Molecular basis of somatic oncogenesis
Hereditary basis of cancer

Pr A. De Leener, Clinical Genetics

09 February 2024

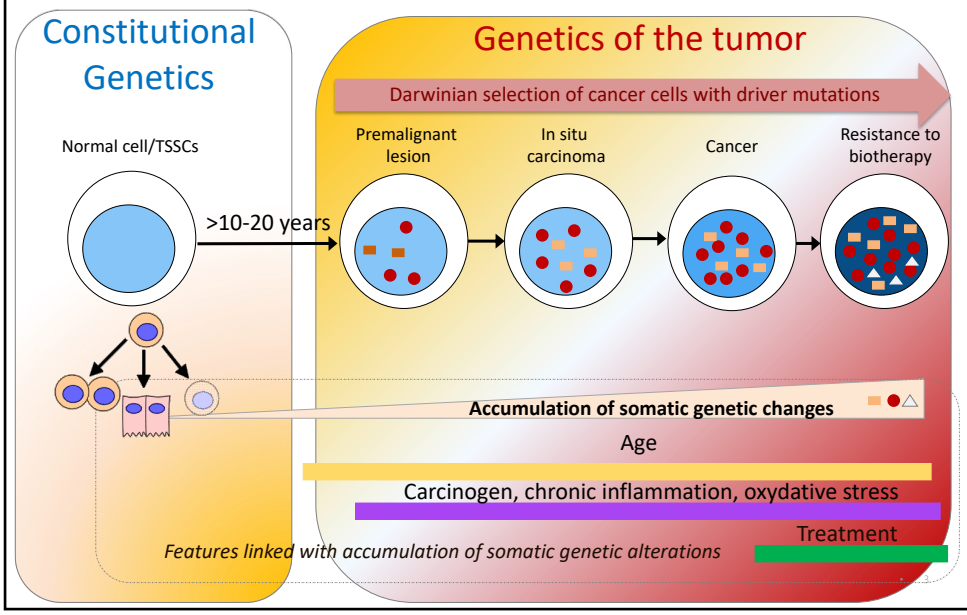
1

Genetic basis of oncogenesis

1. Introduction
2. The discovery of oncogenes
   - ✓ Tumorigenic retrovirus
   - ✓ Transfection of tumoral DNA
3. Cytogenetics
4. Molecular genetics
5. Environment
6. Introduction to inherited or familial cancers

2

Introduction



Cancer is a disease characterized by uncontrolled cell division.
- ✓ disruption of the cellular homeostasis
- ✓ Imbalance between proliferation / differentiation / apoptosis

Monoclonal proliferation: abnormal proliferation of cells originating from a same ancestral cell

Accumulation of genetic changes during carcinogenesis

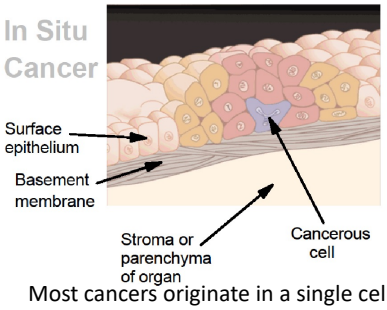
It is a **genetic disease** at the cellular level

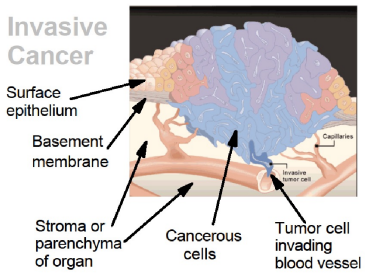
Stratton MR, et al. Nature 2009

3

Cancer Biology : multi-step process

Normal tissue -> in situ tumor → locally invasive cancer -> metastases





1. Most cancers originate in a single cell
   - ✓ In this regard a cancerous growth can be considered to be **clonal**

2. At the cellular level and genetic levels, cancer is usually a **multistep process**
   - ✓ It begins with a precancerous genetic change (benign growth)
   - ✓ Following additional genetic changes, it progresses to cancerous cell growth

3. Once a cellular growth has become malignant, the cells are invasive: they can invade healthy tissues

Cancer is a genetic disorder

Malignant tumors = the cells are able to invade neighbouring tissue and/or spread to more distant sites (metastasizing)

4

Cancer : heterogeneous disease

More than 100 kinds of human cancers are known

3 main forms of cancer according to the cell of origin :

- **Carcinomas** : tumor arising in epithelial tissue *80-90%*
  - Intestine, bronchi, mammary ducts, epiderma,…
- **Sarcomas** : tumor arising in mesenchymal tissue
  - tumor derived from muscle, bone, cartilage, fat or connective tissues,…
- **Hematological** malignancies :
  - Leukemia : derived from bone marrow hematopoïetic precursors
  - Lymphoma : derived from lymphocytes responsible for the immune response

Classification within each major group :

- By site, tissue type, histological appearance, biological characteristics, degree of malignancy,… -> **W**orld **H**ealth **O**rganization classification
- TNM (Tumor, Node, Metastases)

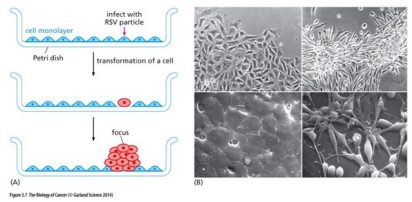
5

The discovery of oncogenes: Tumorigenic retrovirus

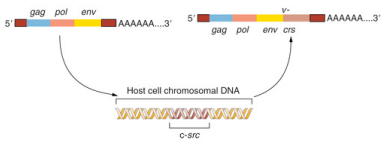
1900 : "filtrable" agents may induce chicken tumors
- *discovery of the Rous Sarcoma Virus (Peyton Rous, 1911)*

1970 : transforming properties of viral RNA (v-SRC)

1976 : Nobel Prize Varmus & Bishop (Stehelin)



Retrovirus : may induce cellular transformation
- Rous Sarcoma Virus → Sarcoma (chicken)
- Abelson murine leukemia virus → Sarcoma, Leukemia (mouse, cat)



Isolation of **viral oncogenes** v-SRC, v-ABL,…

v-SRC, v-ABL derived from host cellular sequences (SRC, ABL)

Viral **oncogenes** have cellular normal counterpart named cellular **proto-oncogenes**, which may become tumorigenic when mutated (or activated by a pre-viral insertion)

Oncogenes induce dysregulation of normal cellular functions

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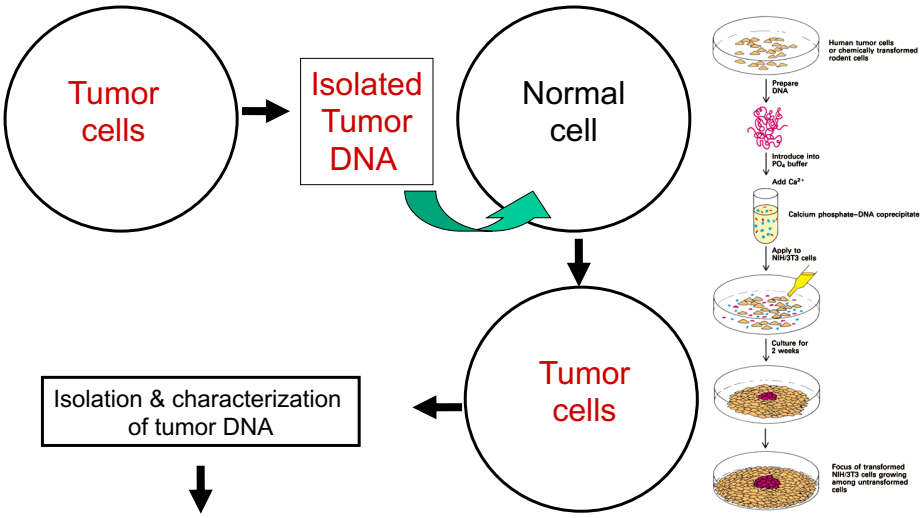
Tumor phenotype transfer to normal cells due to DNA transfection



Identification of activated oncogenes in human tumor
(*RAS* family : *HRAS, KRAS, NRAS*)

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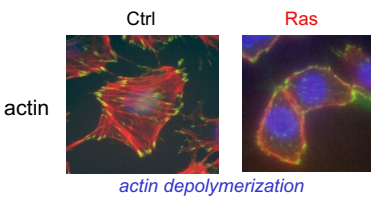
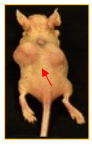
Activation of the *RAS* oncogenes involved in multiple cellular processes

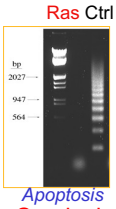
- *RAS* mutations in 15-20% of human tumors
  50% colorectal cancer
  95% pancreatic cancer



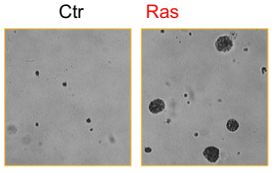
actin depolymerization
Cytoskeleton



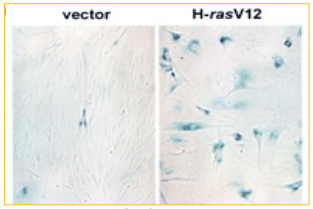
Tumor induction
Proliferation



Apoptosis
Survival



Anchorage-independent Growth
Adhesion



Aging

8

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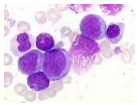
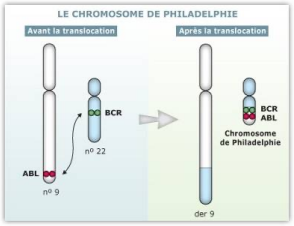
Translocation leading to a chimeric gene t(9;22)(q34;q11) in CML





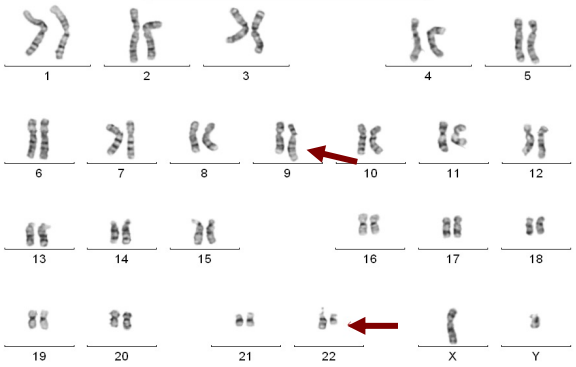
Chronic myeloid leukemia:

Chronic myeloproliferative syndrome.

It is a proliferation of the granular lineage with the presence of an acquired cytogenetic abnormality: the Philadelphia(Ph) chromosome with its molecular equivalent, the BCR/ABL rearrangement.

The etiology of CML is idiopathic (unidentified) in over 99% of cases, but ionising radiation and exposure to certain solvents appear to play a role. No genetic predisposition has been identified.

The incidence rate is 1 per 100,000. It accounts for 10-15% of leukemias, and more often affects adult men aged between 20 and 60.



1956: human chromosome number (Tijo & Levan)
1960: marker chromosome – Philadelphia - in chronic myeloid leukemia – CML- (Nowell & Hungerford)

10

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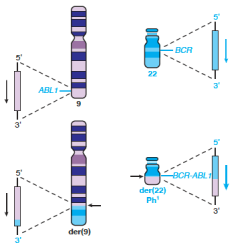
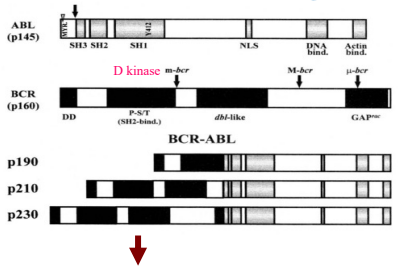
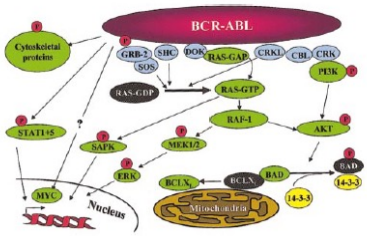
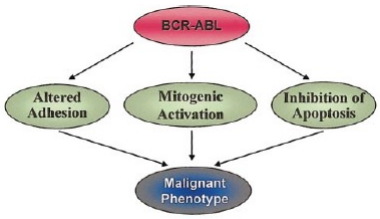




Constitutive activation of a chimeric tyrosine kinase (fusion protein)



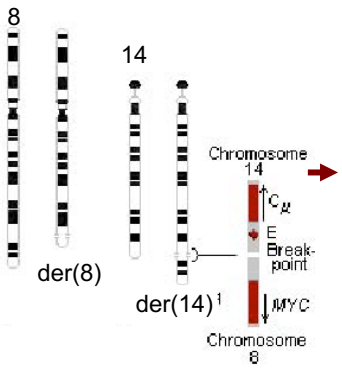


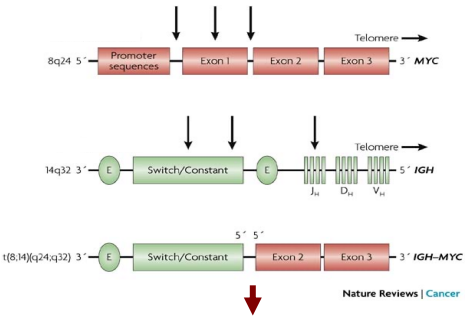
Targeted therapy with TK inhibitors

https://dumas.ccsd.cnrs.fr/dumas-02873853

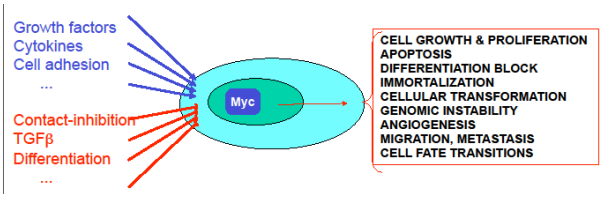
11

Translocation leading to upregulation t(8;14)(q24;q32) in Burkitt lymphoma





Constitutive activation of a normal MYC protein driven by immunoglobulin enhancers



12

Cytogenetic aberration in cancers

Structural:

- ✓ Translocation
- ✓ Insertion
- ✓ Inversion
- ✓ Duplication
- ✓ Deletion
- ✓ Amplification

TABLE 15-4 Characteristic Chromosome Translocations in Selected Human Malignant Neoplasms

Neoplasm	Chromosome Translocation	Percentage of Cases	Proto-oncogene Affected
Burkitt lymphoma	t(8;14)(q24;q32)	80	*MYC*
	t(8;22)(q24;q11)	15	
	t(2;8)(q11;q24)	5	
Chronic myelogenous leukemia	t(9;22)(q34;q11)	90-95	*BCR-ABL1*
Acute lymphocytic leukemia	t(9;22)(q34;q11)	10-15	*BCR-ABL1*
Acute lymphoblastic leukemia	t(1;19)(q23;p13)	3-6	*TCF3-PBX1*
Acute promyelocytic leukemia	t(15;17)(q22;q11)	≈95	*RARA-PML*
Chronic lymphocytic leukemia	t(11;14)(q13;q32)	10-30	*BCL1*
Follicular lymphoma	t(14;18)(q32;q21)	≈100	*BCL2*

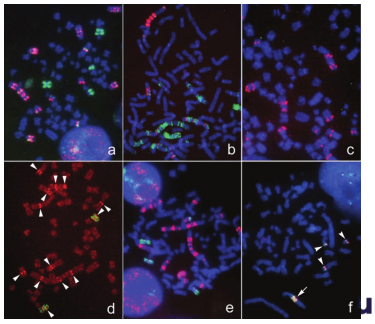
Based on Croce CM: Role of chromosome translocations in human neoplasia, *Cell* 49:155-156, 1987; Park M, van de Woude GF: Oncogenes: genes associated with neoplastic disease. In Scriver CR, Beaudet AL, Sly WS, Valle D, editors: *The molecular and metabolic bases of inherited disease*, ed 6, New York, 1989, McGraw-Hill, pp 251-276; Nourse J, Mellentin JD, Galili N, et al: Chromosomal translocation t(1;19) results in synthesis of a homeobox fusion mRNA that codes for a potential chimeric transcription factor, *Cell* 60:535-545, 1990; and Borrow J, Goddard AD, Sheer D, Solomon E: Molecular analysis of acute promyelocytic leukemia breakpoint cluster region on chromosome 17, *Science* 249:1577-1580, 1990.

Numerical:

- ✓ Loss or gain of whole chromosome
- ✓ Loss or gain of whole chromosome set

Karyotype (conventional/molecular), FISH, PCR, OGM, …

Cf Pr. V. Havelange



13

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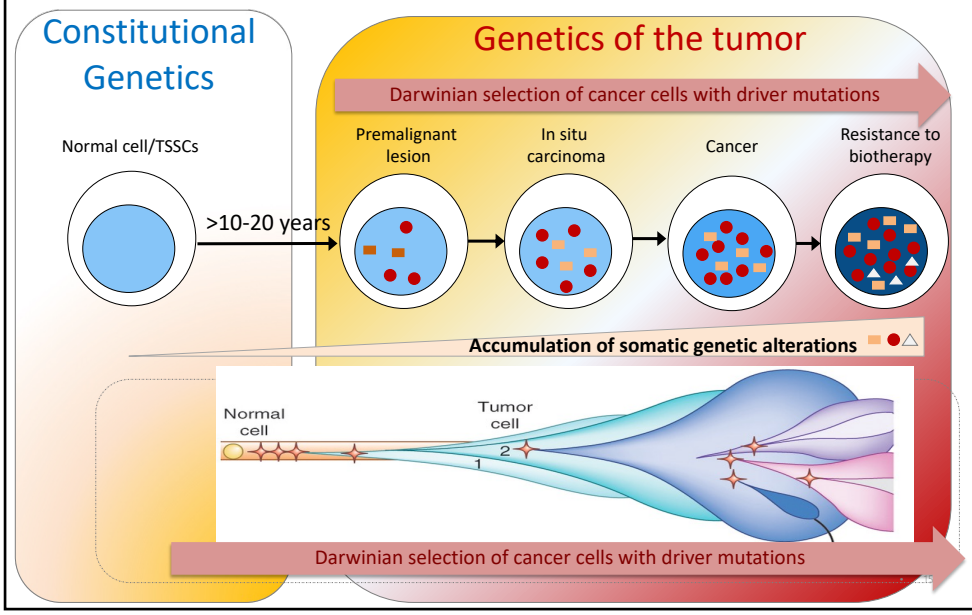
14

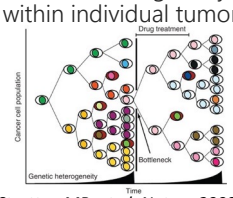
Genetic basis of oncogenesis



NGS technology -> cancer genome atlas

Darwinian selection of cancers cells

Cellular heterogeneity within individual tumors



Stratton MR, et al. Nature 2009
British Journal of Cancer (2010)103,1139–1143

15

Driver and passenger:

The number of mutations varies according to the type of cancer

- ✓ (Very) high in colon cancer
- ✓ (Very) low in rhabdoid tumors

Passenger mutations are not recurrent in any particular type of cancer and occur as the cancer develops.

Driver mutations / driver genes:

- ✓ Mutated at high frequency in the same cancer type
- ✓ Involved in the development of progression of the cancer
- ✓ Genes with effects on cell proliferation/apoptosis or genome/DNA integrity and gene expression
- ✓ Activated oncogenes vs tumor suppressor genes
  - ✓ Single nucleotide change, ins/del
  - ✓ Translocations and others chromosomal aberrations
  - ✓ Amplifications

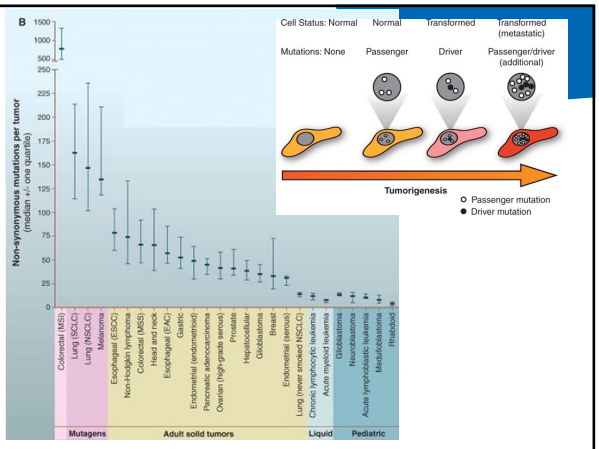


TABLE 15-1 Classes of Driver Genes Mutated in Cancer

Genes with Specific Effects on Cellular Proliferation or Apoptosis	Genes with Global Effects on Genome or DNA Integrity or on Gene Expression
Cell-cycle regulation Cell-cycle checkpoint proteins Cellular proliferation signaling • Transcription factors • Receptor and membrane-bound tyrosine kinases • Growth factors • Intracellular serine-threonine kinases • PI3 kinases • G proteins and G protein–coupled receptors • mTOR signaling • Wnt/β-catenin signaling • Transcription factors Differentiation and lineage survival • Transcription factors protecting specific cell lineages • Genes involved in exit from cell cycle into G_0 Apoptosis	Genome integrity • Chromosome segregation • Genome and gene mutation • DNA repair • Telomere stability Gene expression: abnormal metabolites affecting activity of multiple genes/gene products Gene expression: epigenetic modifications of DNA/chromatin • DNA methylation and hydroxymethylation • Chromatin histone methylation, demethylation, and acetylation • Nucleosome remodeling • Chromatin accessibility and compaction (SWI/SNF complexes) Gene expression: post-transcriptional alterations • Aberrant mRNA splicing • MicroRNAs affecting mRNA stability and translation Gene expression: protein stability/turnover

mRNA, Messenger RNA; mTOR, mammalian target of rapamycin; PI3, phosphatidylinositol-3.

16

Tumor suppressor genes vs Oncogenes

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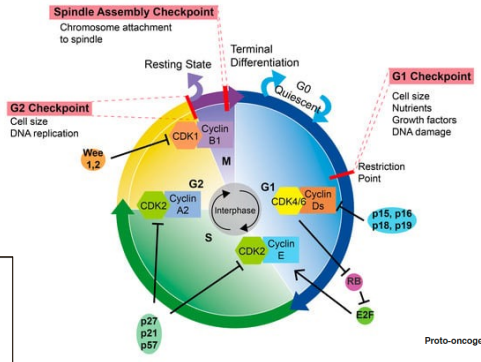
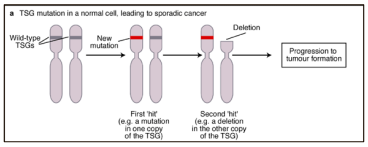


Tumor suppressor genes:

Loss-of-function mutations
Recessive effect



Oncogenes:

Gain-of-function mutations
Dominant effect

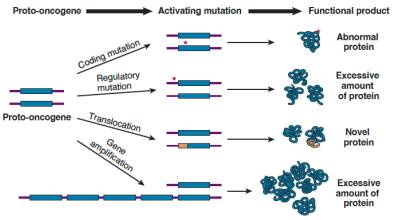


Figure 15-3 Different mutational mechanisms leading to proto-oncogene activation. These include a single point mutation leading to an amino acid change that alters protein function, mutations or translocations that increase expression of an oncogene, a chromosome translocation that produces a novel product with oncogenic properties, and gene amplification leading to excessive amounts of the gene product.

Gatekeepers: directly regulate cellular checkpoints
RB1, *TP53*

Caretakers: maintain genome integrity
MMR complex, *ATM*

17

P53: guardian of the genome

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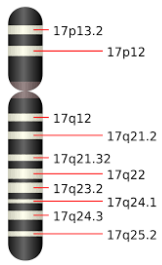
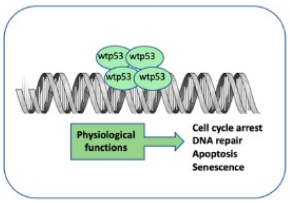
TP53: located on the short arm of chromosome 17p13.1
11 exons -> 393 AA P53 protein
Transcription factor*





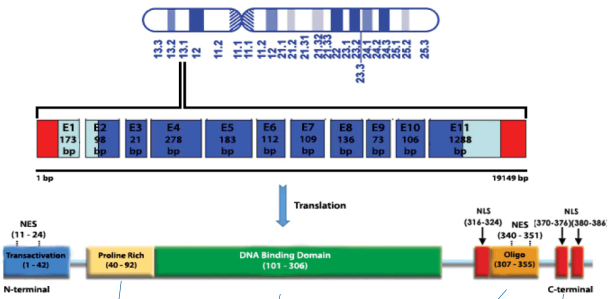


Figure 2. *TP53* locus, gene organization and protein domains [36].

MDM2 binding
Binding of transcription factors

Stabilisation
Activation

*DNA binding

Regulates tetramerisation

Negative regulation
Detection of DNA damage

Cancers 2022, 14, 3664
J Mol Genet Med, Volume 15:6, 2021

18

P53: guardian of the genome

Multiple roles, mutated in 50% of cancers

TP53 gene: tumour suppressor gene

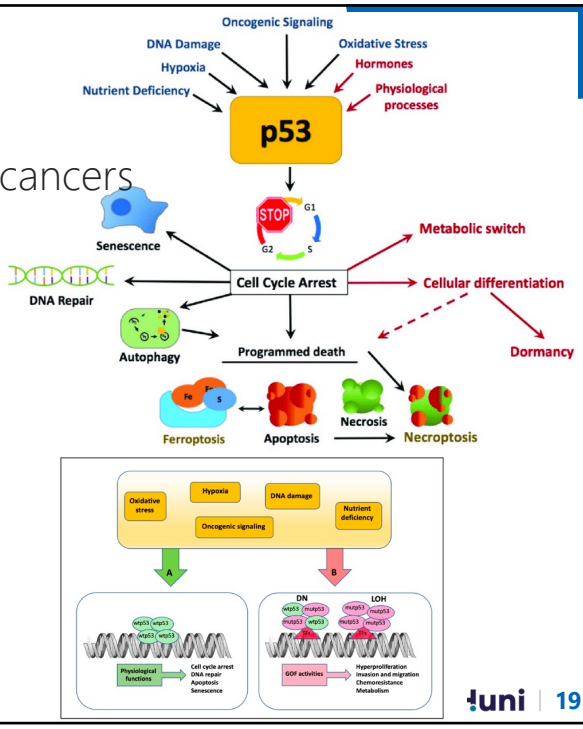
- ✓ In the absence of stress: low intracellular concentration.
- ✓ Very short half-life (5-10 minutes) due to rapid degradation.

In the event of stress/cellular aggression/metabolic deprivation:

- ✓ Activation of the protein: post-translational modification
- ✓ Stabilization and cellular accumulation through reduced degradation

Most often "missense" mutations (80%) involving the DNA-binding domain

- ✓ In the binding domain directly
- ✓ Loss of the three-dimensional structure
- ✓ TSG: Gain of function mutation with dominant negative effect

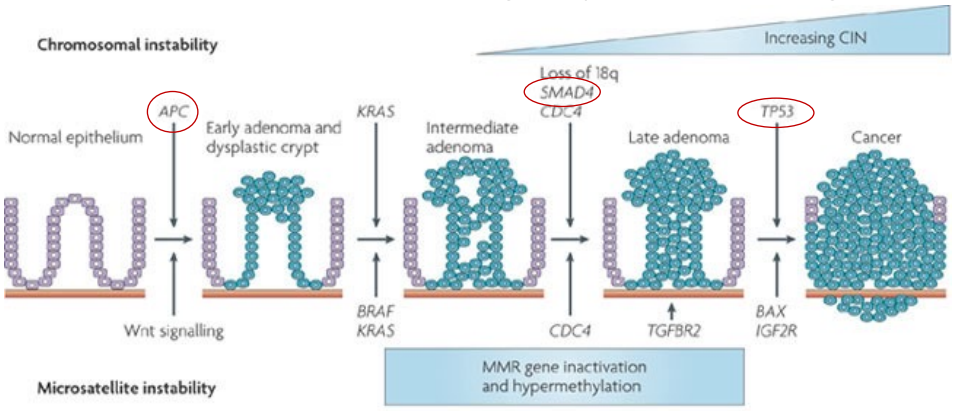


Cancers 2018, 10, 189;
doi:10.3390/cancers10060189

19

Multistep process: accumulation of multiple somatic alterations

Colorectal cancer: a model for understanding the process of tumorigenesis



Accumulation of synergistic genetic damages through mutation in master genes

Nature Reviews | Cancer

APC is mutated in more than 80% of CRC.
Loss of heterozygocity by del5q is reported in 30-40%.

Nat Rev Cancer **9**, 489–499 (2009).
https://doi.org/10.1038/nrc2645

20

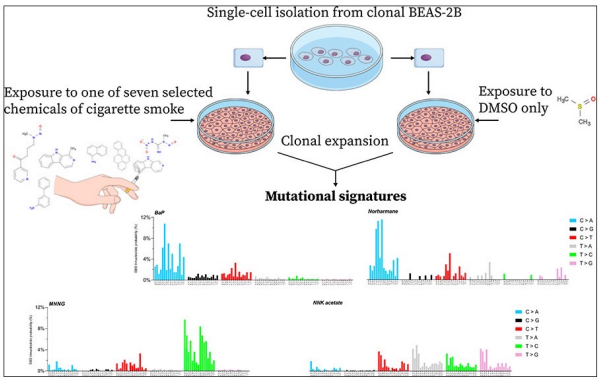
Cancer and environment

The risk of cancer varies

- Among different populations
- In different environments within the same population

Exposure to mutagens and carcinogens in the environment → somatic mutations → carcinogenesis

- Radiation
  - Ionizing radiation
  - UV
- Chemical Carcinogens
  - Tobacco
  - Benzene
  - Components of the diet
  - Role of drug-metabolizing enzymes
- Infectious agents
  - EBV, HTLV-I, HBV…



Chem. Res. Toxicol. 2023, 36, 4, 714−723

21

Cancer Biology : Multistep tumorigenesis
Not always in the same order

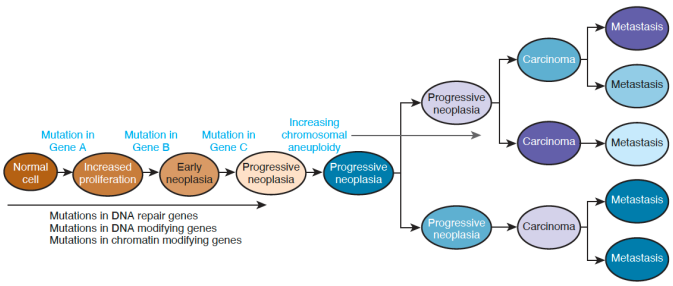
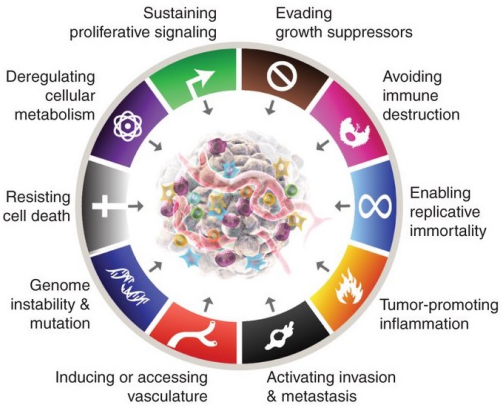


Figure 15-4 Stages in the evolution of cancer. Increasing degrees of abnormality are associated with sequential loss of tumor suppressor genes from several chromosomes and activation of proto-oncogenes, with or without a concomitant defect in DNA repair. Multiple lineages, carrying different mutations and epigenomic profiles, occur within the primary tumor itself, between the primary and metastases and between different metastases.



Hanahan D, Cancer Discovery 2022

22

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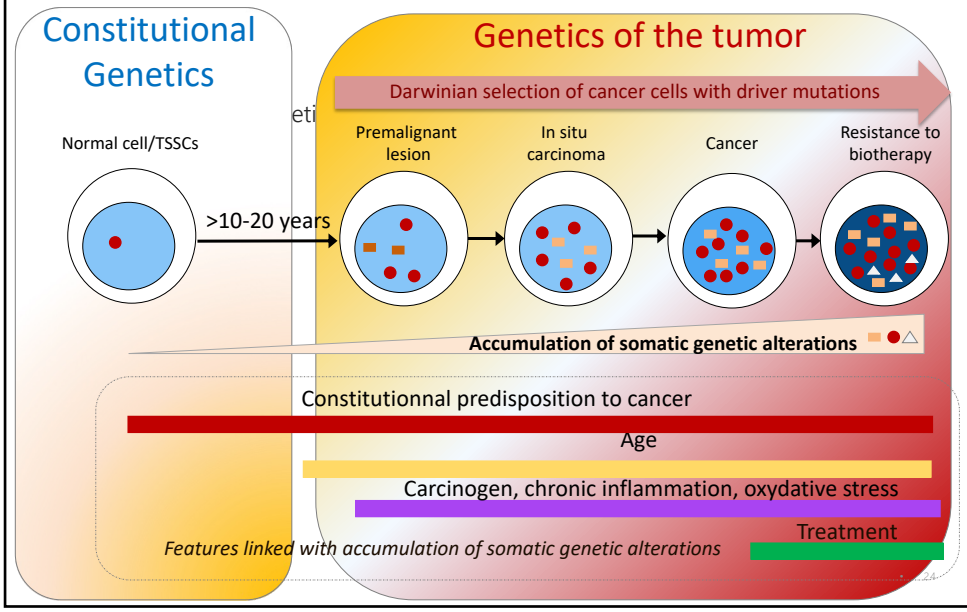
   - ✓ Tumorigenic retrovirus
   - ✓ Transfection of tumoral DNA
3. Cytogenetics
4. Molecular genetics
5. Environment
6. Introduction to inherited or familial cancers

23

Hereditary cancer syndromes



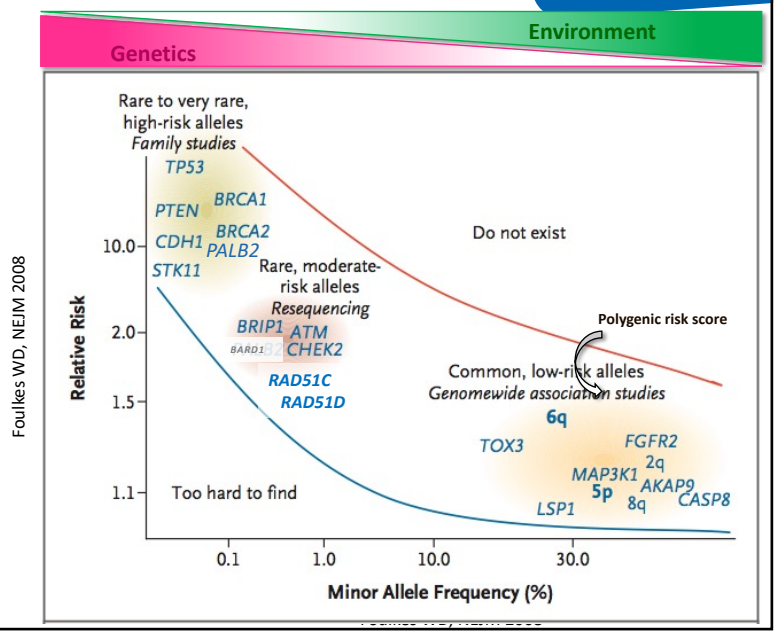
Stratton MR, et al. Nature 2009

24

Heredity?

It is estimated that 5-10% of the cancers are due to inherited gene mutation or deletion.

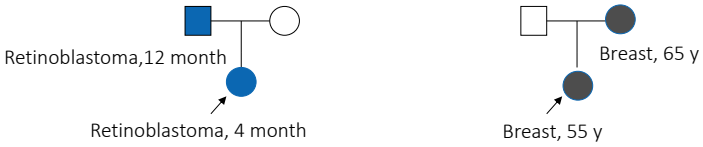
However, a much higher proportion of cancers (30-40%?) may be due to moderately penetrant cancer susceptibility gene coupled with exposure to carcinogens.



Foulkes WD, NEJM 2008

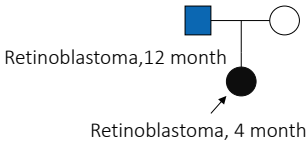
25

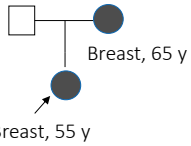
Familial history of cancer: when do we have to think about heredity?



26

Familial history of cancer: when do we have to think about heredity?





Retinoblastoma risk: 1/ 15000

50 new cases/year in France, and familial cases are 5 times more frequent than expected by coincidence!

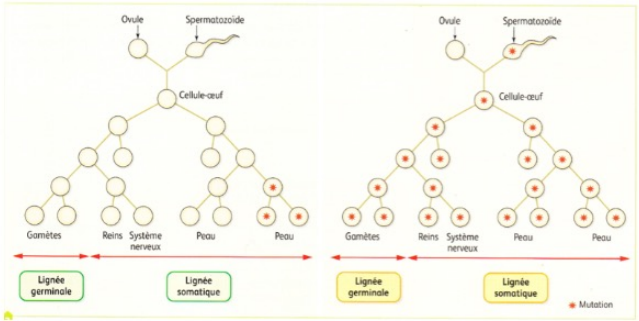
Breast cancer risk: 1/10

10% of FDR will have a breast cancer < 70y

There are family histories by coincidence

27

Somatic NGS: when to suspect a germline mutation?

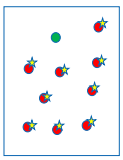


Any mutation with VAF>30% is not germline.

✓ TP53 mutated in 50% of cancers

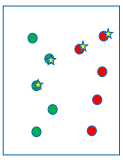
Also refer to personal and family history

✓ Syndromic form!



Tumor:

- WT cells
- Cancer cells
- Mutation



Somatic analysis:

- Mixture of tumour cells and healthy cells
- Notion of VAF > 30%: allelic frequency:
  - ✓ good indicator of whether a mutation is potentially germline but ! Depends on :
    - ✓ the proportion of tumour cells
    - ✓ the loss or otherwise of the mutated or wild-type allele in the tumour (second hit)

! Molecular Tumor Board

Guidelines ESMO

Z. Kuzbari, C. Bandlamudi, C. Loveday *et al.* Ann Oncol. 2023

28

Germline-focused analysis of tumour-detected variants in 49,264 cancer patients: ESMO Precision Medicine Working Group recommendations

Z. Kuzbari[1†], C. Bandlamudi[2†], C. Loveday[1], A. Garrett[1], M. Mehine[2], A. George[1,3], H. Hanson[1,4], K. Snape[4], A. Kulkarni[5], S. Allen[1], S. Jezdic[6], R. Ferrandino[6], C. B. Westphalen[7], E. Castro[8], J. Rodon[9], J. Mateo[10,11], G. J. Burghel[12], M. F. Berger[2], D. Mandelker[2†] & C. Turnbull[1,3*†]

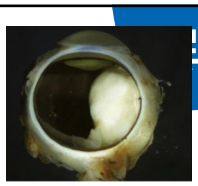
Box 1. Recommendations for genes for inclusion for germline-focused analysis and follow-up

CSG actionability class	All ages			Age <30
Most	BRCA1 BRCA2	MLH1 MSH2	MSH6 PALB2 RET	
High	BRIP1 MUTYH[c] PMS2 RAD51C	RAD51D SDHAF2[d] SDHB SDHC[d]	SDHD[d] TMEM127[d] **TSC2**[f] VHL[a]	APC **PTEN**[d,f] RB1 **TP53**[b,f]
Standard	ATM **BAP1**[f] BARD1 CHEK2 DICER1	FH FLCN **NF1**[f] PTCH1[e] POLD1	POLE SDHA SMAD3[e] **SMARCB1**[a,f] SUFU[e]	CDKN2A SMARCA4

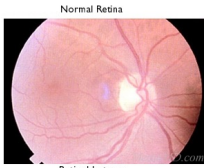
Guidelines ESMO
Z. Kuzbari, C. Bandlamudi, C. Loveday *et al.* Ann Oncol. 2023

29

Retinoblastoma

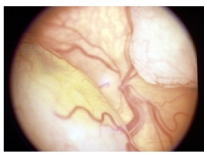


- ✓ Tumor of precursor cell of the retina
- ✓ Biallelic inactivation of a tumor suppressor gene: Rb1
- ✓ 1/15.000 to 1/20.000 children (0-8y)

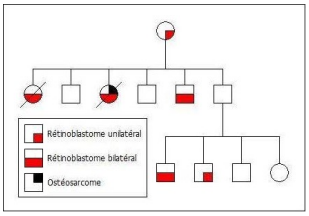


1st sign: Leukocoria

90% of cases: no familial history
- ✓ 60% unilateral
- ✓ 30% bilateral



10% of cases: familial history



30

Retinoblastoma :

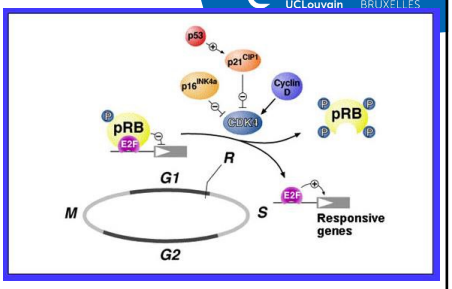
Gene responsible = *Rb1* (which codes for the Rb protein), located on chromosome 13

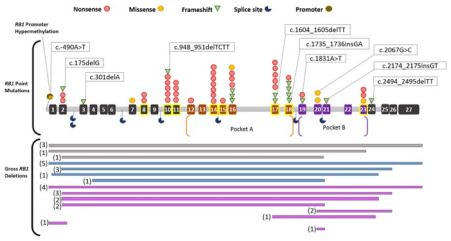
Tumour suppressor gene.

Inhibits excessive cell proliferation: blocks the cell division cycle at the G1>S transition stage

Recruits various enzymes that modulate chromatin conformation (acetylases, methylases etc)

When the gene is inactivated on both alleles, cell division is uncontrolled. Tomar et al, Plos One, june 2017





*90% of mutations are "loss of function" (nonsense, large deletions, splice site, insertions/deletions) and associated with high penetrance. Incomplete penetrance is noted in the case of promoter, in-phase or missense mutations.

Huni 31

31

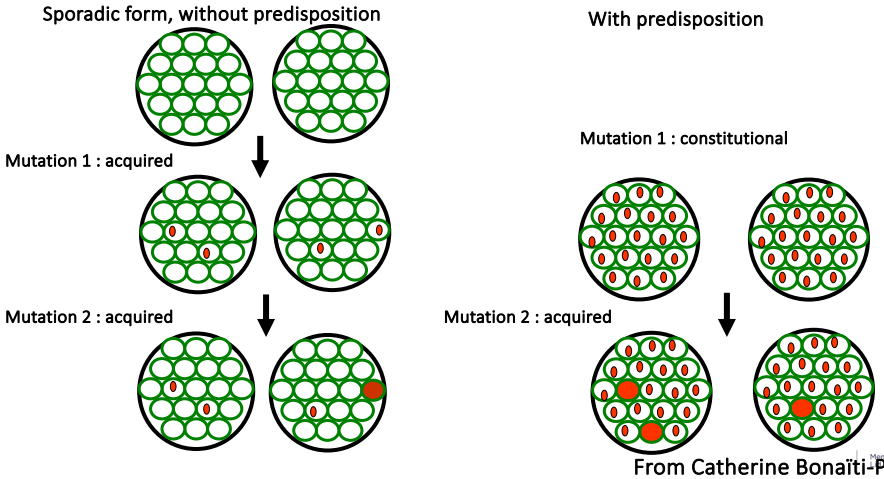
Knudson et Comings

1971, Knudson model

- 2 genetic alterations in one cell of the retina are needed (but maybe not enough)
- In the bilateral forms: one mutation is constitutional (inherited or the novo in the early embryogenesis), the other mutation is acquired
- In the unilateral forms, both mutations are somatic

1973, Comings hypothesis

- The 2 mutations necessary for the apparition of a retinoblastoma correspond to the inactivation of both alleles of the same gene



From Catherine Bonaïti-Pellie

Huni 32

32

Retinoblastoma:

- Sporadic cases (60-80%)
  - ✓ Late (80% >2yo), unilateral and unique
  - ✓ No risk for the siblings
  - ✓ No risk for other cancers
- Hereditary cases (20-40%)
  - ✓ A.D. transmission with **high** (but incomplete) penetrance (90%)
  - ✓ **Early** (90% ≤ 2yo), bilateral (25%) and/or multifocal
  - ✓ **"sporadic"** early bilateral cases are hereditary cases caused by neomutations: 15% of retinoblastomas are unique but hereditary
  - ✓ Be careful with the risk of somatic **mosaicism**
  - ✓ Increased risk of **other cancers**: osteosarcoma, soft tissues sarc., melanoma etc
  - ✓ Avoid radiations

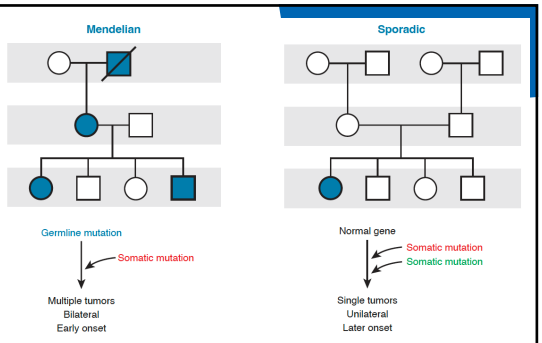
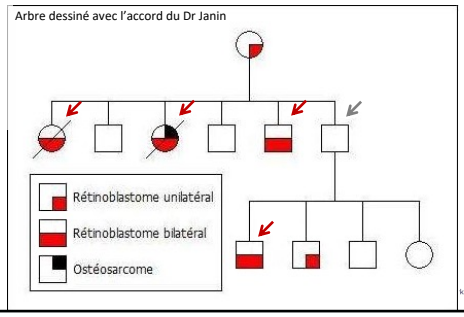


Figure 15-6 Comparison of mendelian and sporadic forms of cancers such as retinoblastoma and familial polyposis of the colon. See text for discussion.



33

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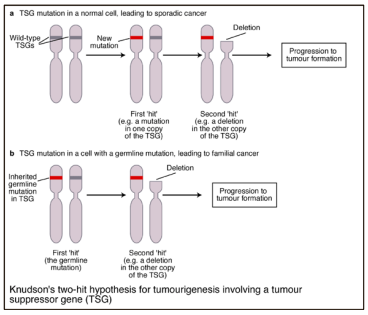
Genetic predisposition to cancer :

Definitions

- ✓ Generally dominant transmission
- ✓ High penetrance but generally incomplete
- ✓ Early onset cancer development
- ✓ Multifocal or bilateral disease
- ✓ Risk to develop other types of cancers



Knudson's two-hit hypothesis for tumourigenesis involving a tumour suppressor gene (TSG)

- ✓ Risk? relative notion : corresponds to an increase in an individual's inherited risk of developing cancer(s), or a given cancer, as compared to the mean risk in the general population; this increase can be expressed as a **relative risk**

diagnostic genetic tests can be offered in the case of genetic predispositions to cancer if the risk of developing a tumor has been well established, and if the there is a defined strategy for **managing** the affected individuals; the aim is to reduce the morbidity and the mortality; early surveillance is the most common approach

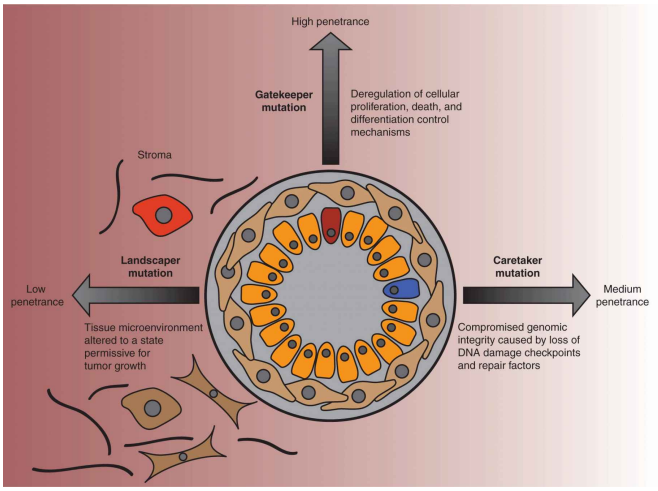
34

Genes involved in inherited cancers:

- ✓ Germline inactivation of a tumor suppressor gene
- ✓ Germline activation of a proto-oncogene
- ✓ Germline inactivation of a DNA repair gene

} Gatekeeper

} Caretaker



35

Genes involved in tumor processes : gatekeepers (1) "Loss of function" mutation

Tumor suppressor genes

- Signal transduction:
  - *APC* (FAP)
  - *PTCH1* (Gorlin syndrome)
  - *CDH1* (E. Cadherin, Gastric cancer), *NF1*
- Interaction membrane - matrix:
  - *PTEN* (Cowden)
  - *NF2*
- Cell cycle:
  - *RB1* (Retinoblastoma)
  - *CDKN2A* (Malignant melanoma)
  - *TP53* (Li Fraumeni)

1st mutation constitutional (germline)
2d mutation acquired

36

Genes involved in tumor processes : gatekeepers (2)
« gain of function » mutation
Oncogene

Signal transduction :

- *RET* (Thyroid medullar cancer, MEN2A et B)
- *MET* (Gastric)
- *c-Kit* (GIST)
- *Alk* (Neuroblastoma)
- *RAS,* MAP kinase pathway

The mutation itself is sufficient

Cell cycle:

- *CDK-4* (Malignant melanoma)

37

Genes involved in DNA repair: caretaker
« Loss of function » mutations

- Recessive transmission with associated disease
  - Ataxia Telangiectasia : *ATM, MRE11*
  - Bloom : *BLM*
  - Fanconi : *FANC (A, B, C, BRCA2 (D1), D2, E, F, G, ...)*
  - Xeroderma pigmentosum : *XP-A, XP-B, XP….*
- Dominant transmission
  - LYNCH : *MLH1, MSH2, MSH6, PMS2, EPCAM*
  - HBOC : *BRCA1, BRCA2*
- Recessive transmission without associated disease !
  - Predisposition in childhood : CMMRD : biallelic mutation in MMR genes

38

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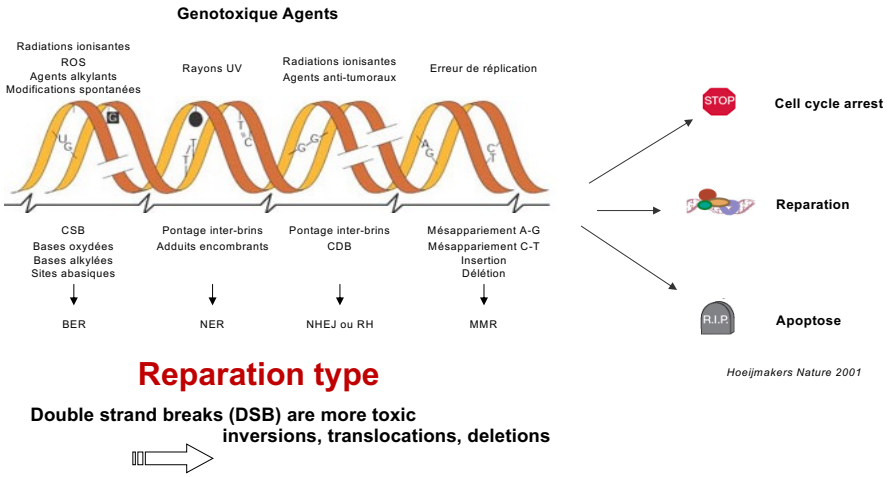
DNA damages



Hoeijmakers Nature 2001

Reparation type

Double strand breaks (DSB) are more toxic
inversions, translocations, deletions

39

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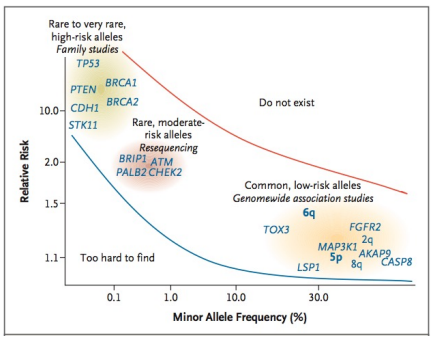
Definitions

- Penetrance = the likelihood a given gene will result in disease
- High penetrance genes :
  - rare mutations
  - very high risk of disease
  - independent of other risk factors
- Low penetrance genes
  - frequent genetic variants
  - interact with exogenous factors to cause the diseases



40

Genetic counseling
Risk notion? ..... which risk?

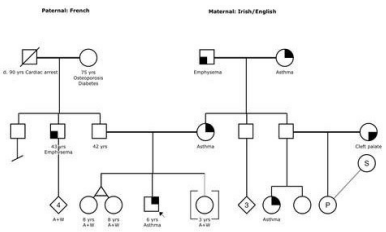
- Role of the (onco)geneticist: clarify the risk
- Probability of inherited syndrome?
- Risk to have a pathogenic mutation?
  - ? Criteria to refer in genetic counselling
  - ? Criteria to perform genetic analysis
  - ? Screening of predisposed patients

Oncogenic consultation: how?

Generally: 2 or 3 visits

✓ Definition of risk: Accurate and complete family history: systematic series of questions to gather relevant personal and family medical information.

✓ Genetic testing
- Criteria (see College of Genetics website https://www.college-genetics.be/)
- Discussion of importance/benefit/cost (reimbursement of health insurance)
- Discussion of restrictions (concept of variant of undetermined significance VUS)
- Discussion of information to family members
- Informed consent



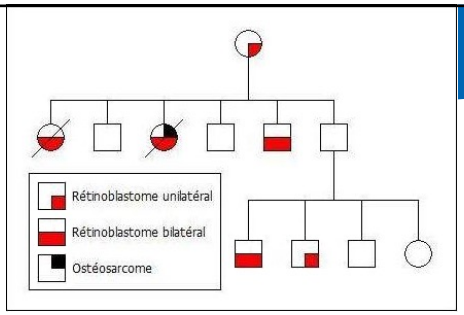
✓ Results disclosure and follow-up
- For the patient
- For the family

Collecting and interpreting cancer histories

- Identify a cancer syndrome
- Determine the need for genetic testing
- Assist with management recommendation
- Uncover other syndromes
- Identify the disorder's inheritance pattern and other relatives at risk
- Ethnic background
- <u>The pedigree is an important clinical record</u>, it is crucial for pedigrees to reflect the most accurate information that is possible:
  - ✓ Pathology report
  - ✓ Physician note
  - ✓ Genetic test result
- Prior permission from the relative in question is needed

43

Anamnesis



Autosomal dominant transmission (most frequently) :

1. Cancers in ≥ 2 generations / One branch of family
2. Risk transmission = 50% <u>for men and for women</u>
3. Beware of incomplete penetrance and/or sex-related expressivity

Tumor risk is very often restricted to one or to a few tissues (spectrum –> syndrome)

People getting cancer in high risk families

- are often younger than people in sporadic cases
- often develop a 2nd cancer within the same tissue or in another tissue

44

Ways to classify family history of cancer

- Hereditary cancer syndrome
  - ✓ Mostly dominant pattern
  - ✓ 3 individuals with similar or related cancers
  - ✓ 2 generations of cancer cases and
  - ✓ 1 person diagnosed at an unusually young age
- Familial Cluster of Cancer
  - ✓ 2 or more relatives who have developed similar cancers but the family does not have any features suggestive of an hereditary cancer syndrome: elevated risk in sibs or children depending of the cancer site
- Sporadic forms of cancer
  - ✓ Most cases of cancer occur randomly without an obvious underlying risk factor
- Environmentally caused cluster of cancer

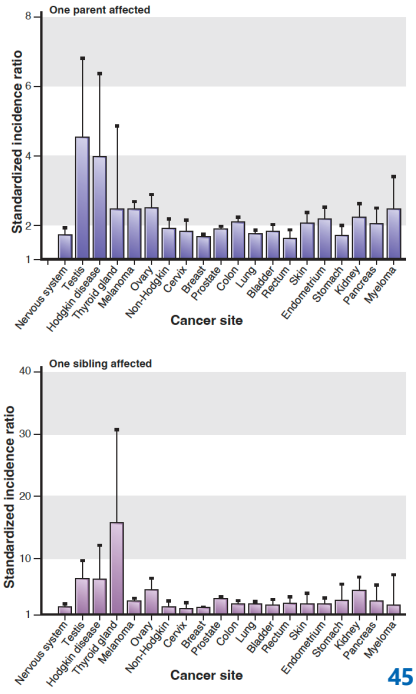


Figure 15-10 Standardized incidence ratios (SIRs) for cancers at various sites in first-degree relatives (child or sibling) of an affected person. A SIR is similar to the relative risk ratio (λ_s) that is based on *prevalence* of disease (as described in Chapter 8), except SIR is the ratio of the *incidence* of cases of cancer in relatives divided by the number expected from the incidence in an age-matched group in the general population. Error bars reflect 95% confidence limits on the SIRs. *See Sources & Acknowledgments.*

45

45

Determine the likelihood that the family could have a hereditary predisposition to cancer.

HIGH risk:

Strong evidence (Retinoblastoma)

Pattern consistent with a specific hereditary cancer syndrome.

MODERATE Risk:

Some features suggestive of cancer syndrome but may not meet criteria for the syndrome.

LOW Risk:

Negative or noncontributory history of cancer: although there are several cases of cancer in the family, the cancer types are ones that frequently occur among older individuals

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46

HBOC: Indication to perform a genetic analysis (KCE 2015):

Cf Pr. F. Duhoux

- High risk woman.
- Risk to find a mutation > 10%
- Test index case if available
- See new guidelines soon

https://www.college-genetics.be/

I. Woman with breast cancer + one of the following:

- diagnosed ≤ 40yrs
- diagnosed < 50yrs and one relative with bilateral breast cancer, or breast cancer < 50yrs, or prostate cancer diagnosed < 60yrs
- a first or second degree relative with male breast cancer, ovarian cancer, pancreatic adenocarcinoma, or metastatic prostate cancer
- bilateral breast cancer if the first cancer was diagnosed < 50yrs
- triple negative breast cancer < 60yrs
- HER2 negative (hormone receptor-negative or hormone receptor-positive) breast cancer eligible for PARP-inhibitors: in high-risk (neo)adjuvant setting or metastatic setting
- ovarian cancer or pancreatic adenocarcinoma at any age
- ≥ 3 individuals with breast cancer and/or prostate cancer, one is a first degree relative of the other two (excluding male transmitters if father is not affected) and one diagnosed at an early age (< 60yrs)
- individual of ethnicity associated with a higher frequency of specific mutations (e.g., Ashkenazi Jewish): eligible for founder mutation testing
- other family situations with a priori chance of mutation >10% according to BRCAPRO or Evans criteria or Manchester score
- test more than one affected relative if criteria remain positive after excluding the negative case as a phenocopy

COLLEGE GENETICS

47

47

Result disclosure

Cancer genetic test results are mainly disclosed in a counseling visit.
It can be disclosed by phone but the mode of result disclosure has to be announced in the pretest visit.

Disclose the result early in the conversation (anxiety for the patient)

Use direct and clear language.

Allow patient time to react.

Discuss about cancer risk management for the patient/the family -> predictive testing available?

Counseling about cancer.
Katherine A. Schneider.

48

48

Diagnostic test, presymptomatic test & Predictive test

- Diagnostic test confirms or exclude a genetic disorder in an individual who had malignancy and features of hereditary cancer syndrome.
  - ✓ There is a good likelihood that the genetic test results will come negative.
  - ✓ The cancer syndrome may be caused by alteration in more than one gene.

- When a mutation is available in the family, presymptomatic or predictive testing has to be offered in at risk asymptomatic individuals.

- Presymptomatic test determines if an asymptomatic individual carries a gene mutation that is associated with an absolute likelihood of cancer (or other syndromic features). *APC* gene for example.

- Predictive test determines if an asymptomatic individual carries a gene mutation that is associated with an increased but not absolute risk of cancer or other syndromic features. *BRCA1 or BRCA2* for example.

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49

Predictive testing:

5 steps procedure

- ✓ Importance of the pretest counseling: discuss about the potential risk and benefits of testing.
- ✓ Psychological assessment (before and after genetic testing).
- ✓ Genetic testing (2 blood samples, not the same day)
- ✓ Result disclosure.
- ✓ Follow-up.

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50