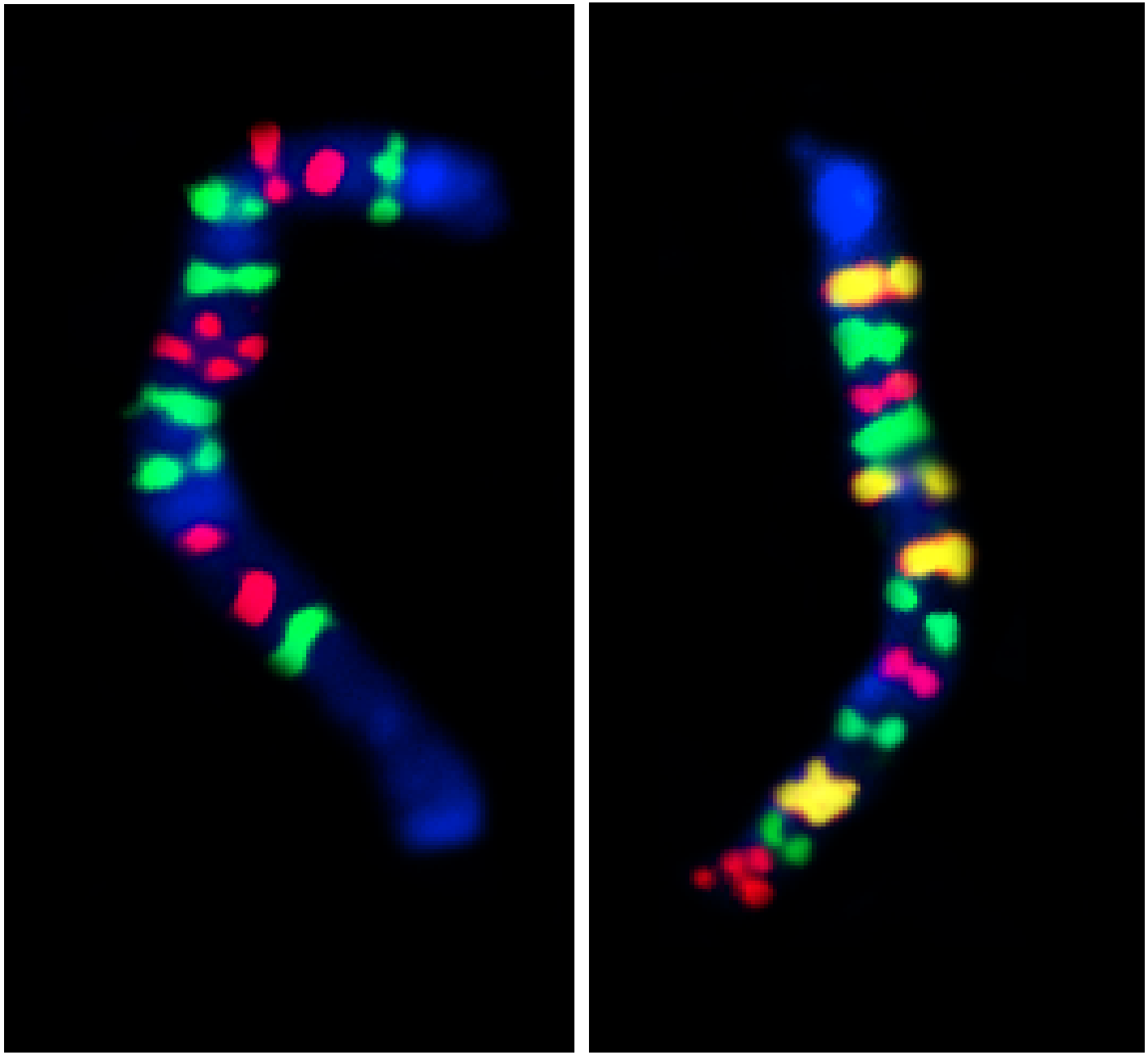

Bruch

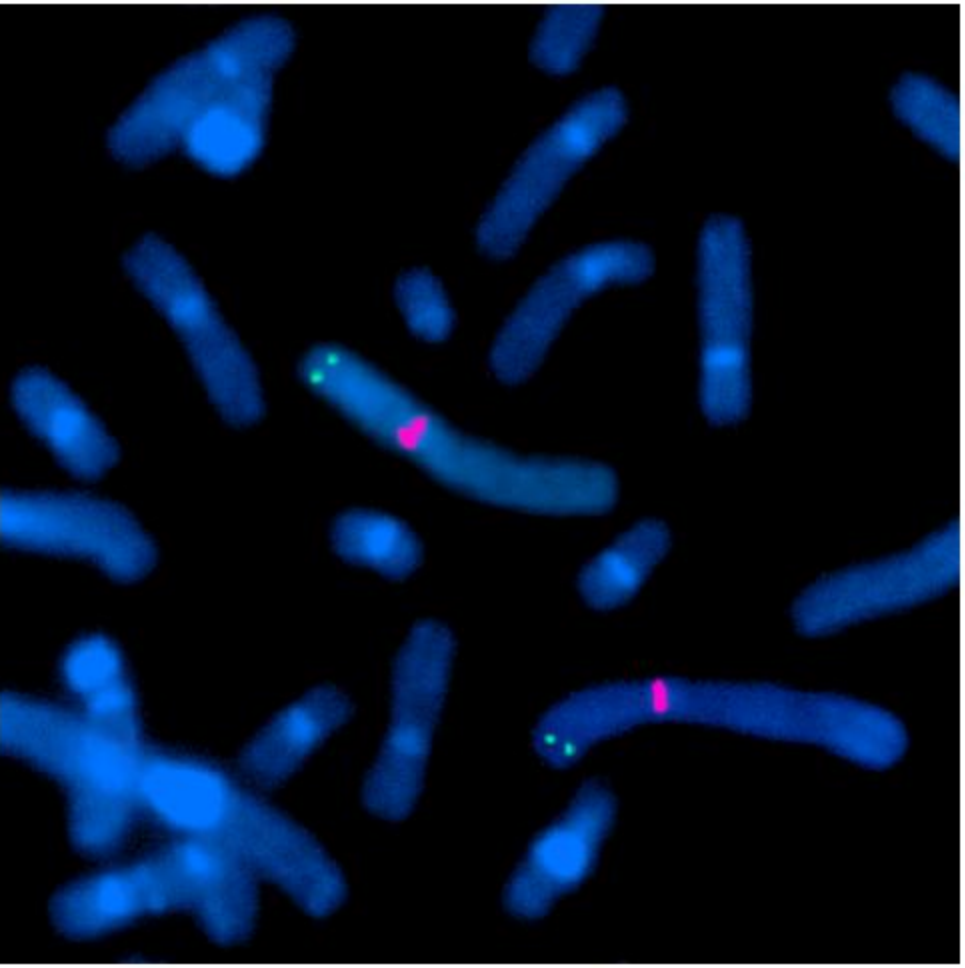

Deletion


invertierte Duplikation

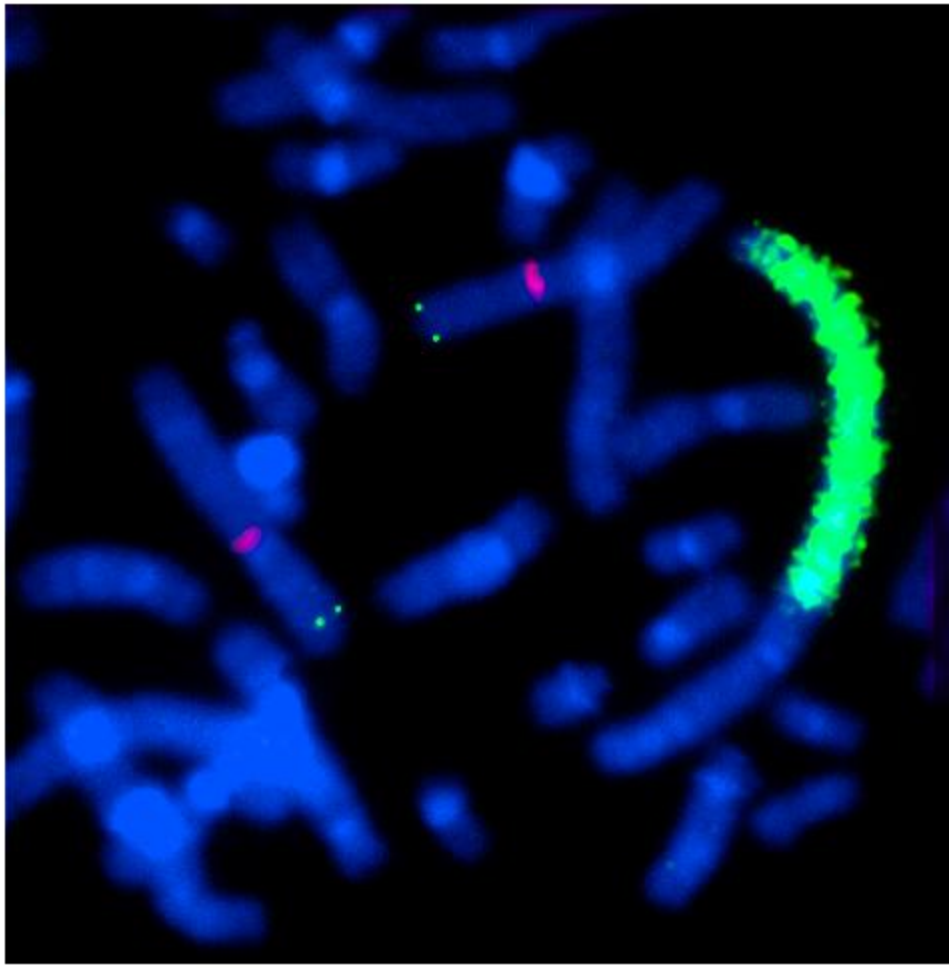

3x
5x
6x
6x


ATCC
2 x
230 -





Normale Zelle



Tumorzelle

The End

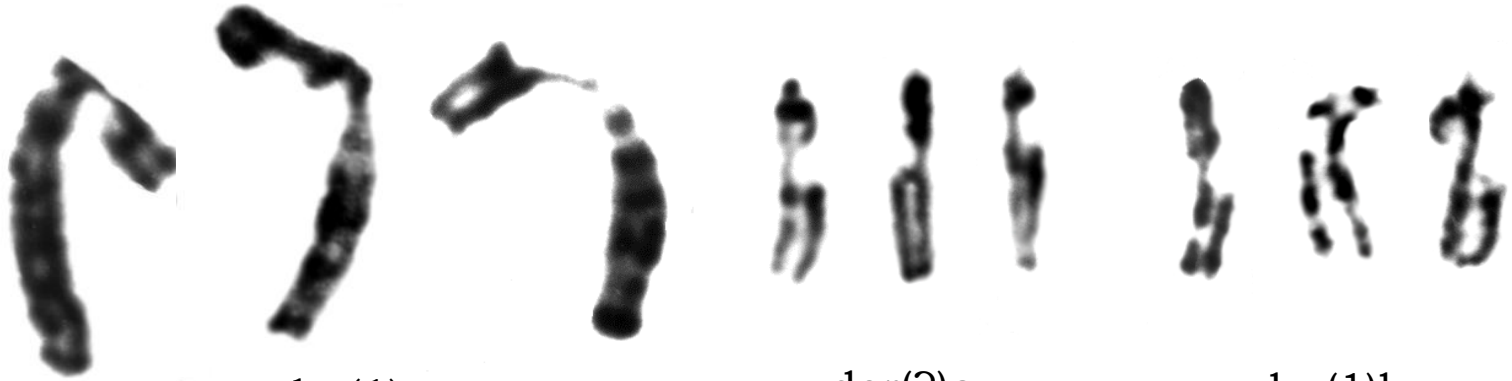
13.2.2006

spontaneously expressed fragile sites

2q21 (3.1%)

der(10) der(2)a der(2)b

1p22 (2,88%)



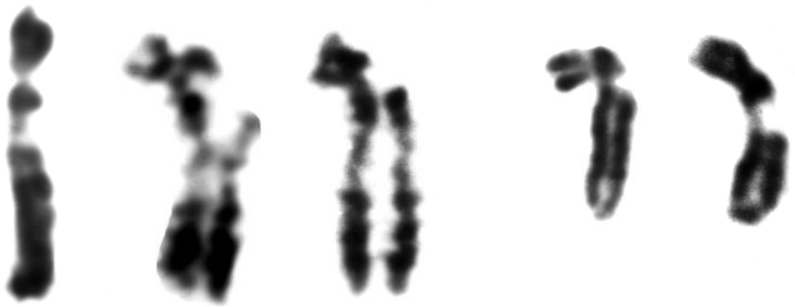
der(1)a der(?)a der(1)b

spontansously expressed fragile sites

3q21 (2.52%)

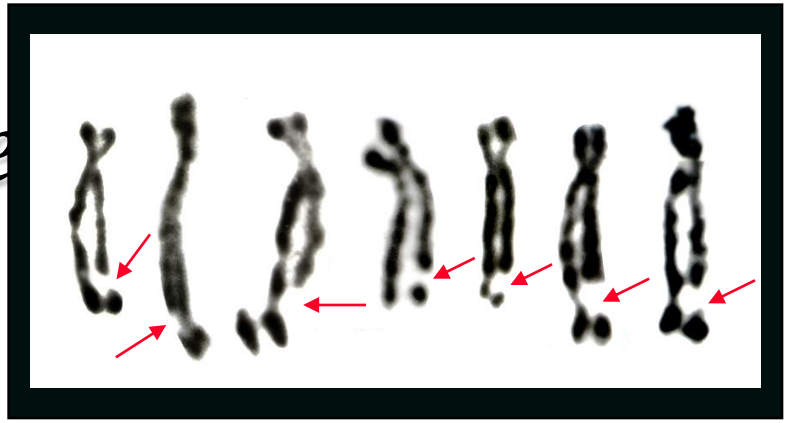
der(7)b der(3)

12q13 (2.16%)



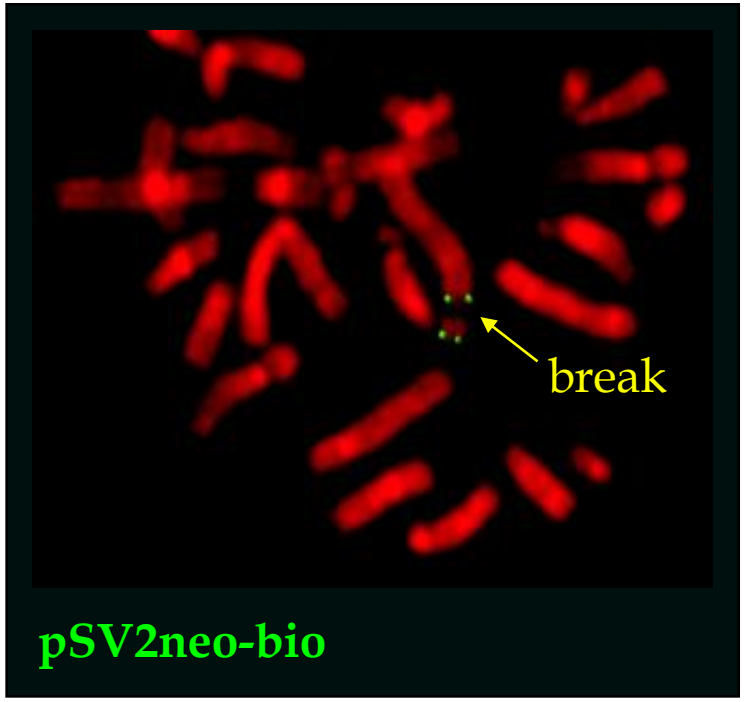
der(X)a der(12)a

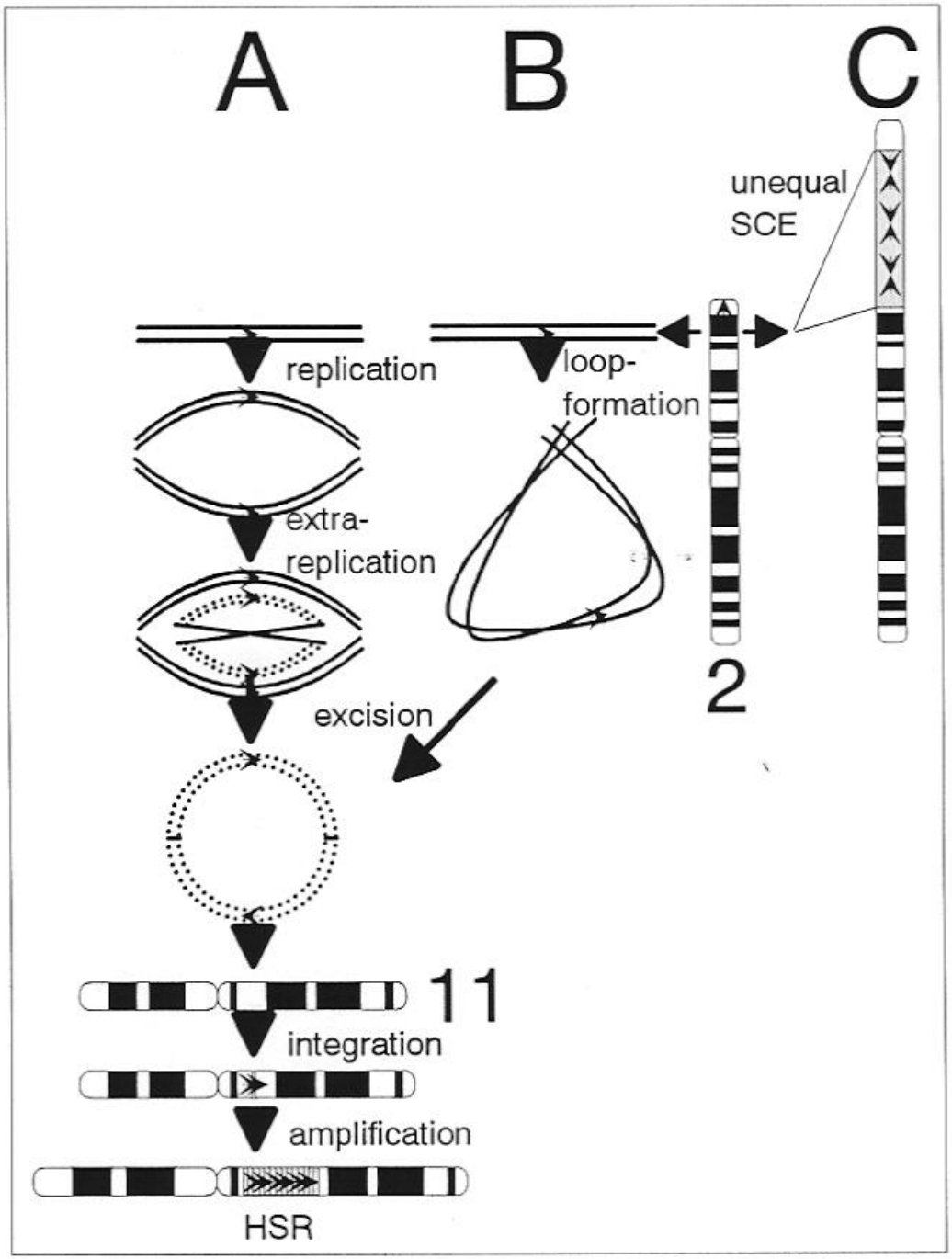
common fragile site
4q31



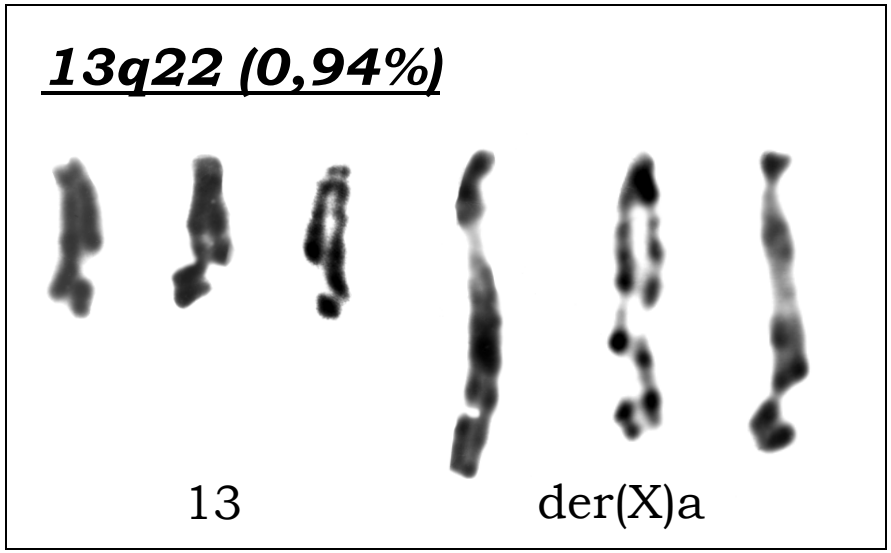
clone 2

has two integrations of *pSV2neo* in chromosome 4, one in 4q31. The FS in this region can still be activated to break the chromosome.




A
B
C
unequal
SCE
replication
loop-
formation
extra-
replication
excision
2
11
integration
amplification
HSR

Four Different Clones have Integration in 13q22.



clone 22:	13
clone 24:	13
clone 63:	der(X)a
clone 83:	der(X)a

Targeted cloning of fragile site DNA by repair-mediated insertional mutagenesis

exposure of cultured cells to FS inducers

↓

transfection of the cells with *pSV2neo*, removal of inducer from culture medium

↓

repair-mediated integration of *pSV2neo* into FS

↓

G418 selection for cell clones with stable integrates

↓

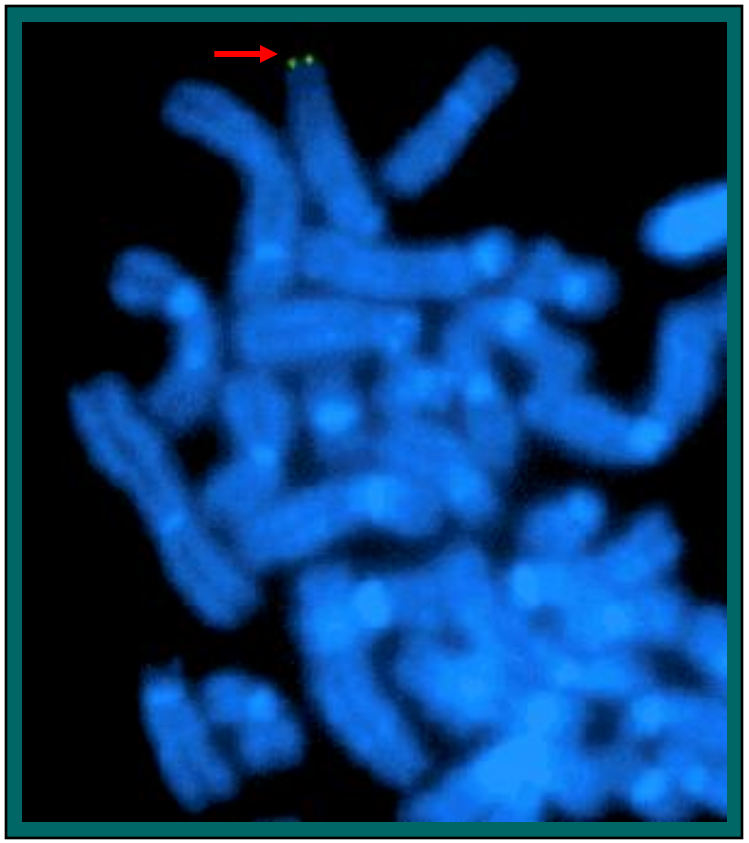
identifying integration sites by FISH

↓

cloning and characterisation of *pSV2neo*-tagged cellular DNA from the integration site

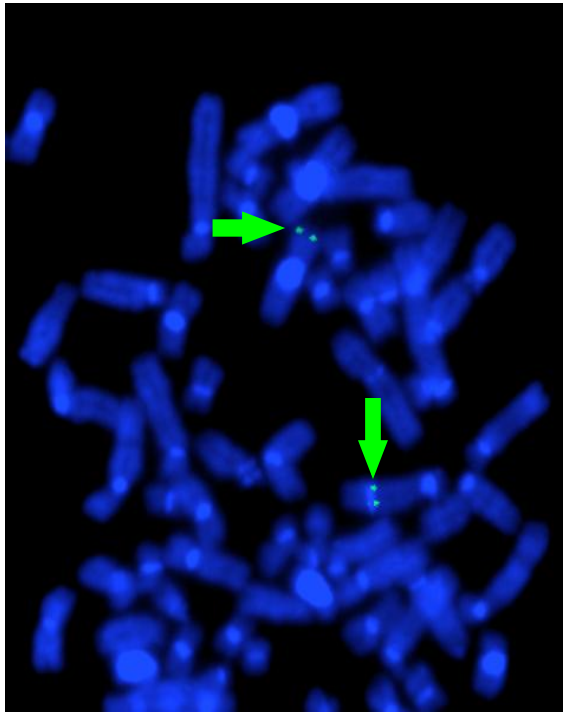
Integration of pSV2Neo in 1p36 - Clone 21

G-Banding

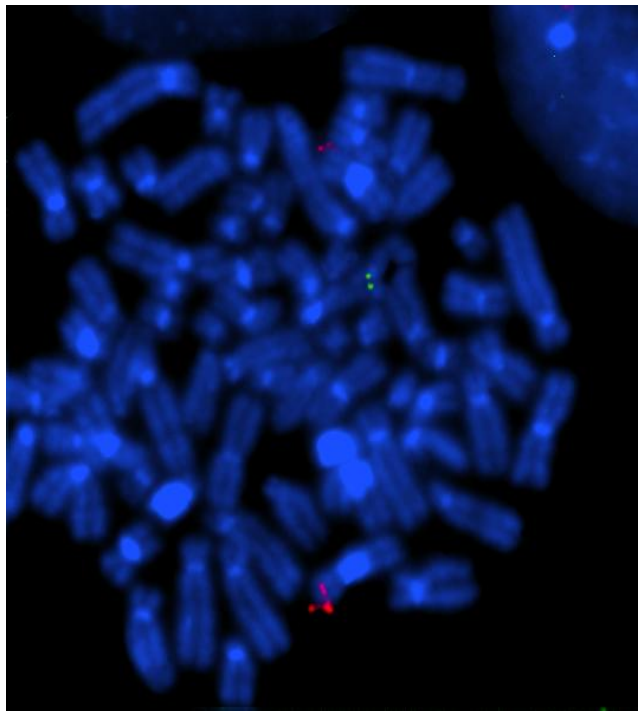


FISH **(pSV2Neo-bio)**

clone 28



pSV2neo-bio



951g6-dig, pSV2neo-bio

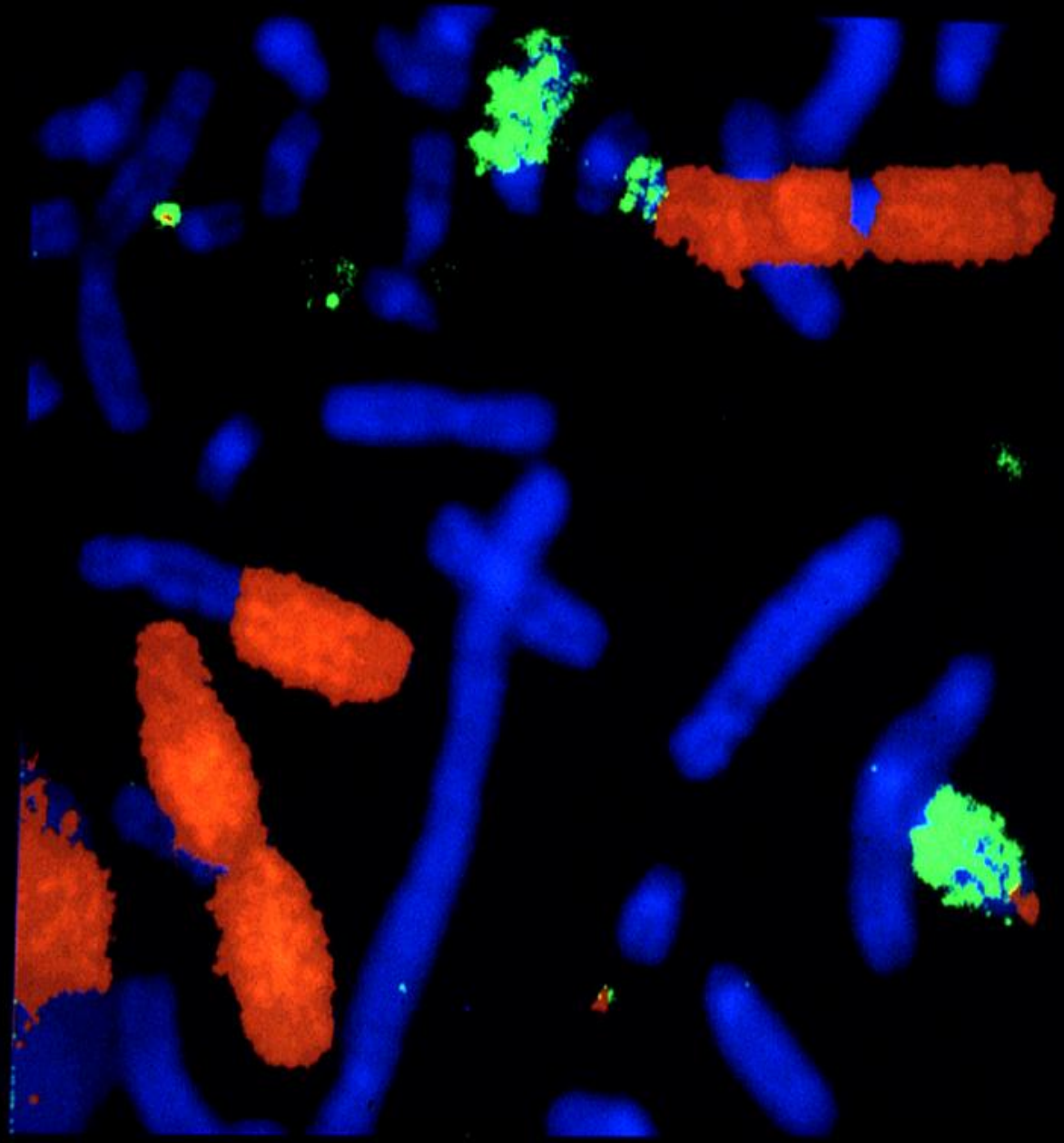
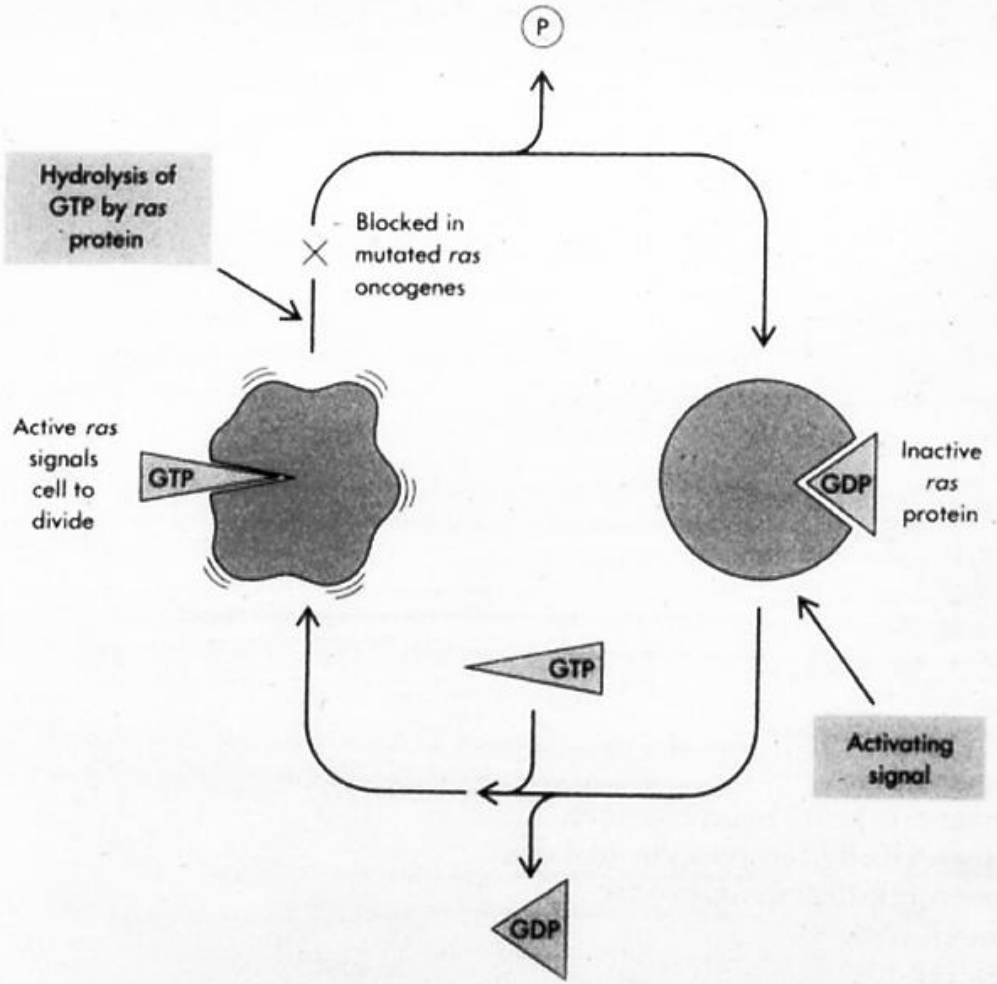
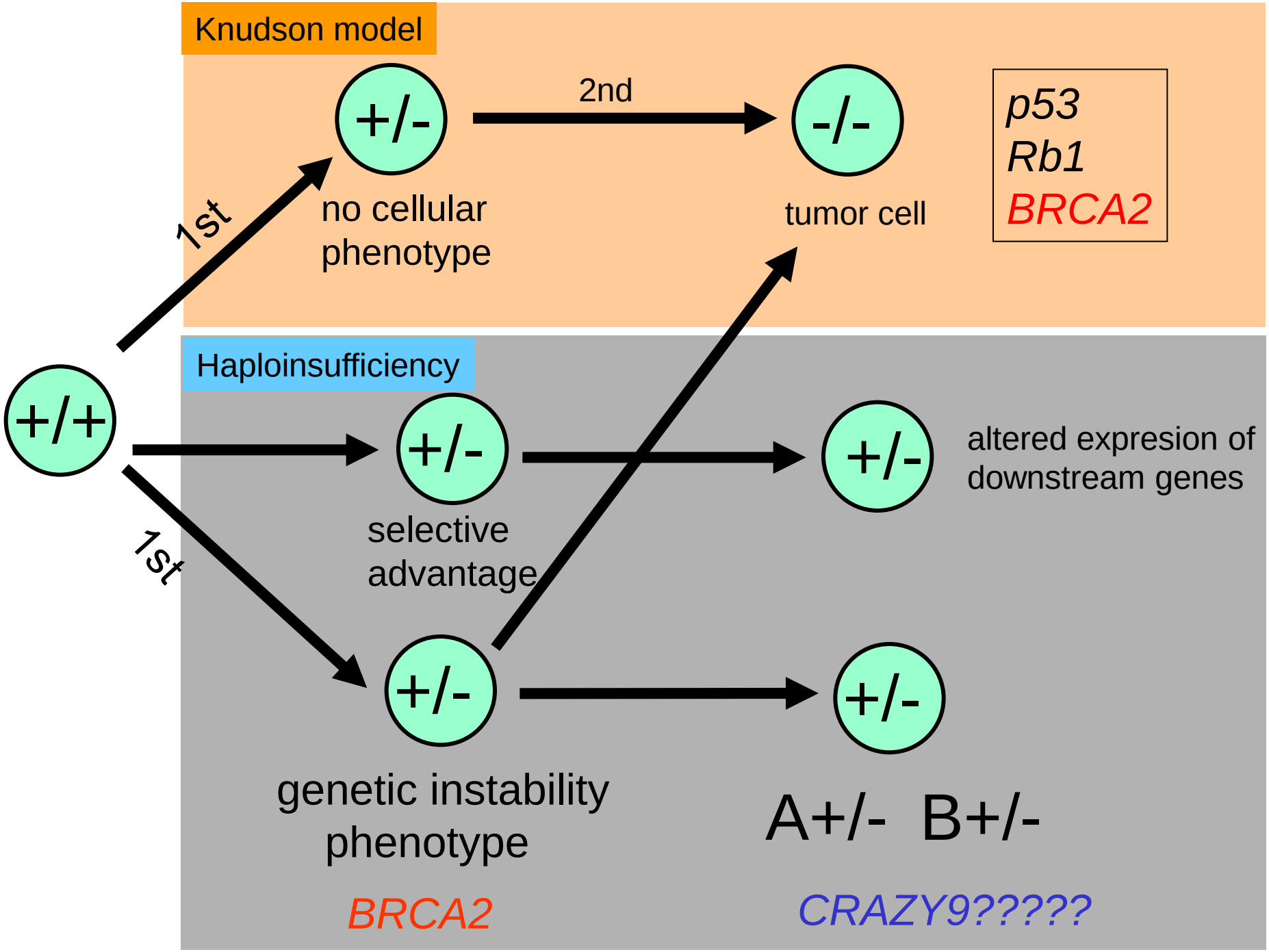
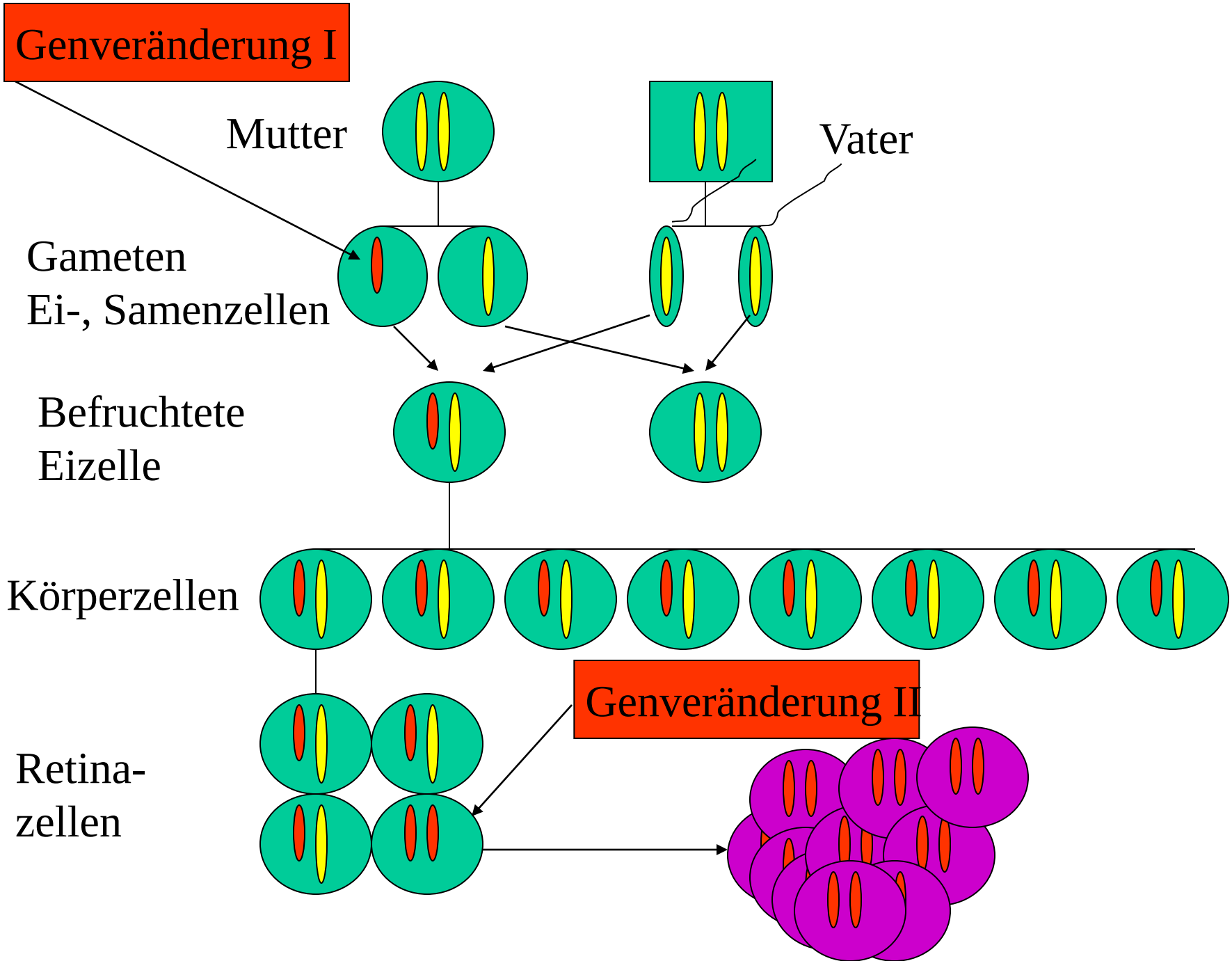


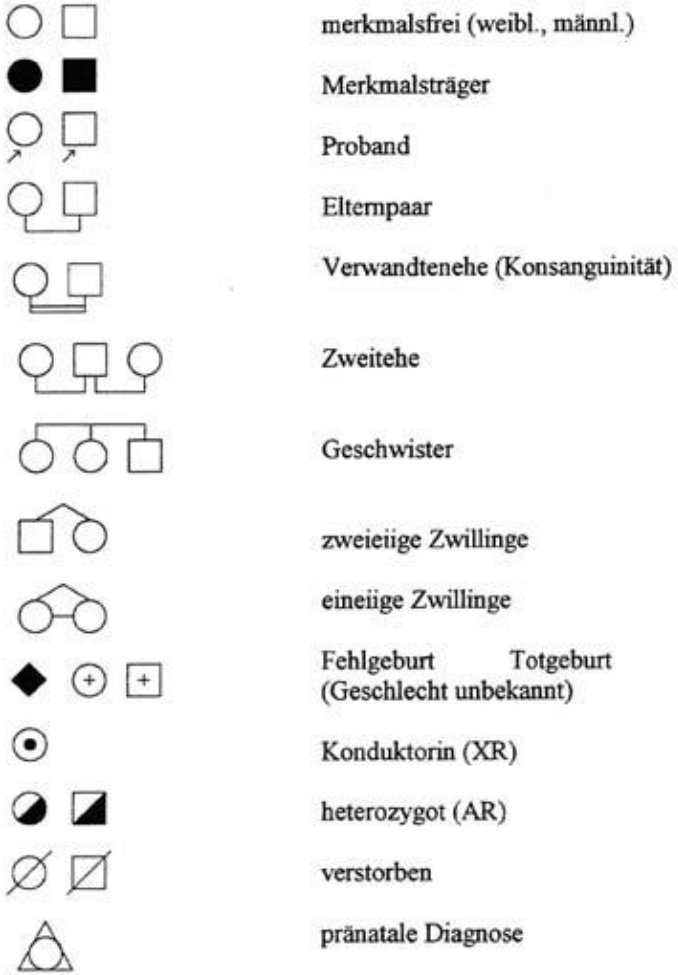
Figure 27-6
Highly schematized view of the inactive form of a *ras* protein binding GDP while the activated form binds GTP. If a mutation destroys the GTPase present in the molecule, then the molecule may remain in the active state.




Knudson model
+/-
2nd
-/-
p53
Rb1
BRCA2
1st
no cellular
phenotype
tumor cell
Haploinsufficiency
+/+
+/-
+/-
altered expresion of
downstream genes
selective
advantage
1st
+/-
+/-
genetic instability
phenotype
A+/- B+/-
BRCA2
CRAZY9?????


Genveränderung I
Mutter
Vater
Gameten
Ei-, Samenzellen
Befruchtete
Eizelle
Körperzellen
Genveränderung II
Retina-
zellen

Stammbaum - Symbole



merkmalsfrei (weibl., männl.)

Merkmalsträger

Proband

Elternpaar

Verwandtenehe (Konsanguinität)

Zweitehe

Geschwister

zweieiige Zwillinge

eineiige Zwillinge

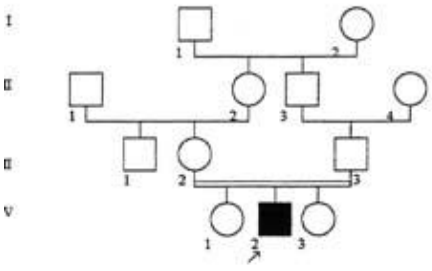
Fehlgeburt Totgeburt
(Geschlecht unbekannt)

Konduktorin (XR)

heterozygot (AR)

verstorben

pränatale Diagnose



Beispiel eines Stammbaumes
über 4 Generationen:
Proband (↗, IV/2)
zB II/4 = Großmutter väterlicherseits
III/2 = Mutter
III/2 und III/3 = Vettern I.Grades
(Konsanguinität)

Grundbegriffe der Genetik III

Penetranz

Manifestationswahrscheinlichkeit; Wahrscheinlichkeit, mit der sich ein dominant wirkendes Gen im Phänotyp ausprägt; 100% Penetranz = alle Genträger sind Merkmalsträger; Penetranzschwankung (verminderte Penetranz) = nicht jeder Genträger ist Merkmalsträger

Expressivität

Manifestationsstärke; Ausmaß der phänotypischen Ausprägung eines Gens; Expressivitätsschwankung = unterschiedlich starke Ausprägung eines Merkmals (Krankheitsbildes)

Pleiotropie = Polyphänie

ein Gen bewirkt mehrere verschiedene Symptome (gleiche molekulare Grundlage)

Grundbegriffe der Genetik II

monogen
durch die Wirkung eines Genlocus bedingtes Merkmal

polygen
durch die gleichzeitige Wirkung mehrerer Genloci bedingtes Merkmal

multifaktoriell
durch die gleichzeitige Wirkung mehrerer Genloci (Polygenie) und nicht genetischer Faktoren bedingtes Merkmal

heterogen
ein bestimmtes monogenes Merkmal kann durch die Wirkung der Allele verschiedener Genloci bedingt sein

dominant
Merkmal auch im heterozygoten Zustand ausgeprägt; einfache Gendosis genügt zur Ausprägung des Merkmals

rezessiv
Merkmal nur im homozygoten Zustand ausgeprägt; doppelte Gendosis für die Ausprägung des Merkmals notwendig (Ausnahme: Hemizygotie)

kodominant
2 Allele prägen unabhängig je 1 Merkmal aus

Grundbegriffe der Genetik I

Genotyp
individuelle Genkombination eines Individuums; individuelle Genkombination an einem Genlocus; jedem Genotyp entspricht ein bestimmter Phänotyp

Phänotyp
Summe aller Merkmale eines Individuums; Einzelmerkmal eines Individuums

homozygot
reinerbig für gegebenen Genlocus; zwei Gene mit identischer Wirkung auf dem Genort homologer Chromosomen

heterozygot
mischerbig für gegebenen Genlocus; zwei Gene mit unterschiedlicher Wirkung (=Allele) auf dem Genlocus homologer Chromosomen

hemizygot
homologer Genort fehlt; ein oder mehrere Genorte sind im sonst diploiden Chromosomensatz nur einmal vorhanden
z.B. X-chromosomale bzw.Y-chromosomale Genorte
beim XY-Mann, bei Monosomie X (45,X)

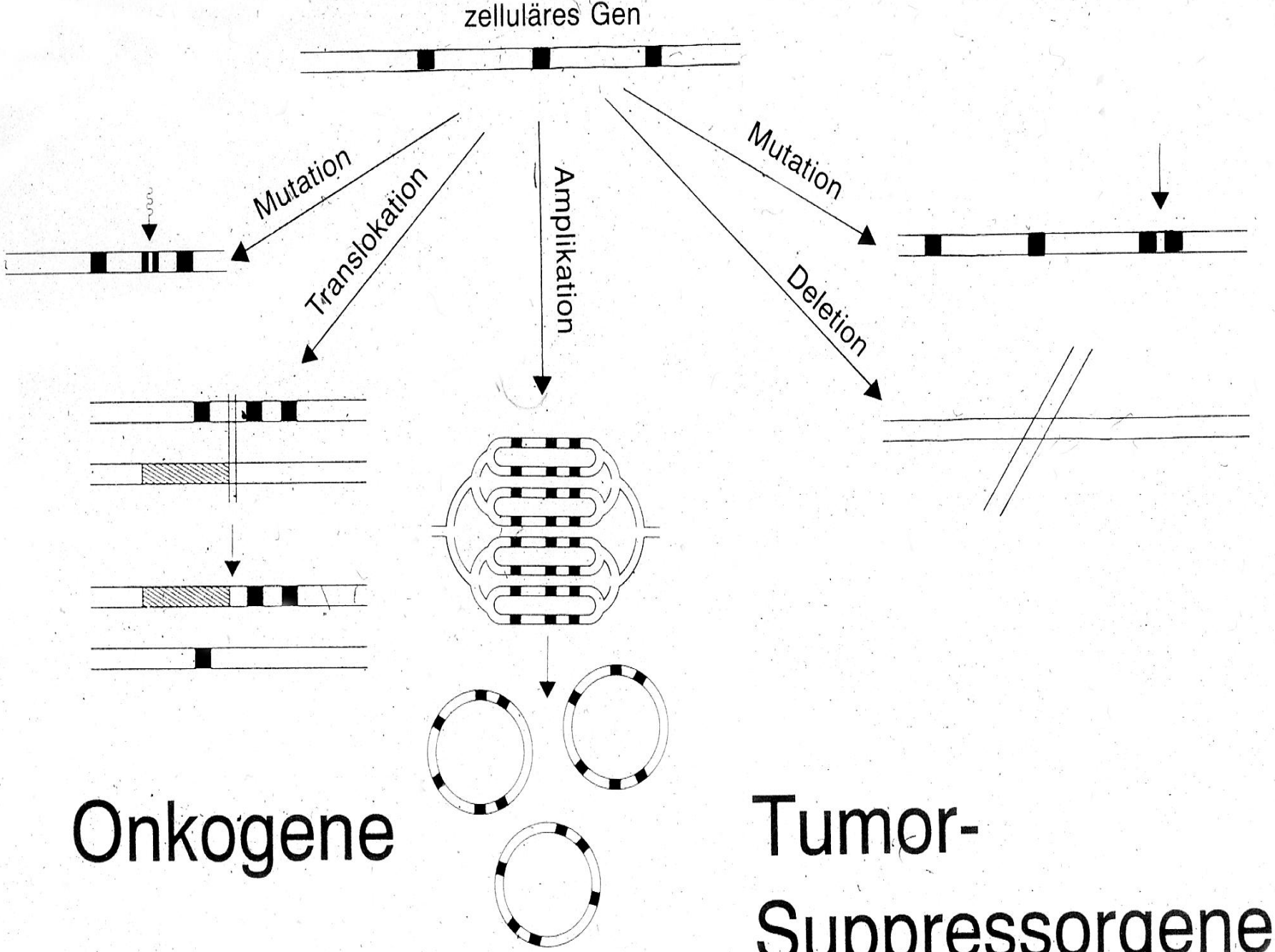
Allele
Gene eines Genlocus mit unterschiedlicher Wirkung
mutierte Gene eines Locus; DNA-Abschnitte eines homologen Locus mit unterschiedlicher Basensequenz (z.B. RFLPs)

Wildtypallel
ursprüngliche Form des Gens innerhalb einer Art

multiple Allelie
in einer Population sind mehr als 2 Allele für einen Genort vorhanden

gekoppelte Gene
liegen auf demselben oder homologen Chromosom
in enger Lagebeziehung; (in Kopplungsphase auf demselben Chromosom lokalisiert, in Abstoßungsphase auf homologen Chromosomen lokalisiert); werden durch Crossing over seltener rekombiniert als nicht gekoppelte Gene; werden während der Meiose nicht zufällig verteilt; für Genlokalisierung wichtig (Genkartierung); für indirekte Gendiagnose wichtig

Haplotyp
Satz eng gekoppelter Gene; werden meistens als Block vererbt



Onkogene

Tumor-
Suppressorgene