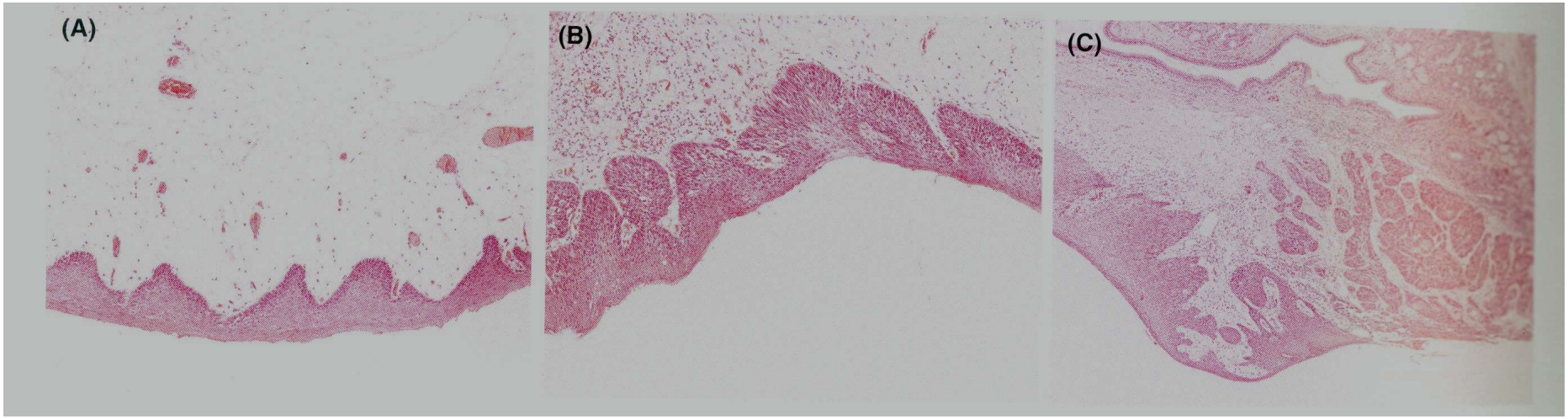
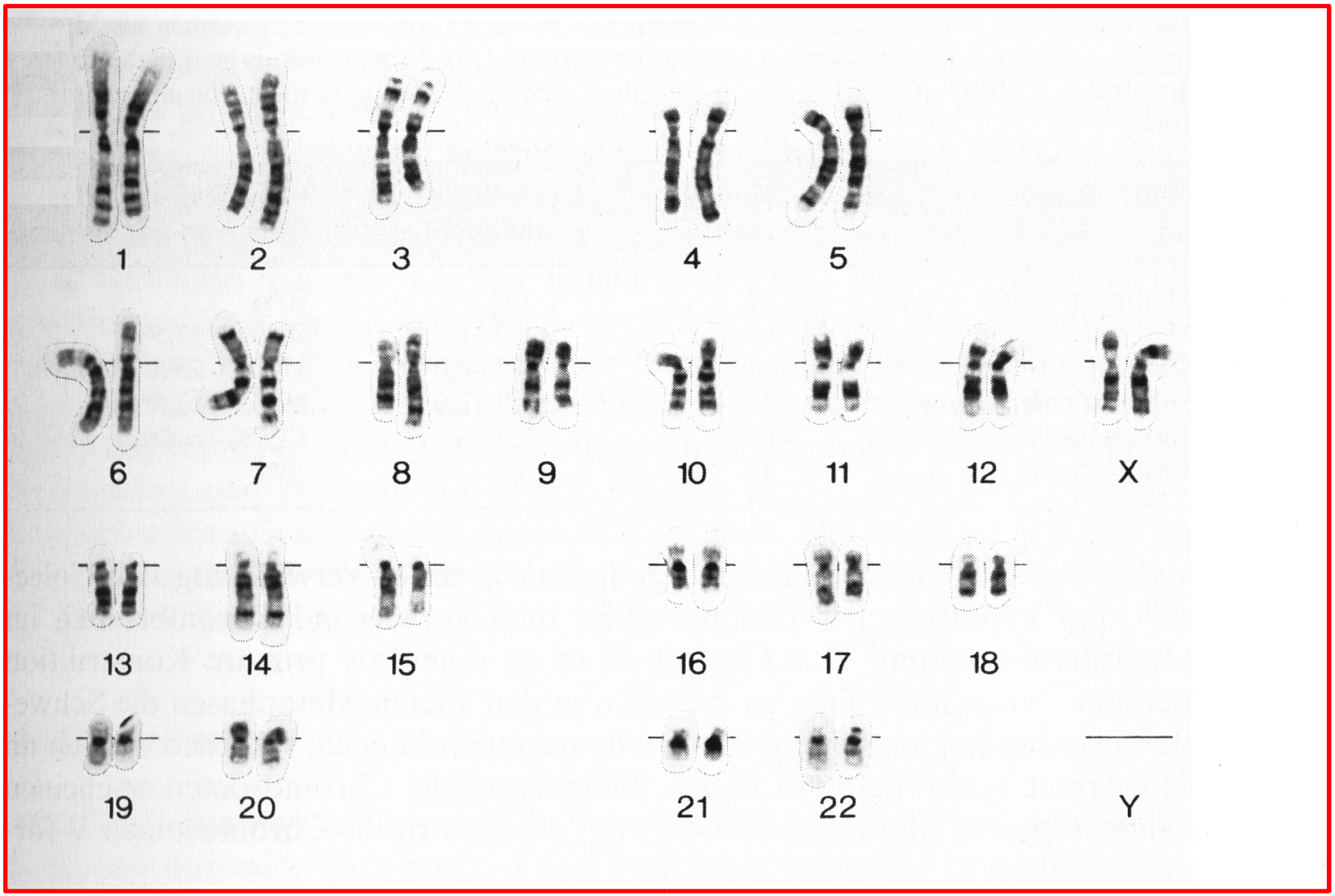
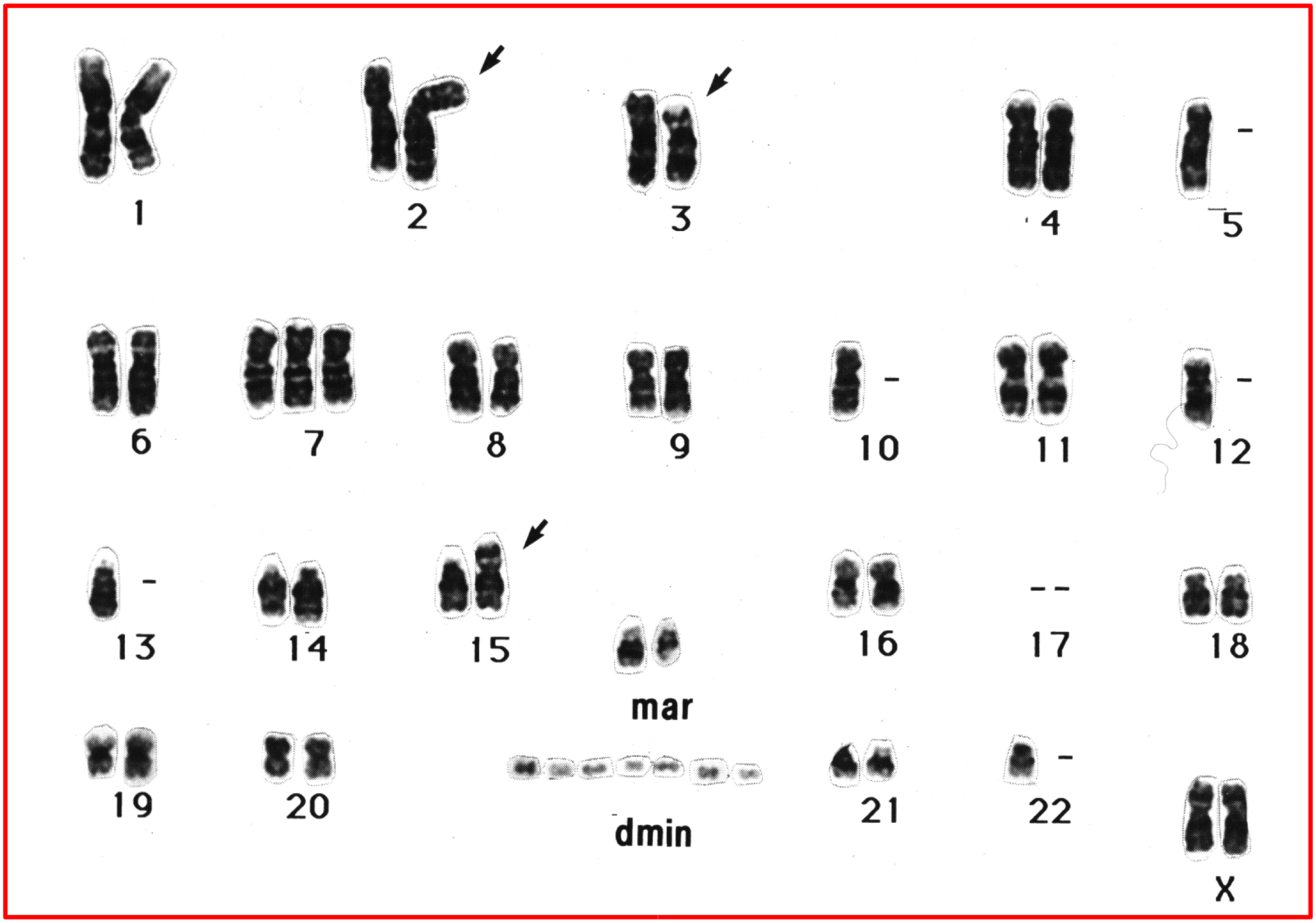

(A)
(B)
(C)


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


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

Extrazelluläre DNA schädigende Einflüsse

- Ionisierende Strahlung
- Ultraviolettes Licht
- Umweltfaktoren

Endogene DNA schädigende Mechanismen

- Depurination
- Deaminierung
- Reaktiver Sauerstoff

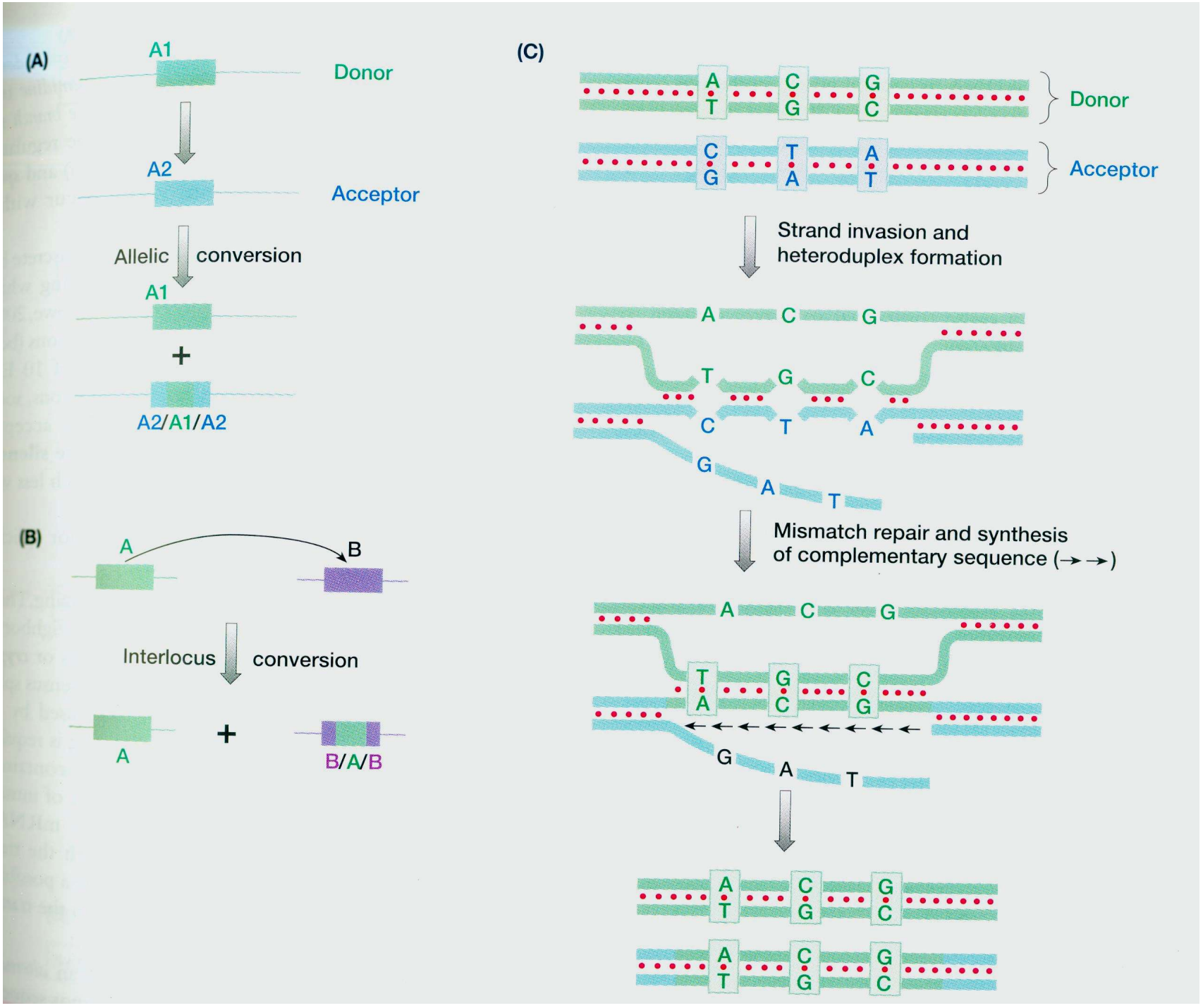
- Fehler bei der Replikation oder Rekombination

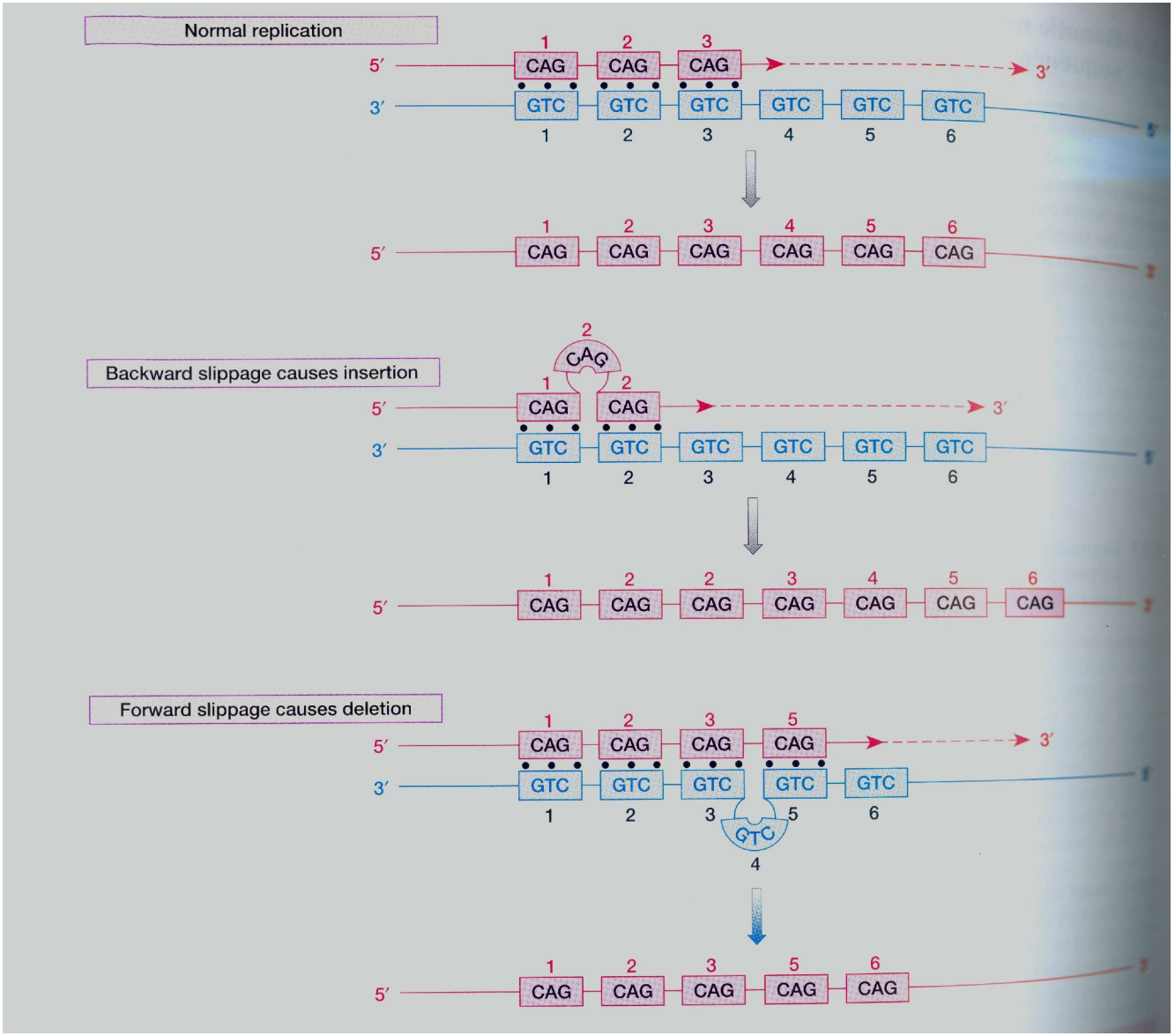
Das Pathogene Potential von Repeats

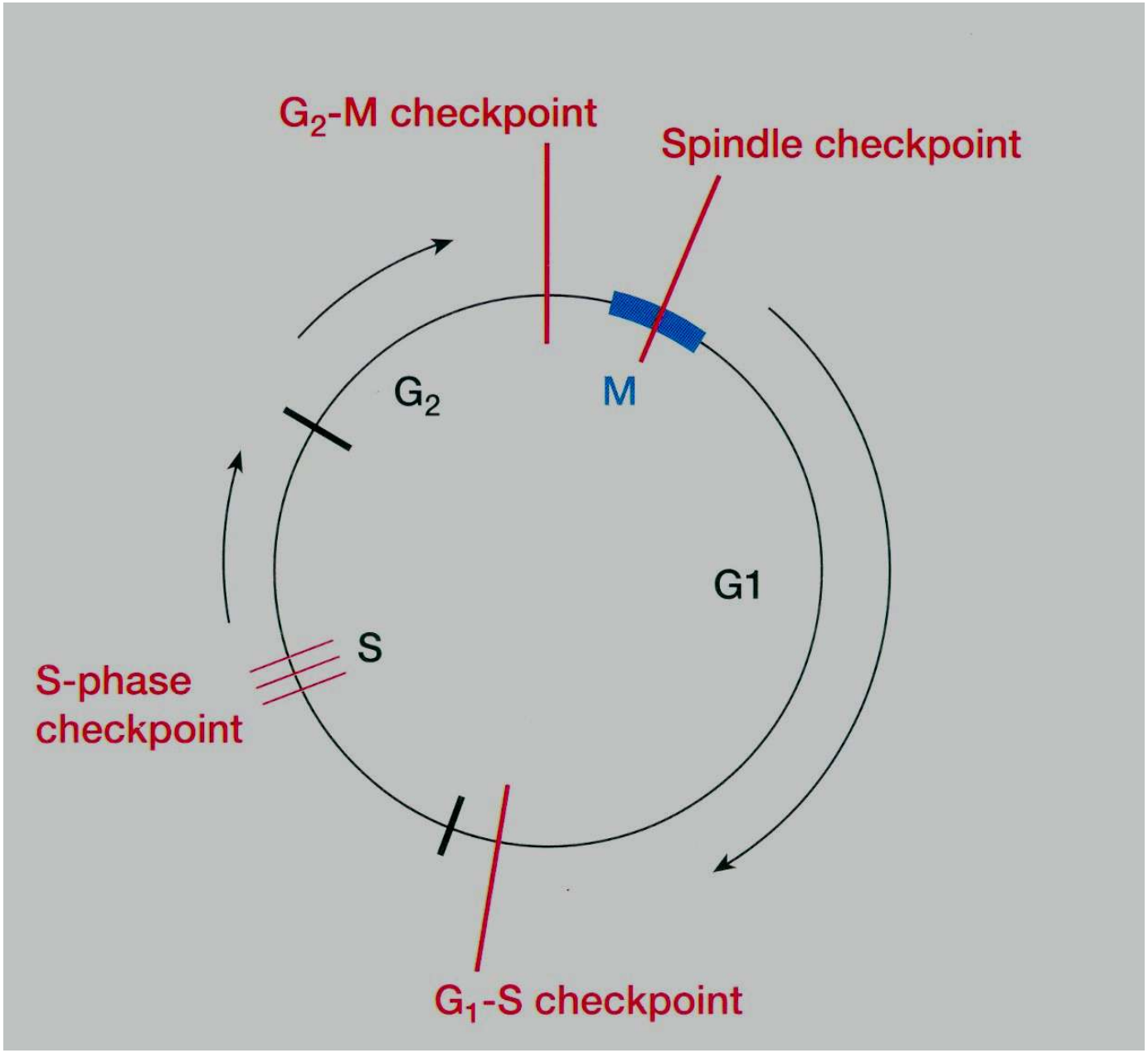
- Short direct repeats
- Alu Repeats
- Low copy number long repeats

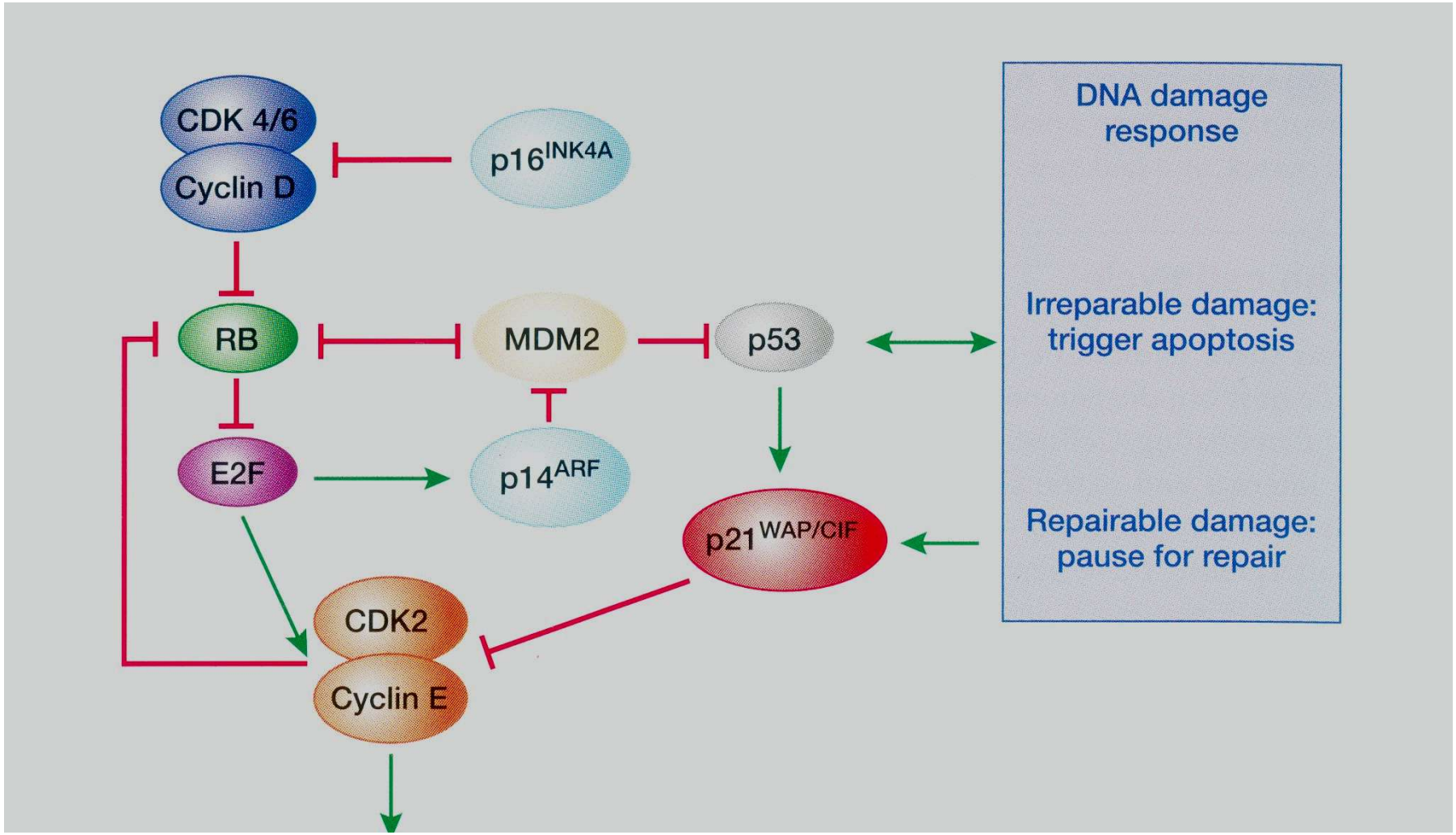
DNA Repair

- Direct Repair
- Base Excision Repair
- Nuceotide Excision Repair
- Post-Replication Repair
- Mismatch Repair


(A)
A1
Donor
A2
Acceptor
Allelic conversion
A1
+
A2/A1/A2
(B)
A
B
Interlocus conversion
A
+
B/A/B
(C)
A C G
T G C
C T A
G A T
Donor
Acceptor
Strand invasion and heteroduplex formation
Mismatch repair and synthesis of complementary sequence (→→)

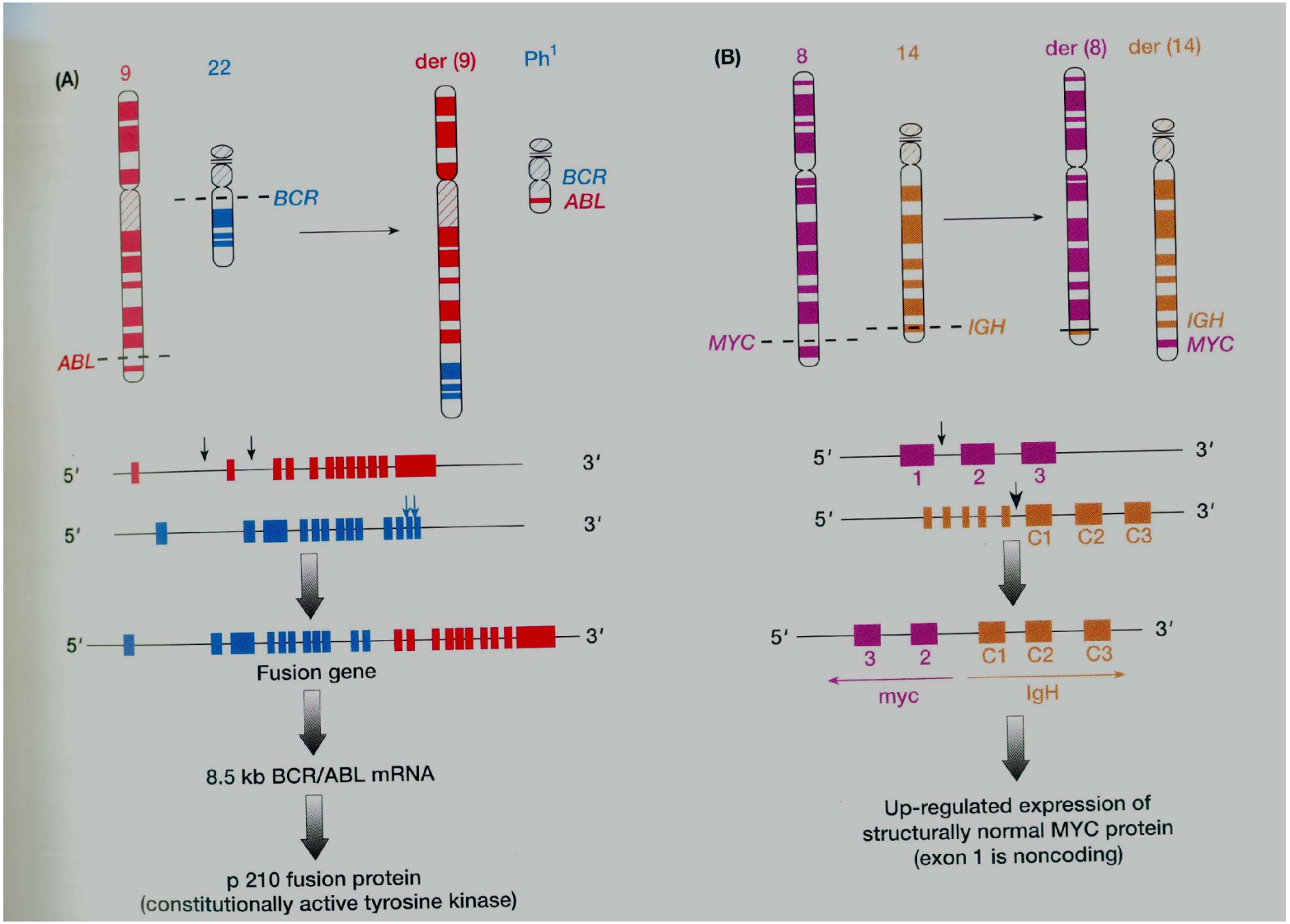

Normal replication
5′
3′
CAG
GTC
Backward slippage causes insertion
Forward slippage causes deletion


G2-M checkpoint
Spindle checkpoint
G2
M
G1
S
S-phase
checkpoint
G1-S checkpoint


CDK 4/6
Cyclin D
p16INK4A
RB
MDM2
p53
E2F
p14ARF
p21WAP/CIF
CDK2
Cyclin E
DNA damage response
Irreparable damage: trigger apoptosis
Repairable damage: pause for repair

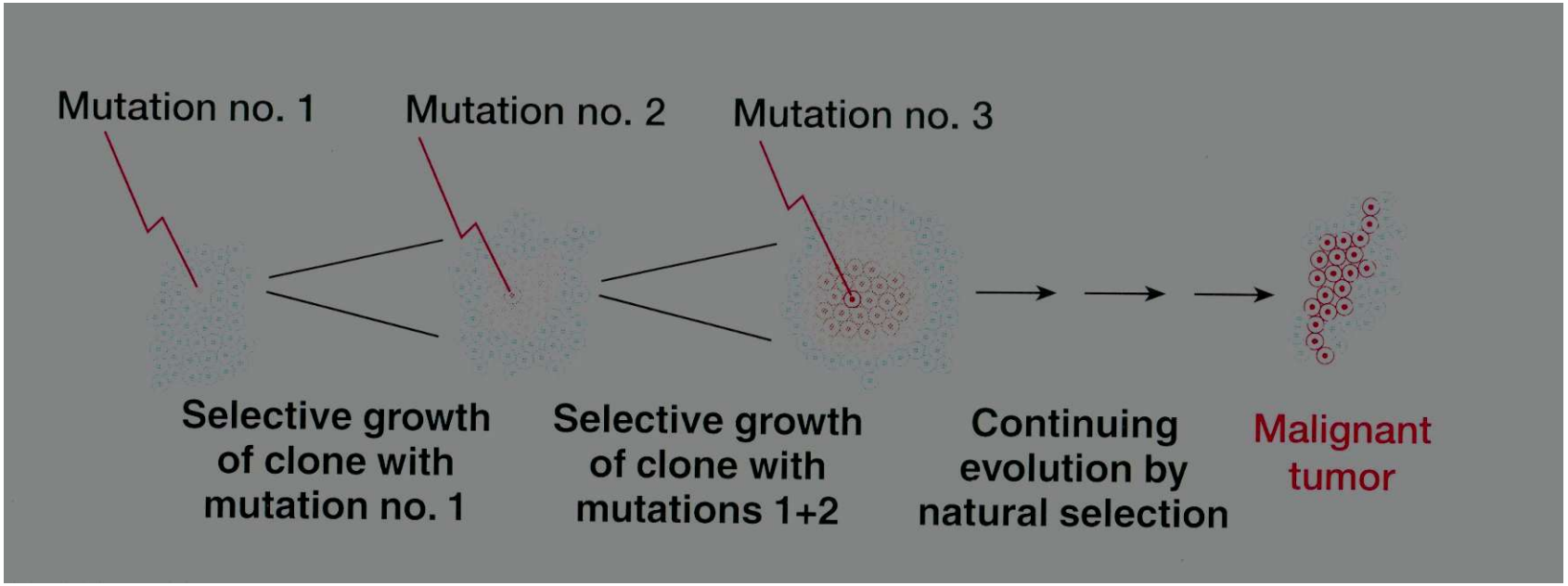
Aktivierung von Onkogenen

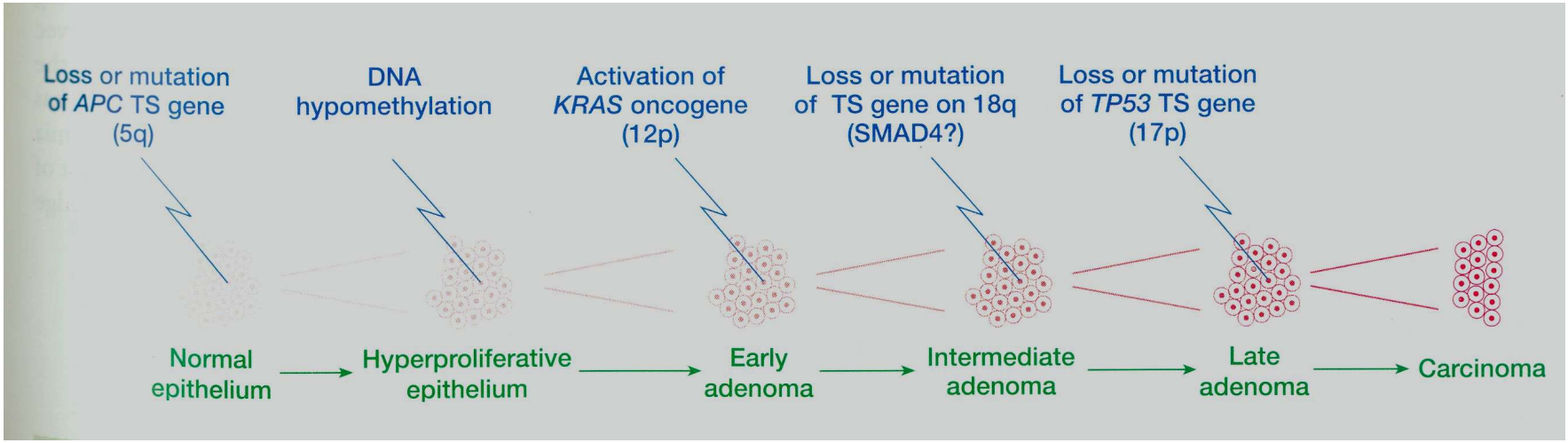
- Amplifikation
- Punktmutationen
- Fusionproteins
- Translokation in aktive Region

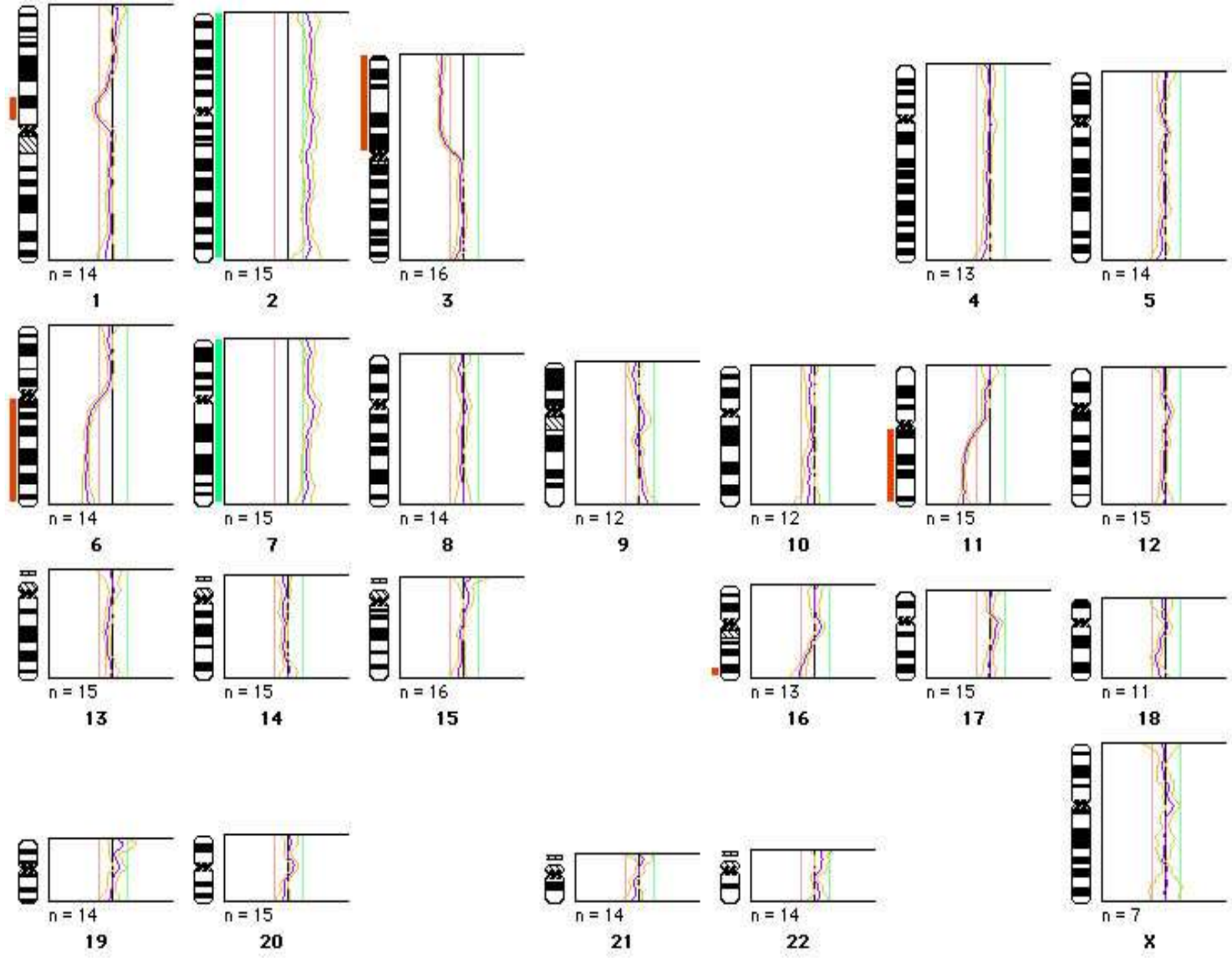

(A)
9
22
der (9)
Ph1
BCR
ABL
BCR
ABL
5′
3′
5′
3′
5′
3′
Fusion gene
8.5 kb BCR/ABL mRNA
p 210 fusion protein
(constitutionally active tyrosine kinase)
(B)
8
14
der (8)
der (14)
MYC
IGH
IGH
MYC
5′
3′
1
2
3
5′
3′
C1
C2
C3
5′
3′
3
2
C1
C2
C3
myc
IgH
Up-regulated expression of
structurally normal MYC protein
(exon 1 is noncoding)

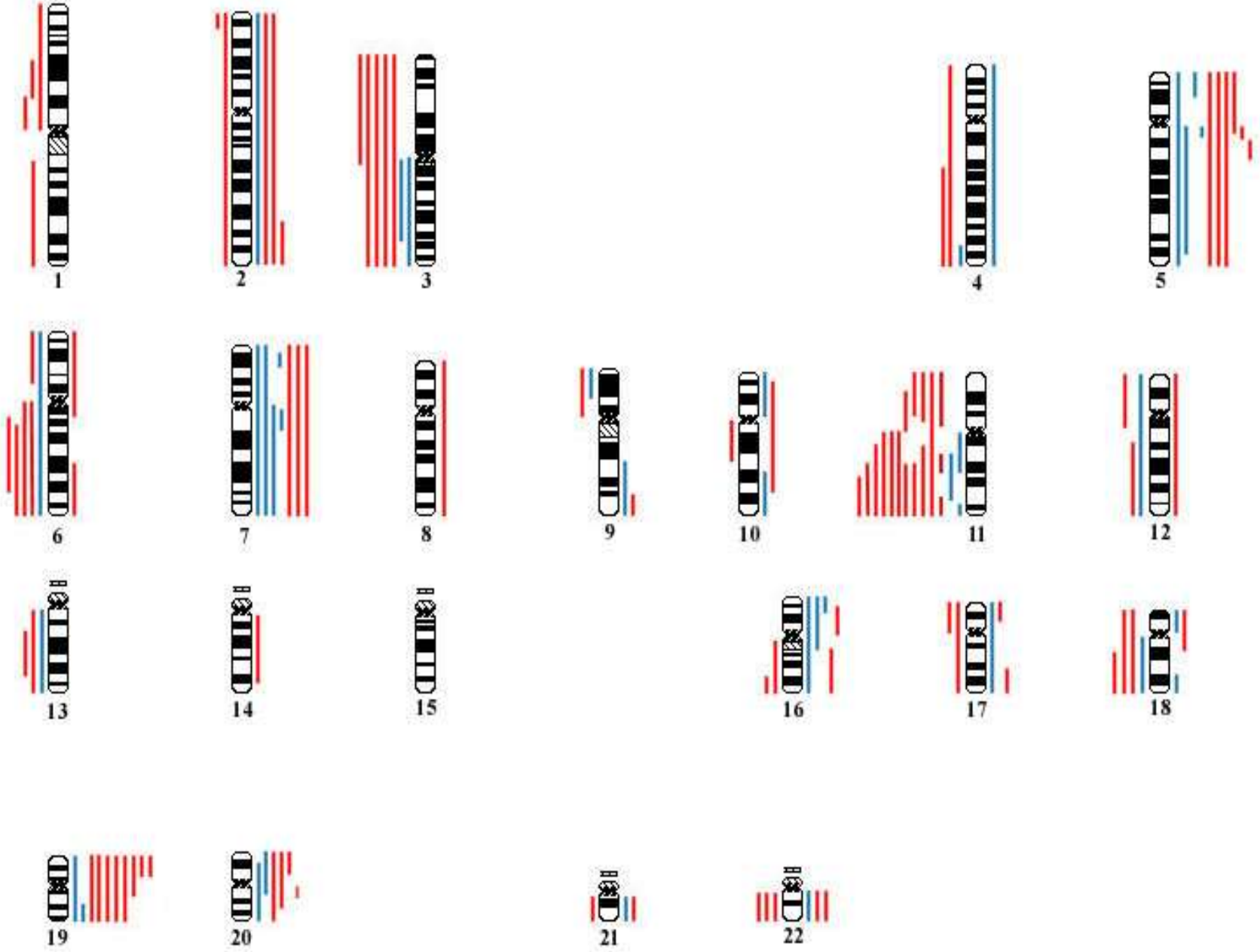
Tumorsuppressorgene

- Knudson´s two hit Hypothese
- Rezessiv
- Haploinsuffizienz


Mutation no. 1
Mutation no. 2
Mutation no. 3
Selective growth of clone with mutation no. 1
Selective growth of clone with mutations 1+2
Continuing evolution by natural selection
Malignant tumor

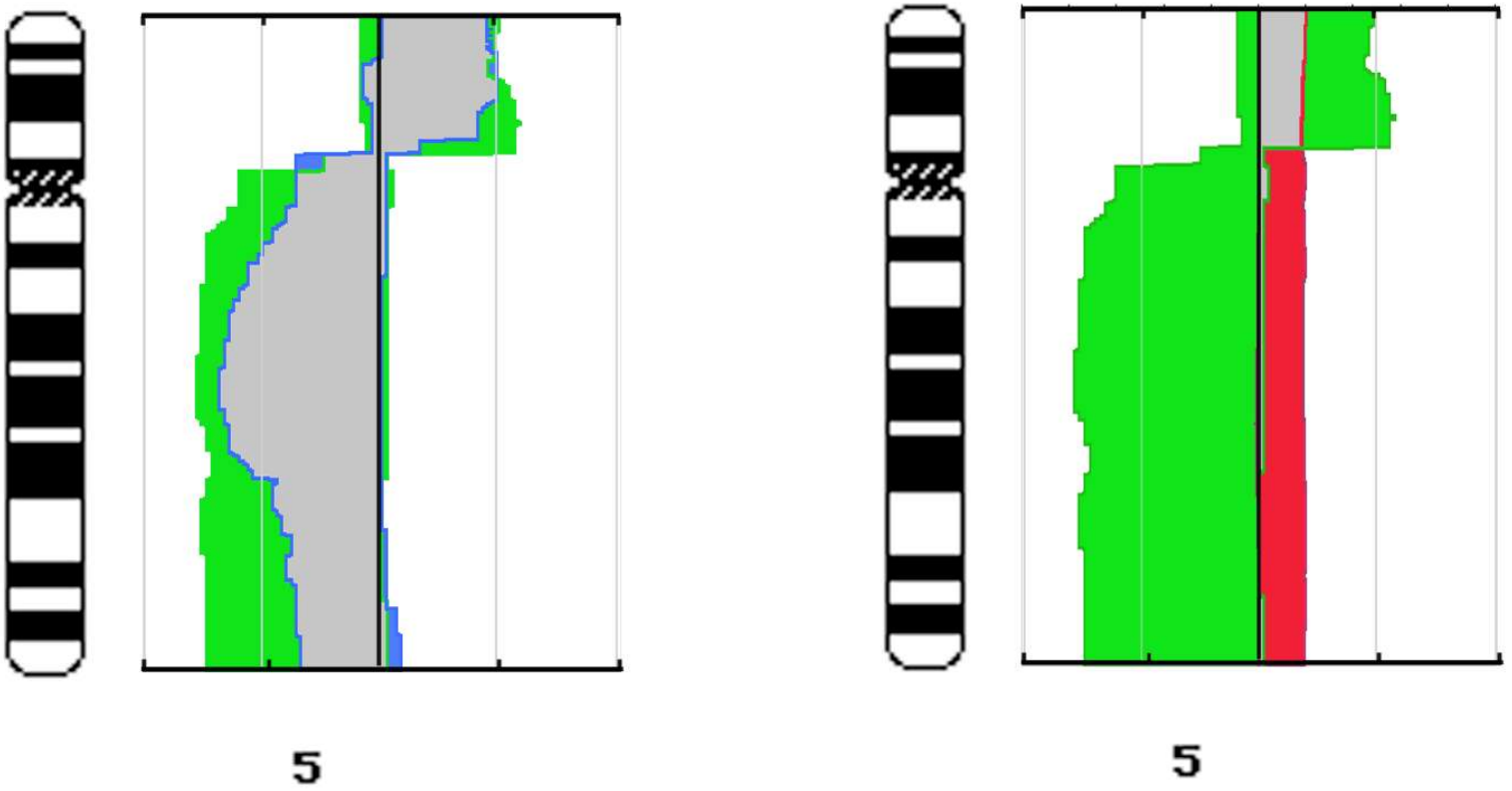

Loss or mutation of *APC* TS gene (5q)
DNA hypomethylation
Activation of *KRAS* oncogene (12p)
Loss or mutation of TS gene on 18q (SMAD4?)
Loss or mutation of *TP53* TS gene (17p)
Normal epithelium
Hyperproliferative epithelium
Early adenoma
Intermediate adenoma
Late adenoma
Carcinoma


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

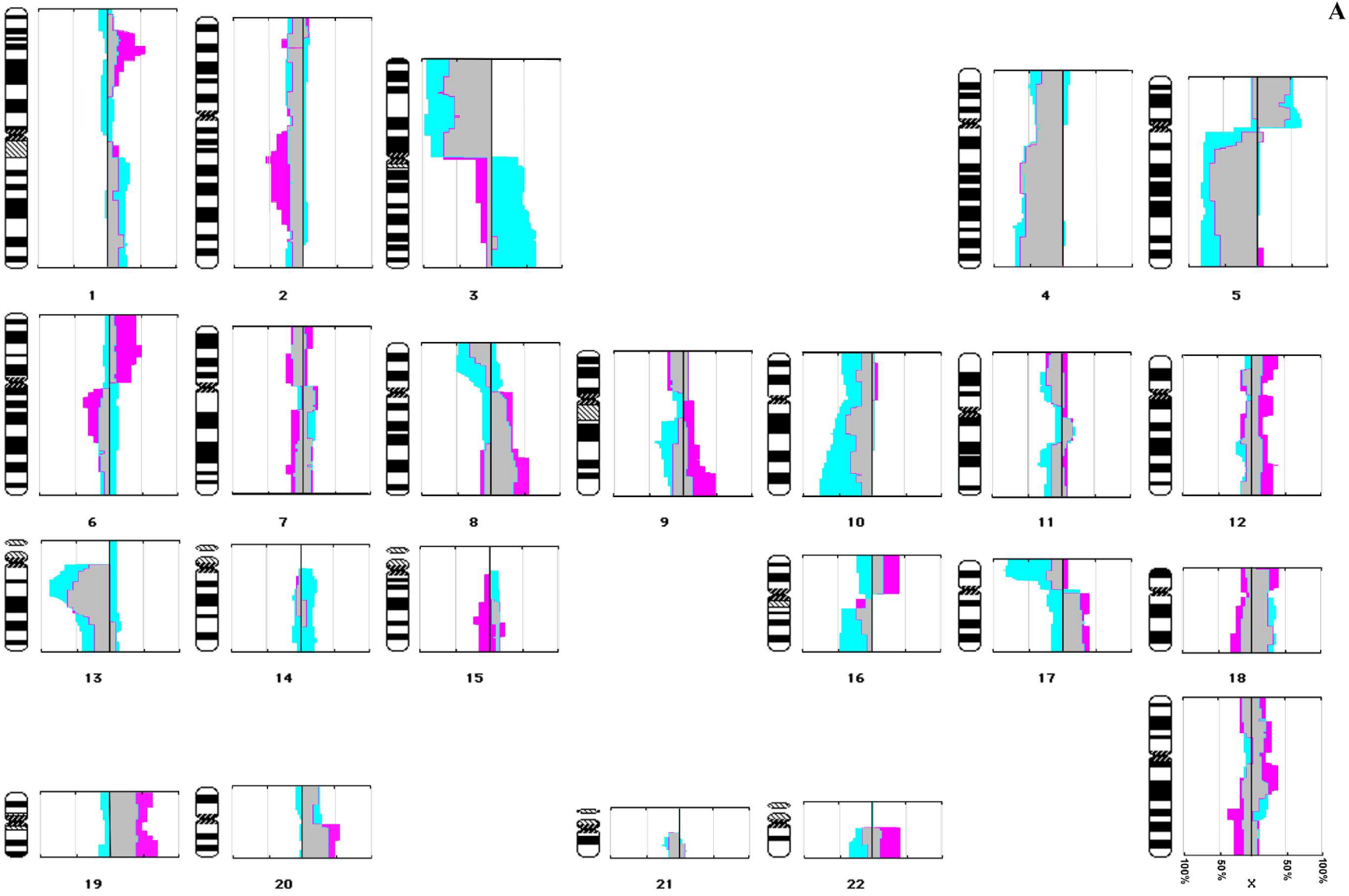


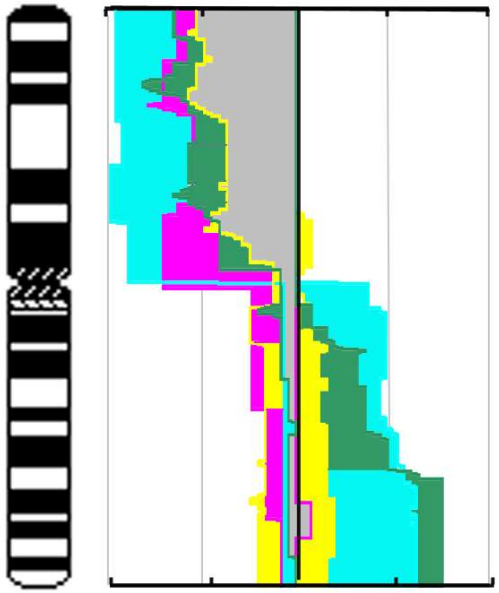
Ullmann et al., 2002

Carcinoid versus carcinoma

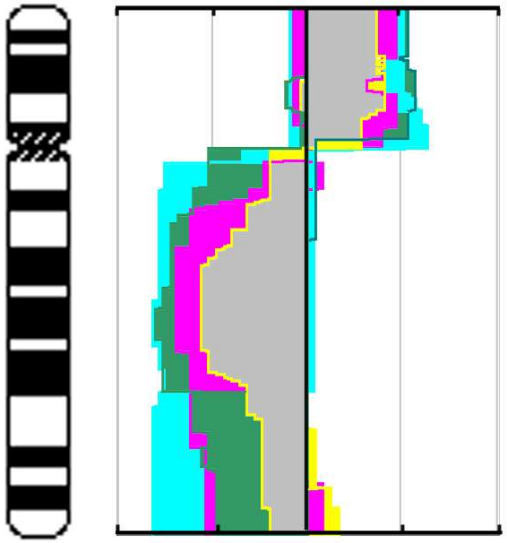


green: SCLC and LCNEC
blue: SQCC and Adenocarcinoma
orange: carcinoids

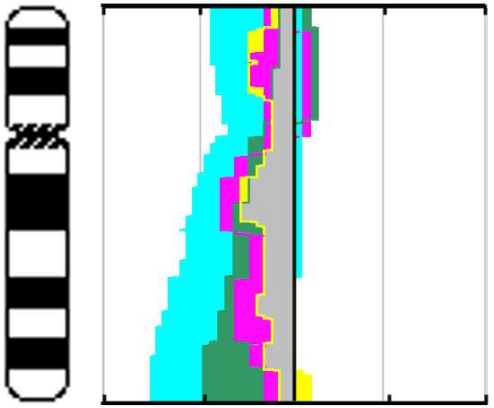

A
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
100%
50%
X
50%
100%



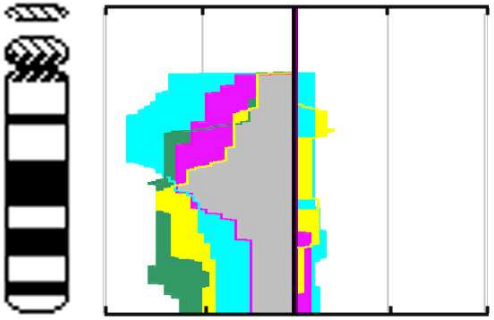
3



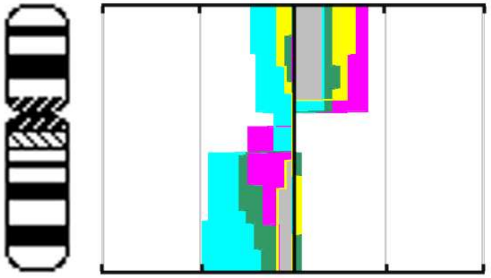
5



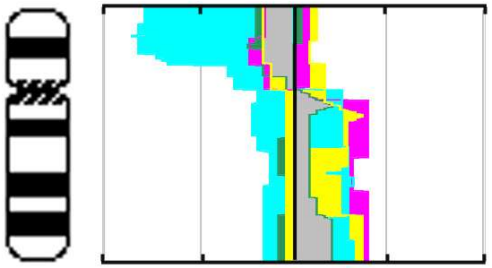
10



13

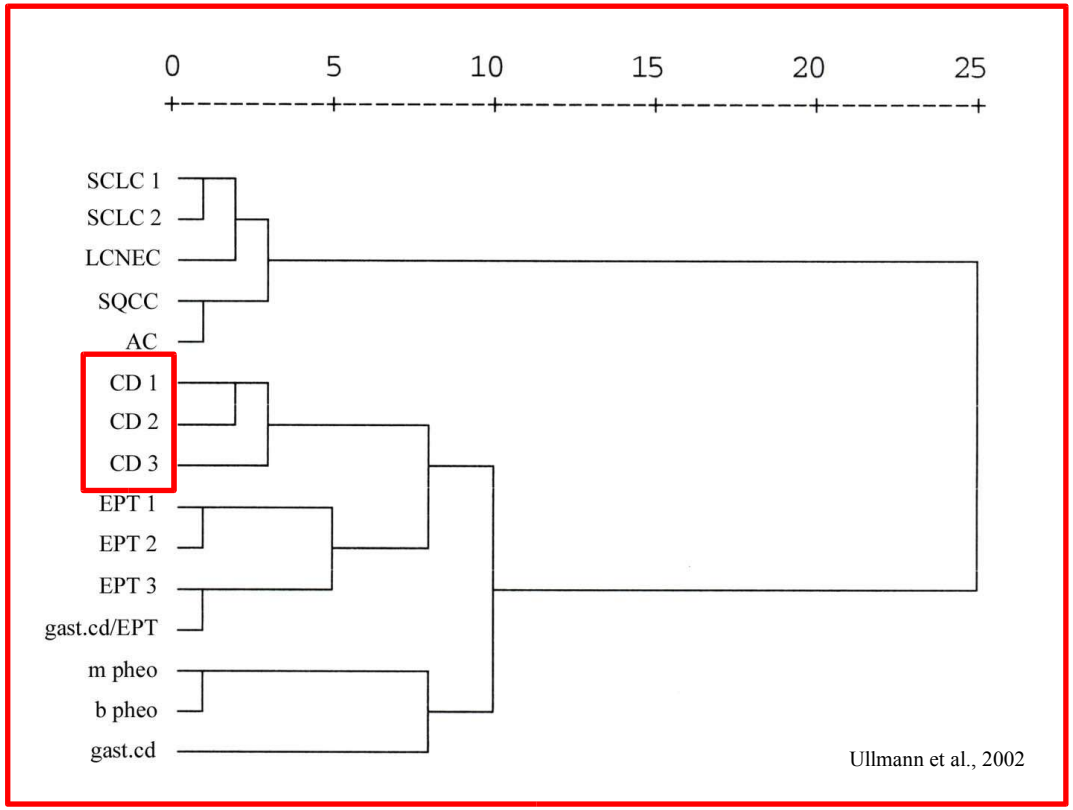


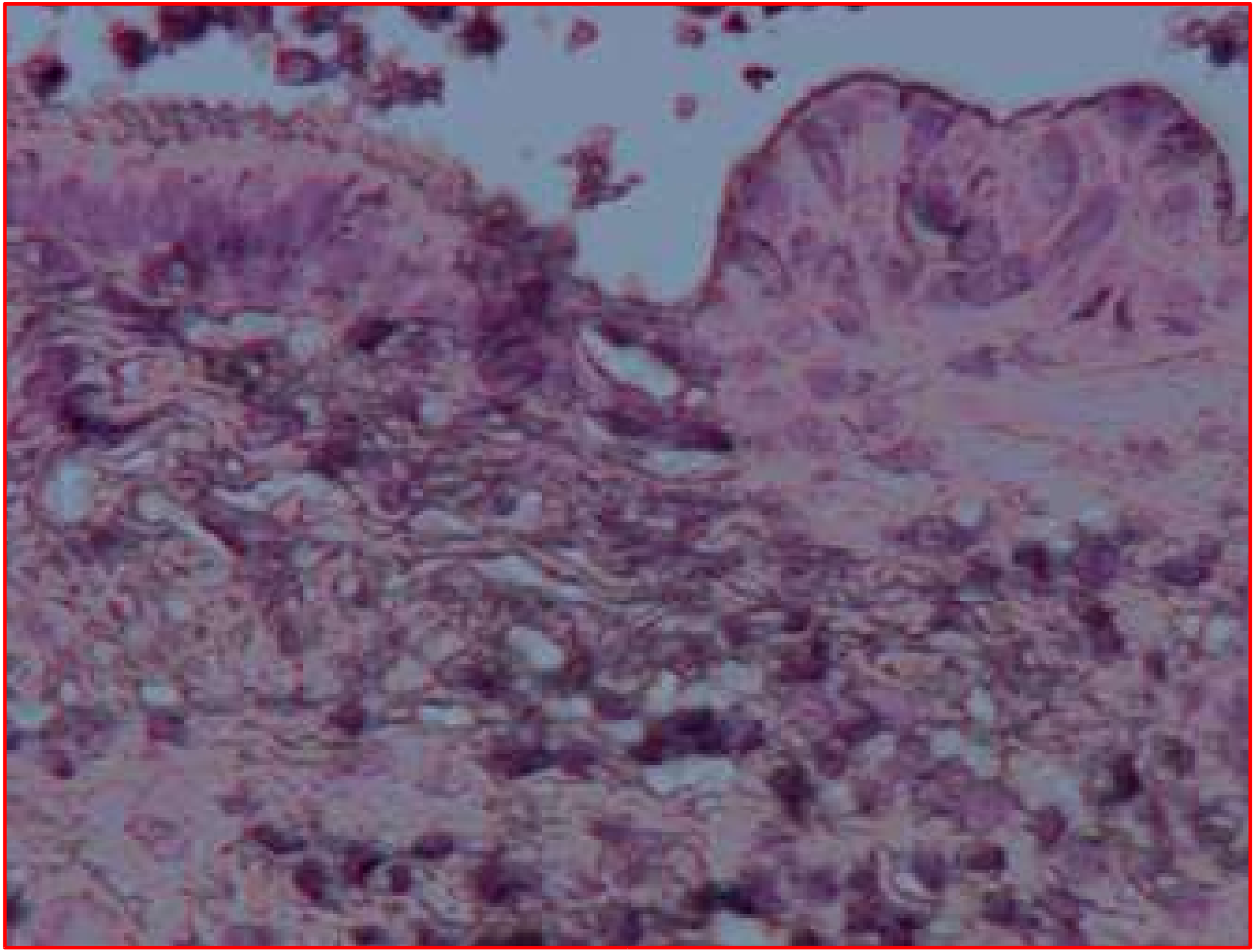
16

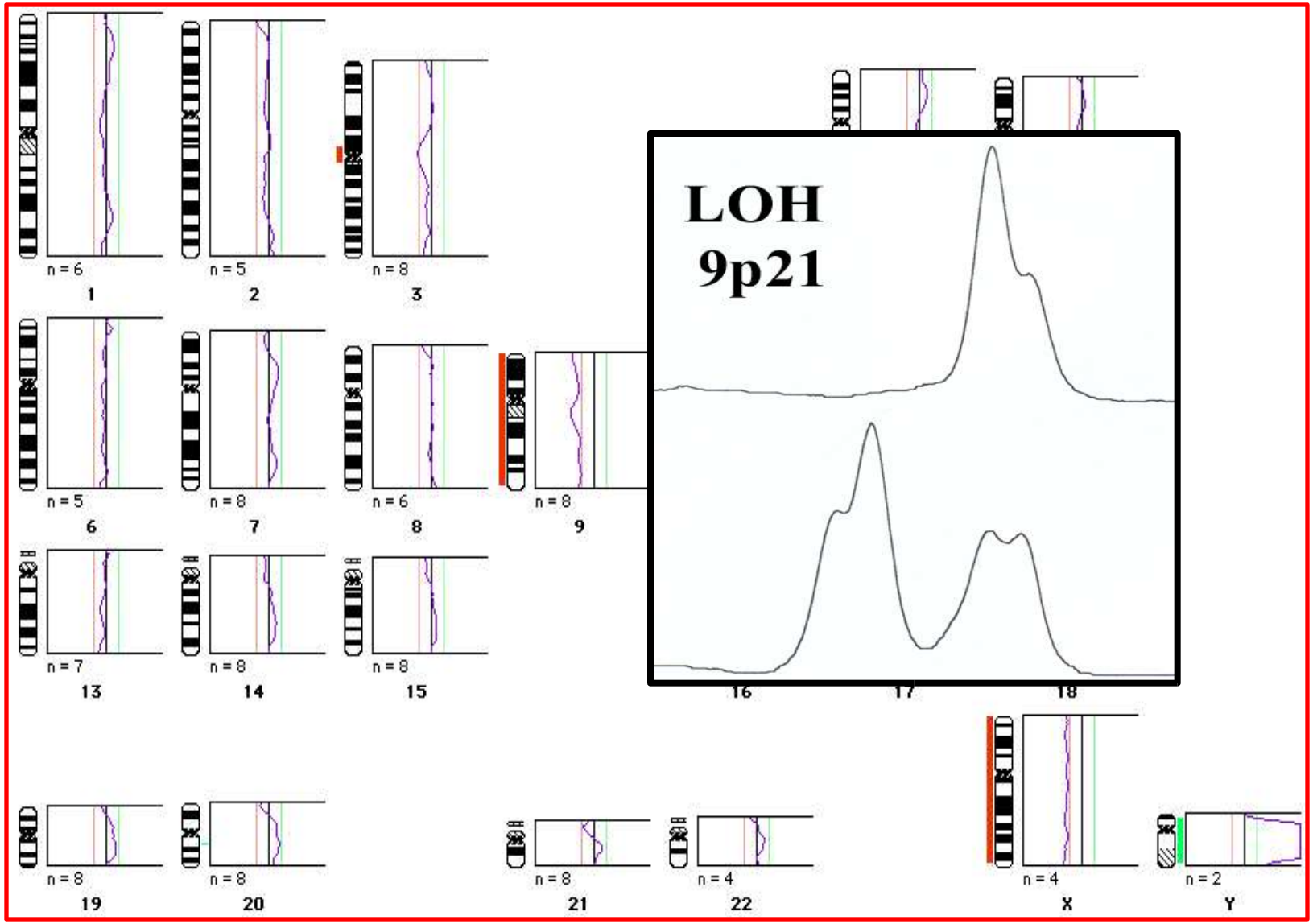


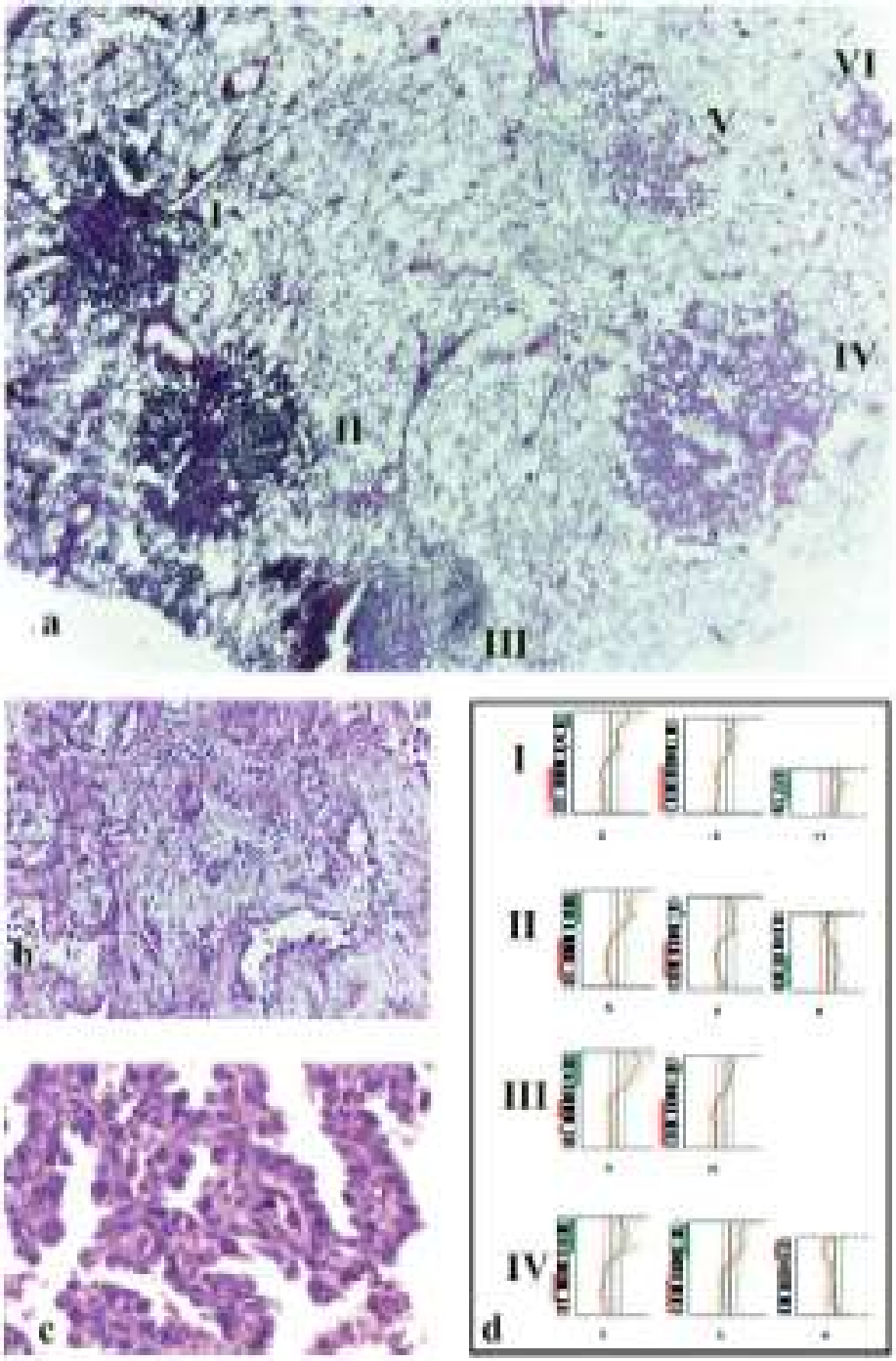
17

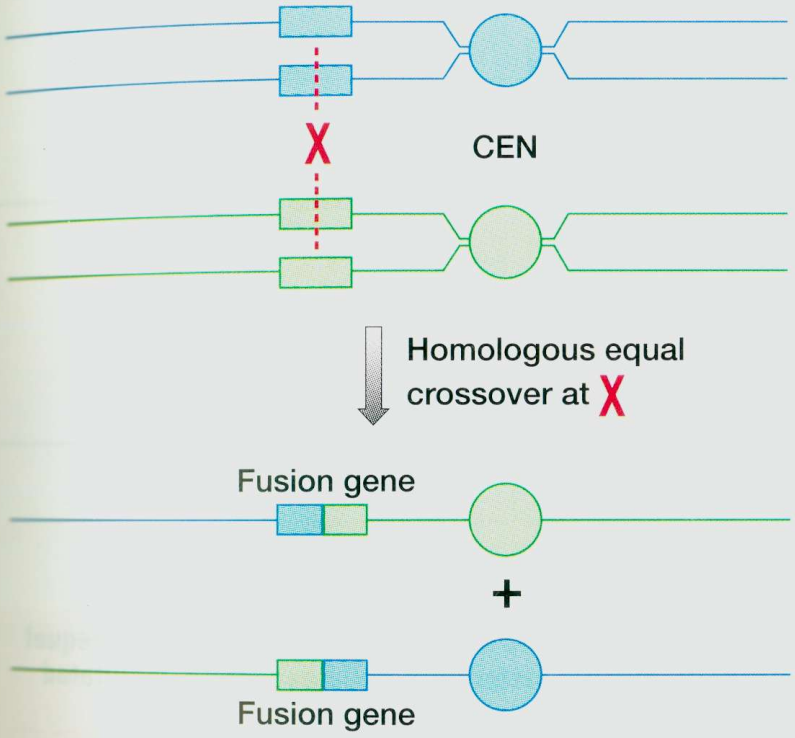
Hierarchisches Clustering chromosomaler Aberrationen






LOH
9p21
n = 6
1
n = 5
2
n = 8
3
n = 5
6
n = 8
7
n = 6
8
n = 8
9
n = 7
13
n = 8
14
n = 8
15
16
17
18
n = 8
19
n = 8
20
n = 8
21
n = 4
22
n = 4
X
n = 2
Y


VI
V
I
IV
II
a
III
b
c
I
II
III
IV
d



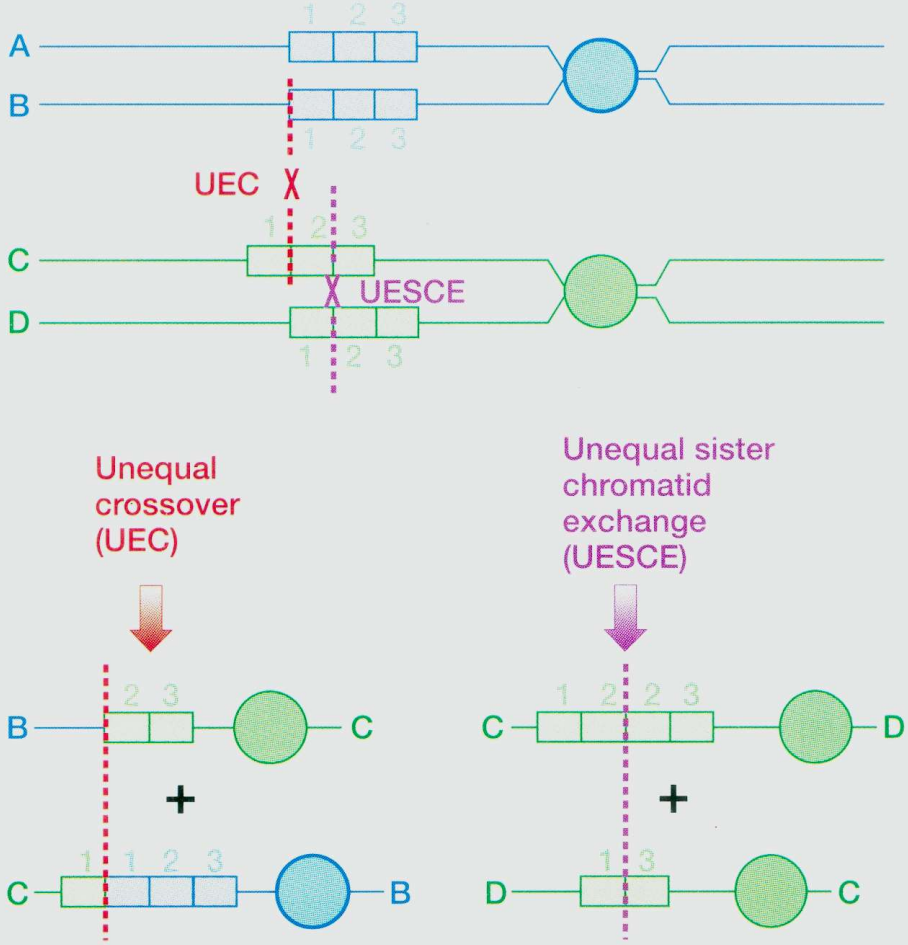


Figure 11.6: Homologous equal crossover can result in fusion genes.

The example shows how intragenic equal crossover occurring between alleles on nonsister chromatids can generate novel