

Understanding Oncogenes and Tumor Suppressors

Pablo Sánchez Vela, MD.

HOPP ResTep/SEP

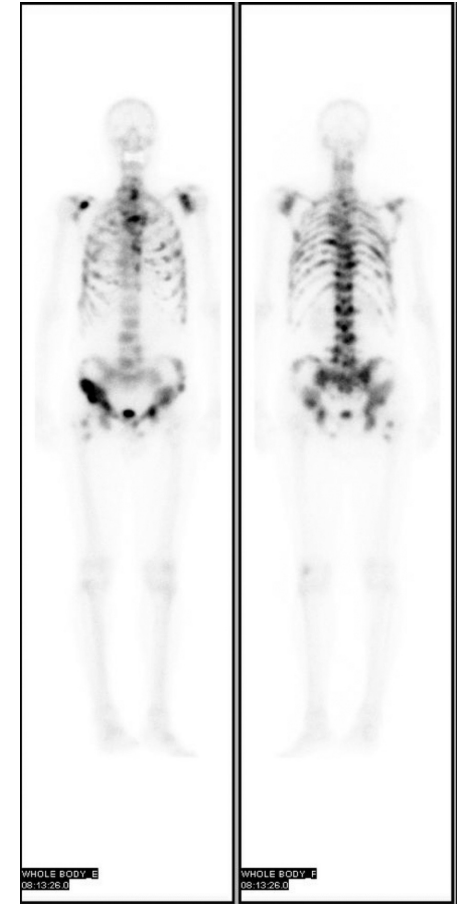
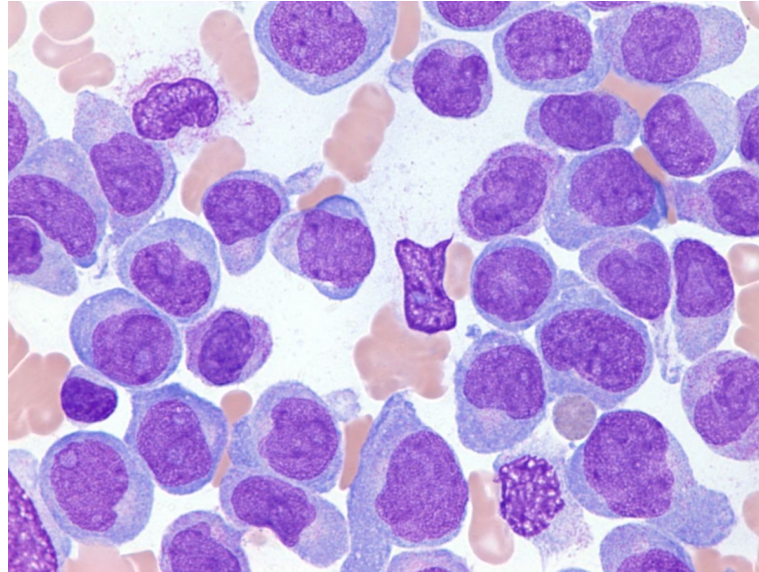
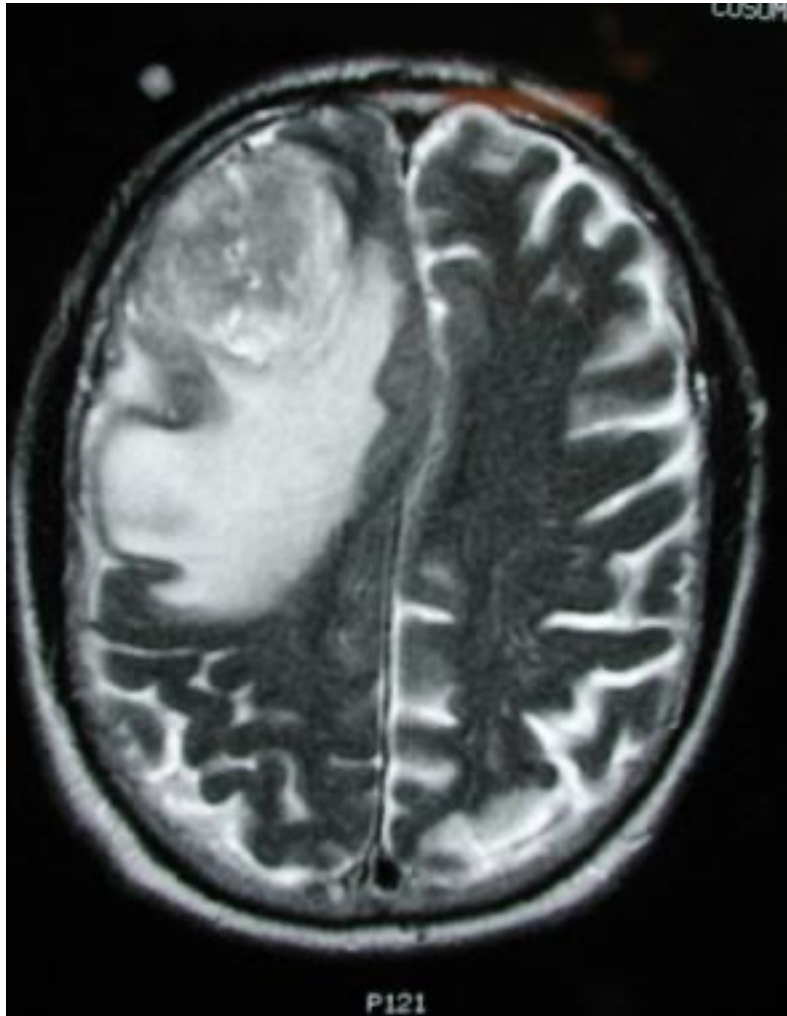
February 8th, 2023

Recommended reads:

The Biology of Cancer. 2nd edition. Weinberg 2014.

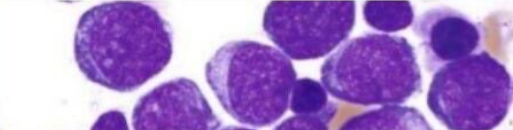
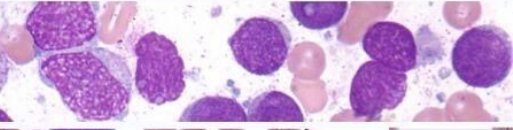
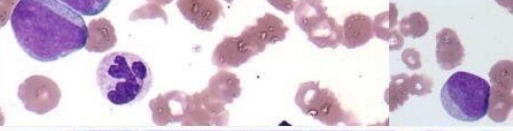
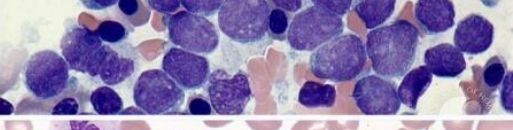
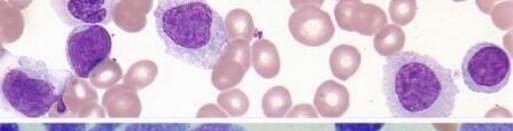
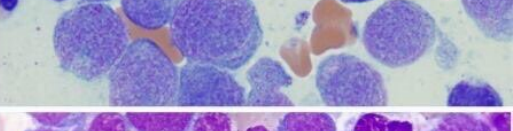
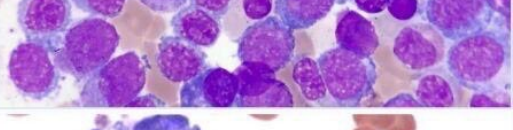
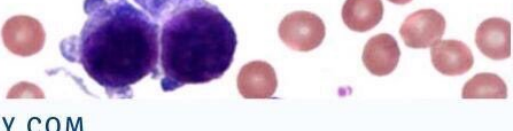
Primer of the Molecular Biology of Cancer. DeVita 2021.

Available through MSK library.

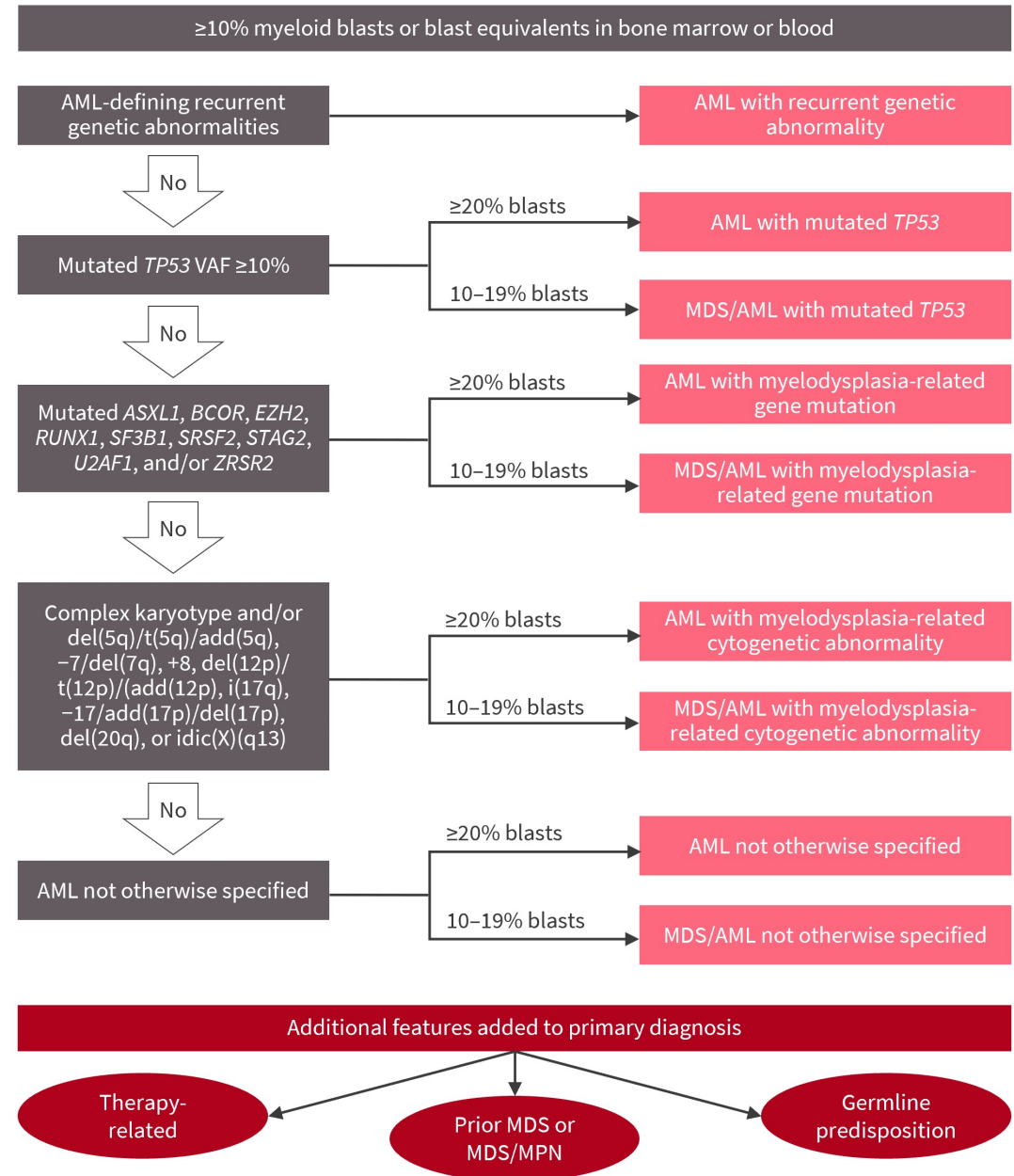


Medscape
SJCH
Wostnizer RCR 2010

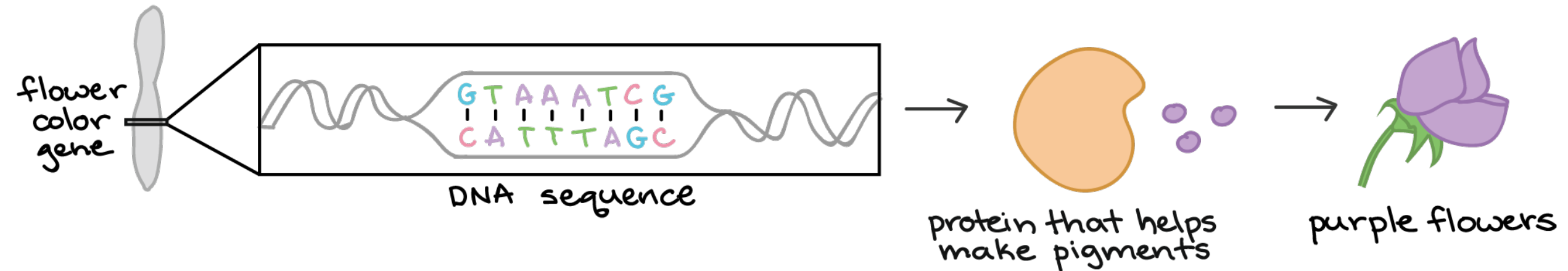
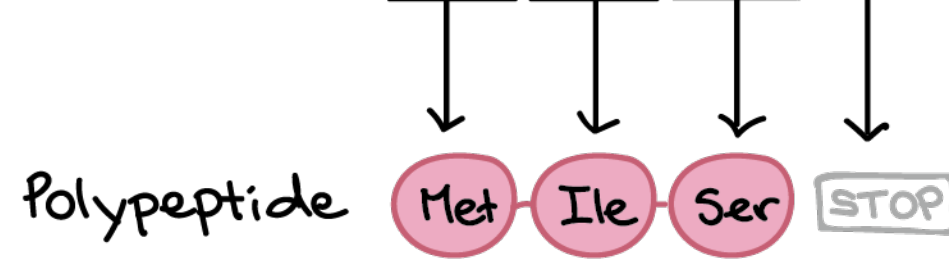
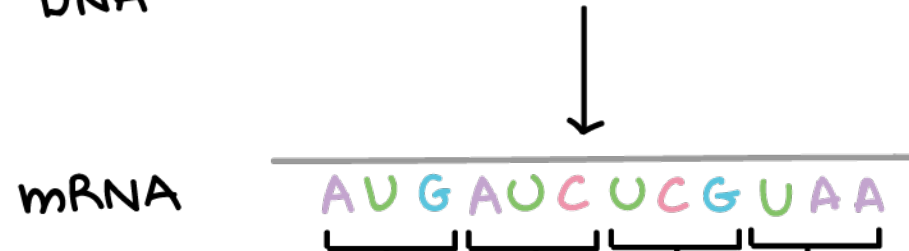
FAB CLASSIFICATION SYSTEM OF ACUTE MYELOID LEUKAEMIA

M0	AML with minimal differentiation	
M1	AML without maturation	
M2	AML with maturation	
M3	Acute promyelocytic leukaemia	
M4	Acute myelomonocytic leukaemia	
M5	Acute monoblastic and monocytic leukaemia	
M6	Pure erythroid leukaemia	
M7	Acute megakaryoblastic leukemia	

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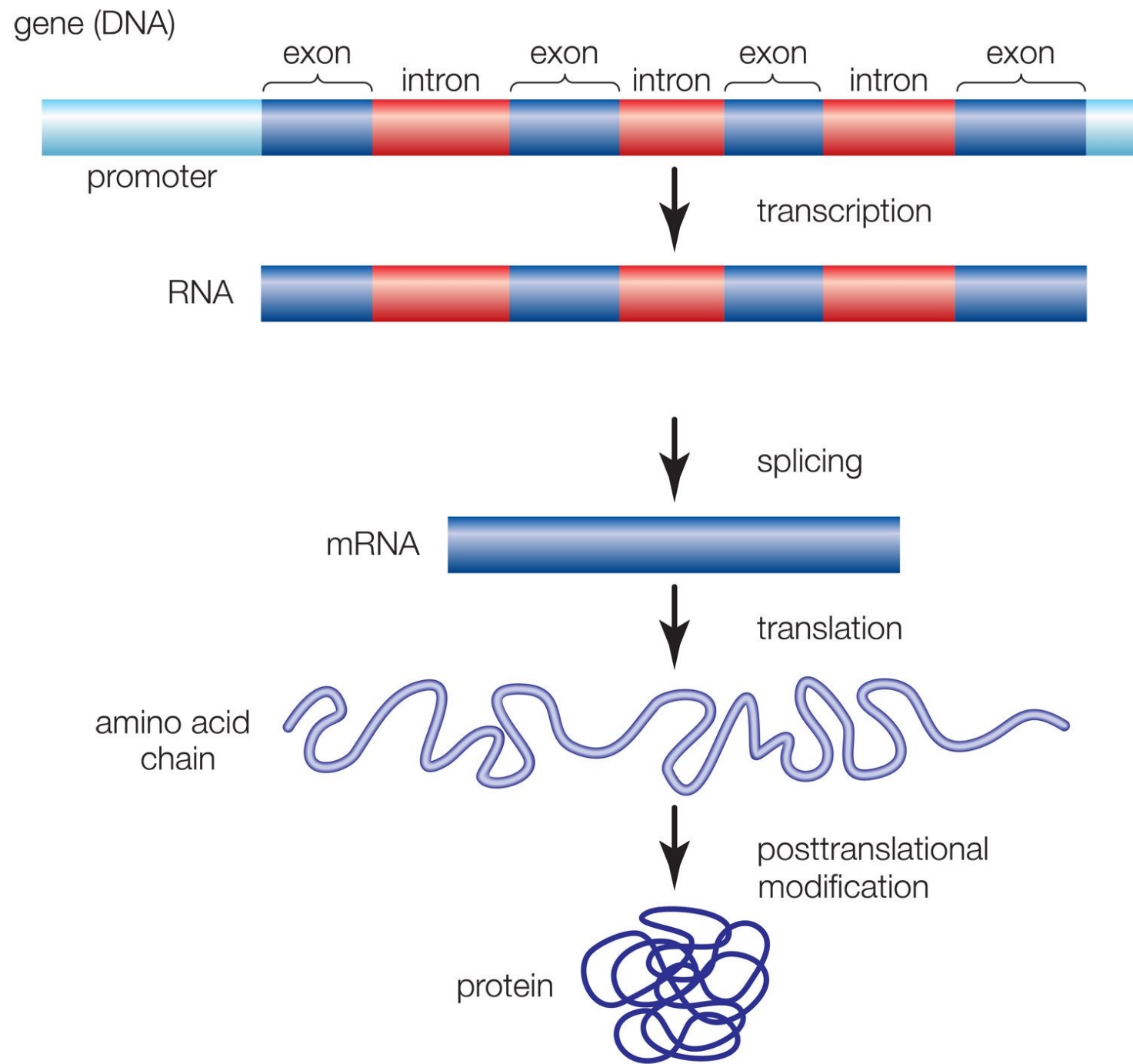


THE CENTRAL DOGMA



What are the differences between:

Gene Promoter and Exon

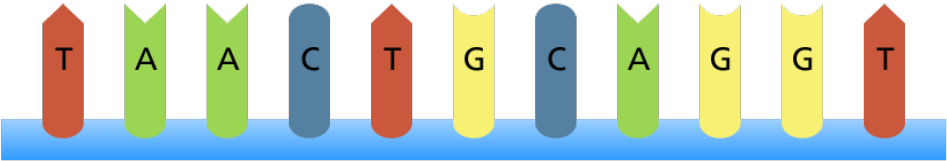


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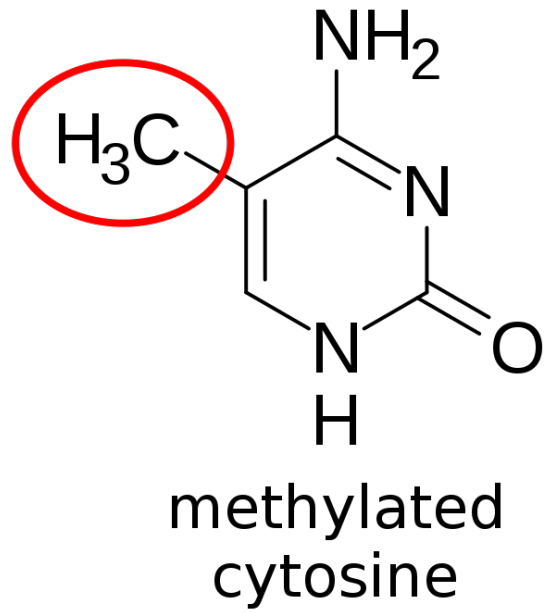
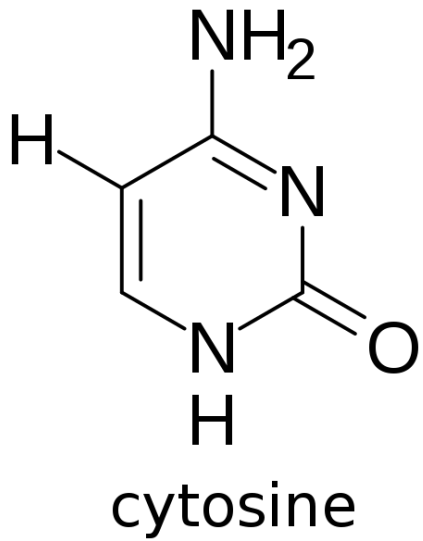
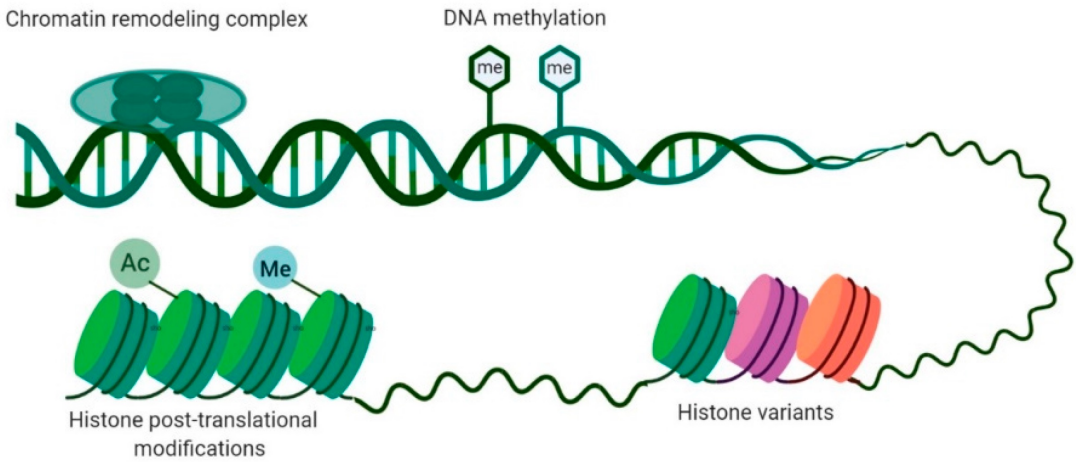
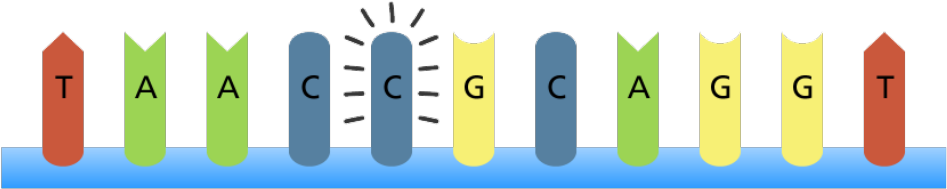
Mutation of the DNA and Methylation of the DNA

DNA mutation vs DNA methylation:

Original sequence



Point mutation



What are the differences between:

Somatic and Germline mutations

Somatic mutations

- Occur in *nongermline* tissues
- Cannot be inherited



Nonheritable

Mutation in tumor only
(for example, breast)

Germline mutations

- Present in egg or sperm
- Can be inherited
- Cause cancer family syndrome

Parent



Mutation in
egg or sperm

Heritable



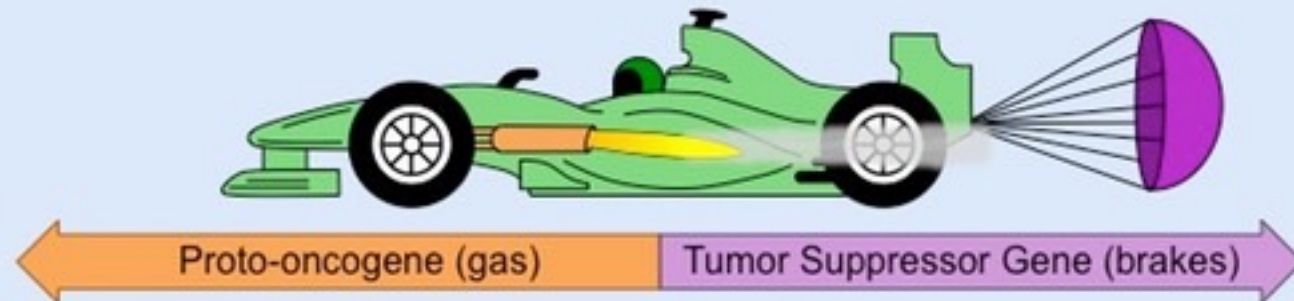
Child



All cells
affected in
offspring

What are the differences between:
Oncogenes and Tumor Suppressors

Normal Cell Cycle



As part of your project, you are interested in modelling mutations that frequently occur in cancer patients. For this purpose, you are reviewing MSK-IMPACT clinical sequencing results using the cBioPortal platform. One of the genes that most commonly is found to be mutated in this dataset is TP53, a known tumor suppressor gene. What are the characteristics of these types of genes?

- A) In cancer patients, inactivating mutations are the most frequent type of mutations occurring in tumor suppressors genes.
- B) Loss of function in tumor suppressors genes cannot occur due to non-mutational processes like promoter methylation.
- C) Loss of tumor suppressors decreases the likelihood of malignant transformation.
- D) Mutation in tumor suppressors genes can only be somatic, and they don't occur in the germline.

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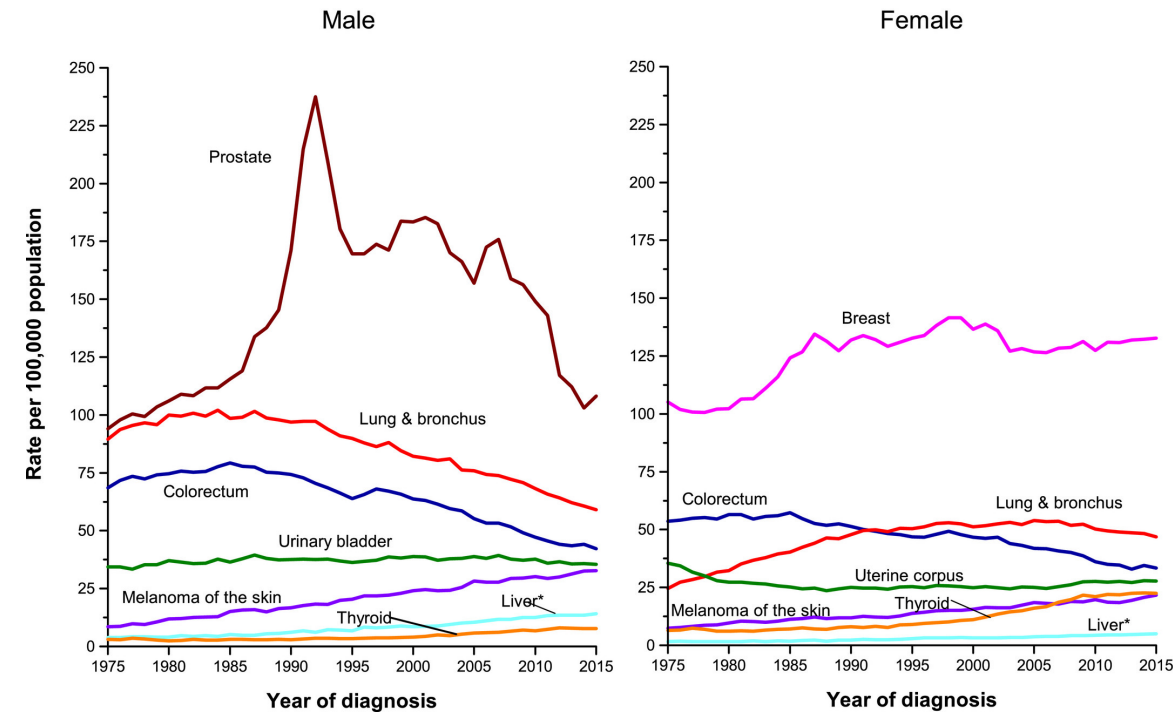
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Estimated New Cases

			Males	Females			
Prostate	174,650	20%			Breast	268,600	30%
Lung & bronchus	116,440	13%			Lung & bronchus	111,710	13%
Colon & rectum	78,500	9%			Colon & rectum	67,100	8%
Urinary bladder	61,700	7%			Uterine corpus	61,880	7%
Melanoma of the skin	57,220	7%			Melanoma of the skin	39,260	4%
Kidney & renal pelvis	44,120	5%			Thyroid	37,810	4%
Non-Hodgkin lymphoma	41,090	5%			Non-Hodgkin lymphoma	33,110	4%
Oral cavity & pharynx	38,140	4%			Kidney & renal pelvis	29,700	3%
Leukemia	35,920	4%			Pancreas	26,830	3%
Pancreas	29,940	3%			Leukemia	25,860	3%
All Sites	870,970	100%			All Sites	891,480	100%

Estimated Deaths

			Males	Females			
Lung & bronchus	76,650	24%			Lung & bronchus	66,020	23%
Prostate	31,620	10%			Breast	41,760	15%
Colon & rectum	27,640	9%			Colon & rectum	23,380	8%
Pancreas	23,800	7%			Pancreas	21,950	8%
Liver & intrahepatic bile duct	21,600	7%			Ovary	13,980	5%
Leukemia	13,150	4%			Uterine corpus	12,160	4%
Esophagus	13,020	4%			Liver & intrahepatic bile duct	10,180	4%
Urinary bladder	12,870	4%			Leukemia	9,690	3%
Non-Hodgkin lymphoma	11,510	4%			Non-Hodgkin lymphoma	8,460	3%
Brain & other nervous system	9,910	3%			Brain & other nervous system	7,850	3%
All Sites	321,670	100%			All Sites	285,210	100%



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(Integrated Mutation Profiling of Actionable Cancer Targets)

ABL1	CALR	DICER1	FGFR1	HLA-C	MALT1	NOTCH1	PP4R2	XRRA	SUZ12
ACVR1	CARD11	DIS3	FGFR2	HNF1A	MAP2K1	NOTCH2	PP6C	RYBP	SYK
AGO1	CARM1	DNAJB1	FGFR3	HOXB13	MAP2K2	NOTCH3	PRDM1	SCG5	TAP1
AGO2	CASP8	DNMT1	FGFR4	HRAS	MAP2K4	NOTCH4	PRDM14	SDHA	TAP2
AKT1	CBFB	DNMT3A	FH	ICOLSG	MAP3K1	NPM1	PREX2	SDHAF2	TBX3
AKT2	CLB	DNMT3B	FLCN	ID3	MAP3K13	NRAS	PRKARIA	SDHC	TCEB1
AKT3	CND1	DOT1L	FLT1	IDH1	MAP3K14	NSD1	PRKCI	SDHB	TCF3
ALB	CNND2	DROSHA	FLT3	IDH2	MAPK1	NTLH1	PRKD1	SDHD	TCF7L2
ALK	CNND3	DUSP4	FLTA	IFNGR1	MAPK3	NTRK1	PTCH1	SERPINB3	TEK
ALOX12B	CNCE1	E2F3	FOXA1	IGF1	MAPKAP1	NTRK2	PTEN	SERPINB4	TER1
ARHGAD11	CD274	EED	FOXF1	IGF1R	MAX	NTRK3	PTP4A1	SESN1	TE1T3
APC	CD276	EGLF7	FOXL2	IGF2	MCL1	NUF2	PTPN11	SESN2	TEF2
APLN	CD79A	EGRF	FOXO1	IKBKE	MDC1	NUP93	PTPRD	SESN3	TGFBF1
AR	CD79B	EIF1A	FOXP1	IKZF1	MDM2	PAK1	PTPRS	SETD2	TGFBF2
ARAF	CDCA2	EIF4A2	FUBP1	IL10	MDM4	PAK7	PTPRF	SETDB1	TMEM127
ARHGAP35	CD7C3	EIF4E	FYN	IL7R	MED12	PALB2	RAB35	SF3B1	TMPRSS2
ARID1A	CDH1	ELF3	GAB1	INHBA	MEF2B	PARK2	RAC1	SH2B3	TNFAIP3
ARID1B	CDK12	EP300	GAB2	INHBA	MEN1	PARP1	RAC2	SH2D1A	TNFRSF413
ARID2	CDK4	EPA51	GATA1	INPP4A	MET	PAX5	RAD21	SHOC2	TOP1
ARID5B	CDK6	EPCAM	GATA2	INPP4B	MGA	PBRM1	RAD50	SHQ1	TP53
ASXL1	CDK8	EPHA3	GATA3	INPP11	MITF	PCDCL1	RAD51	SLFN11	TP53BP1
ASXL2	CDKN1A	EPHA5	GLI1	INSR	MLH1	PCDCL1G2	RAD51C	SLK4	TP63
ATM	CDKN1B	EPHA7	GNAI1	IRF4	MLT1	PDGFRFA	RAD51L1	SMAD2	TRAF2
ATR	CDKN2A	EPHB1	GNAQ	IRS1	MPL	PDGFRB	RAD51L3	SMAD3	TRAF7
ATRX	CDKN2B	ERBB2	GNA5	IRS2	MRE11A	PDKP1	RAD52	SMAD4	TRIP13
ATXN7	CDKN2C	ERBB3	GNB1	JAK1	MSH2	PGBD5	RAD54L	SMARCA2	TS1
AURKA	CEBPA	ERBB4	G2S2	JAK2	MSH3	PGR	RAF1	SMARCA4	TSC2
AURKB	CENPA	ERCC2	GREM1	JAK3	MSH6	PHF6	RARA	SMARCB1	TSHR
AXIN1	CHEK1	ERCC3	GRIN2A	JUN	MSI1	PHOX2B	RASA1	SMARCD1	UZAF1
AXIN2	CHEK2	ERCC4	GSK3B	KBTBD4	MSI2	PIK3C2G	RB1	SMARCE1	UPF1
AXL	CIC	ERCC5	H3F3A	KDM5A	MS11	PIK3C3	RBM10	SMO	USP8
B2M	CMTR2	ERF	H3F3B	KDM5C	MS1R	PIK3CA	RECLQ	SMYD3	VEGFA
BABAM1	CREBBP	ERG	H3F3C	KDM6A	MTOR	PIK3CB	RECLQ4	SOC1	VHL
BAP1	CRKL	ERRF1	HGF	KDR	MTAP	PIK3CD	REL	SOS1	VTGNI
BARO1	CLRF2	ESR1	HIST1H1C	KEAP1	MUTYH	PIK3CG	REST	SOX17	WHSC1
BBG3	CSDE1	ETAA1	HIST1H2BD	K1	MYC	PIK3R1	RET	SOX2	WHSC1L1
BCL10	CSF1R	ETV1	HIST1H3A	KL5	MYCL1	PIK3R2	RFWD2	SOX9	WT1
BCL2	CSF3R	ETV6	HIST1H3B	KL4	MYCN	PIK3R3	RHEB	SPEN	WWIT1
BCL2L1	CTCF	EZH1	HIST1H3C	KMT2A	MYD88	PIM1	RHOA	SPOP	XIAP
BCL2L11	CTLA4	EZH2	HIST1H3D	KMT2B	MYD01	PLCG2	RICTOR	SPRED1	XPO1
BCL6	CTNNB1	FAM123B	HIST1H3E	KMT2C	NBN	PLK2	RTI1	SPRNT	XRCC2
BCOR	CT9	FAM137A	HIST1H3F	KMT2D	NADK	PMAIP1	RNF43	SRC	YAP1
BIRC3	CUL3	FAM46C	HIST1H3G	KMT5A	NCOA3	PMS1	ROS1	SRSF2	YES1
BLM	CXCR4	FAM58A	HIST1H3H	KNSTN	NCO1	PMS2	RPS6KA4	STAG2	ZFXH3
BMPP1A	CXORF67	FAM58B	HIST1H3I	KRAS	NEGR1	PNR1	RPS6KB2	STAT3	ZNRF3
BRAF	CYLD	FANCC	HIST1H3J	LATS1	NF1	POLD1	RPTOR	STAT5A	ZRSR2
BRC4	CYP19A1	FAT1	HIST2H3C	LATS2	NF2	POLE	RAGTS	STAT5B	
BRC42	CYSYLR2	FBXW7	HIST2H3D	LMO1	NFE2L2	POT1	RRAS	STK11	
BRD4	DAXX	FGF19	HIST3H3	LYN	NFKBIA	PPARG	RRAS2	STK19	
BRIP1	DCUN1D1	FGF3	HLA-A	LZTR1	NKX2-1	PPM1D	RTKL	STK40	
RTK	DDR2	FGF4	HLA-B	MDAD2	NKX3-1	PPP2R1A	RUNX1	SJFJ	

Memorial Hospital For Cancer & Allied Diseases

Molecular Diagnostics Service, Department of Pathology

1275 York Avenue New York, NY, 10042

Tel: (212) 858-8283 Fax: (212) 717-3818

MSK-IMPACT Testing Report

Memorial Sloan Kettering
Cancer Center

Patient Name	Redacted	Medical Record #	Redacted
Date of Birth	Redacted	Accession #	Redacted
Gender	Redacted	Specimen Submitted	LYMPH NOC
Tumor Type	Lung Adenocarcinoma	Surgical Path. #	Redacted
Ref. Physician	Redacted	Account #	Redacted
Date of Report	Redacted	Date of Report	Redacted

Summary 2 mutations, 19 copy number alterations, no structural variants detected, 2 alterations have OncoPrint interpretations.

MSI Status MICROSATLLITE STABLE (MSS). See MSI note below.

Tumor Mutation Burden The estimated tumor mutation burden (TMB) for this sample is 1.8 mutations per megabase (mut/Mb) assessed by MSK-IMPACT for all patients; is 9.9 mut/Mb and for patients with Non-Small Cell Lung Cancer (NSCLC) as of the date this report was issued.

Comments Note: The number and pattern of mutations is consistent with a hypermutator phenotype arising from a mechanism to temozolomide or similar agents

Somatic alterations detected in this sample:

Gene	Type	Alteration	Location	Additional Info
Mutations				
EGFR	In-frame Deletion	L747_P753delinsS	exon 19	MAF: 42.3%
CTNNB1	Missense Mutation	S43P (p.133T>C)	exon 3	MAF: 25.5%
Copy Number Alterations				
MDM2	Whole gene	Amplification	12q15	FC: 13.5
MFC	Whole gene	Amplification	8p24.21	FC: 2.0
AGO2	Whole gene	Amplification	8p24.3	FC: 2.0
Structural Variants				
EML4-ALK	Fusion	c.667+4775 EML4_c.2089-389 ALK	MLA spots 1-5 with ALK spots 19-29	

FDA Approved and/or NCCN recommended biomarker:

Alteration(s)	Drugs(s)	Annotation
Level 1 EGFR L747_P753delinsS MAF: 42.3%	Erlotinib, Afatinib, Gefitinib	EGFR, a receptor tyrosine kinase, is altered by amplification, mutation and/or overexpression in various cancers, most frequently in lung and brain cancers. The EGFR L747_P753delinsS alteration is known to be oncogenic. The EGFR tyrosine kinase inhibitors erlotinib, afatinib and gefitinib are FDA-approved for the treatment of patients with non-small cell lung cancer harboring an EGFR exon 19 deletion such as L747_P753delinsS. OncoKB version: v1.12

Investigational biomarker:

Level 2B EML4-ALK Fusion	Crizotinib, Ceritinib, Alectinib, Brigatinib	ALK, a receptor tyrosine kinase, is recurrently altered by chromosomal rearrangements in various cancers including anaplastic large cell lymphoma, non-small cell lung cancer and inflammatory myofibroblastic tumor. The EML4-ALK fusion is known to be oncogenic. While crizotinib, ceritinib, alectinib and brigatinib are FDA-approved for the treatment of patients with ALK-fusion positive lung cancer, their clinical utility in patients with ALK-fusion positive adenocarcinoma, NOS is unknown. OncoKB version: v1.12.
Level 3B MDM2 Amplification FC: 13.5	RG7112, DS-3032b	MDM2, a ubiquitin ligase and p53 inhibitor, is amplified in a diverse range of cancers including well-differentiated liposarcomas. MDM2 amplification is known to be oncogenic. While there is promising clinical data supporting the use of MDM2-inhibitors such as RG7112 and DS-3032b in patients with MDM2-amplified liposarcomas, their clinical utility in patients with MDM2-amplified lung adenocarcinoma is unknown. OncoKB version: v1.12.

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MSK-IMPACT Clinical Sequencing Cohort (MSKCC, Nat Med 2017)
Targeted sequencing of 10,000 clinical cases using the MSK-IMPACT assay PubMed

Click gene symbols below or enter here

Query

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Summary Clinical Data

Selected: 10,336 patients | 10,945 samples ☐ 10,945 w/ mutation data ☐ 10,945 w/ CNA data

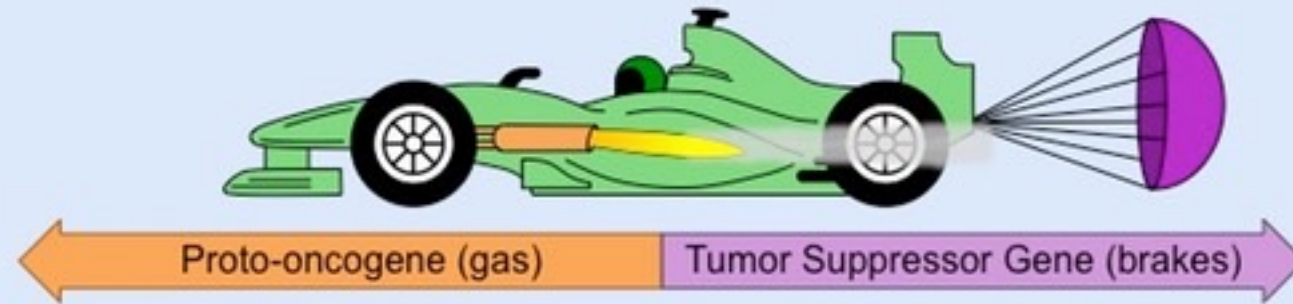
Cancer Type	#	Freq %	Cancer Type Detailed	#	Freq %
Non-Small Cell Lung Cancer	1,668	15.2%	Lung Adenocarcinoma	1,357	12.4%
Breast Cancer	1,324	12.1%	Breast Invasive Ductal Carcinoma	927	8.5%
Colorectal Cancer	1,007	9.2%	Colon Adenocarcinoma	724	6.6%
Prostate Cancer	717	6.6%	Prostate Adenocarcinoma	698	6.4%
Glioma	553	5.1%	Pancreatic Adenocarcinoma	384	3.5%
Pancreatic Cancer	502	4.6%	Bladder Urothelial Carcinoma	312	2.9%
Soft Tissue Sarcoma	443	4.0%	Glioblastoma Multiforme	286	2.6%
Bladder Cancer	423	3.9%	Renal Clear Cell Carcinoma	202	1.8%
Melanoma	365	3.3%	Cutaneous Melanoma	195	1.8%
Renal Cell Carcinoma	361	3.3%	Breast Invasive Lobular Carcinoma	190	1.7%
Hepatobiliary Cancer	355	3.2%	Lung Squamous Cell Carcinoma	170	1.6%

Gene	Mutated Genes (10945 profiled samples)	# Mut	Freq %	Gene	CNA Genes (10945 profiled samples)	Cytoband	CNA	#	Freq %
TP53	4,985	4,561	41.7%	CDKN2A	9p21.3	DEL	834	7.6%	
KRAS	1,671	1,643	15.0%	CDKN2B	9p21.3	DEL	762	7.0%	
TERT	1,564	1,474	13.5%	CCND1	12q13.3	AMP	472	4.3%	
PIK3CA	1,519	1,356	12.4%	MYC	8q24.21	AMP	440	4.0%	
APC	1,696	1,135	10.4%	ERBB2	17q12	AMP	434	4.0%	
ARID1A	1,086	888	8.1%						

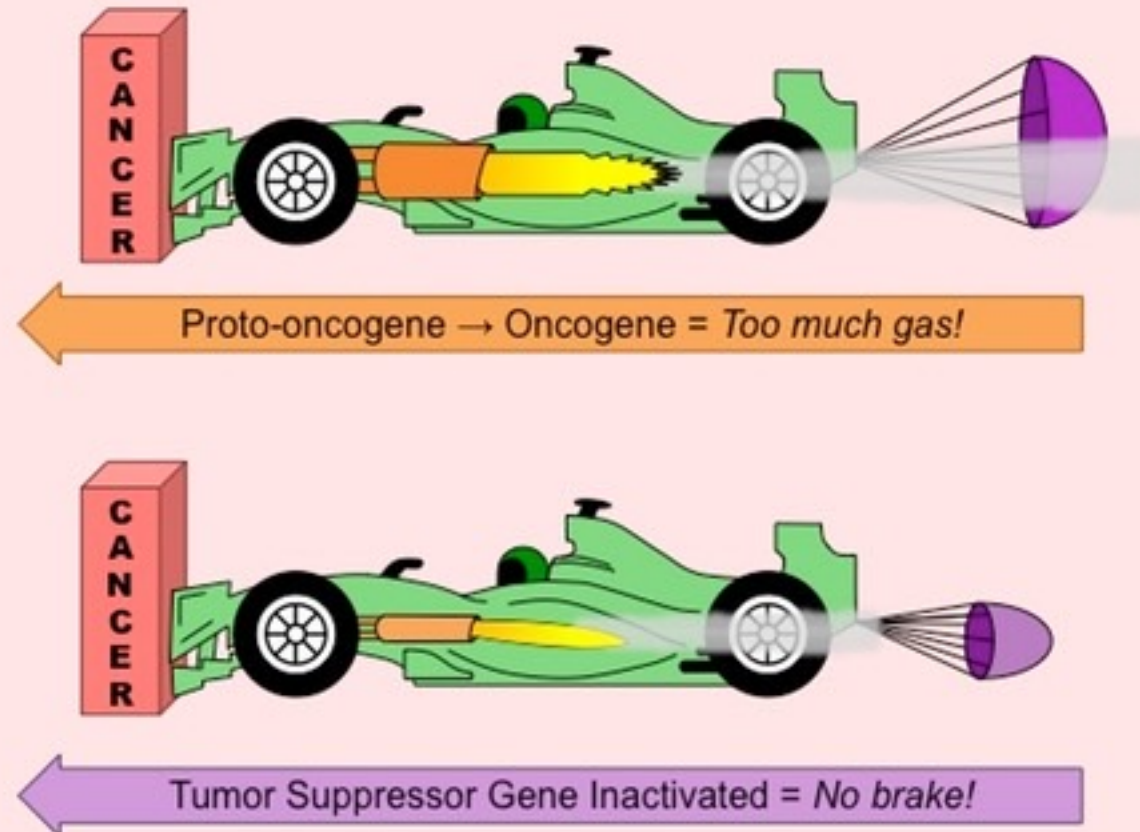
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Normal Cell Cycle



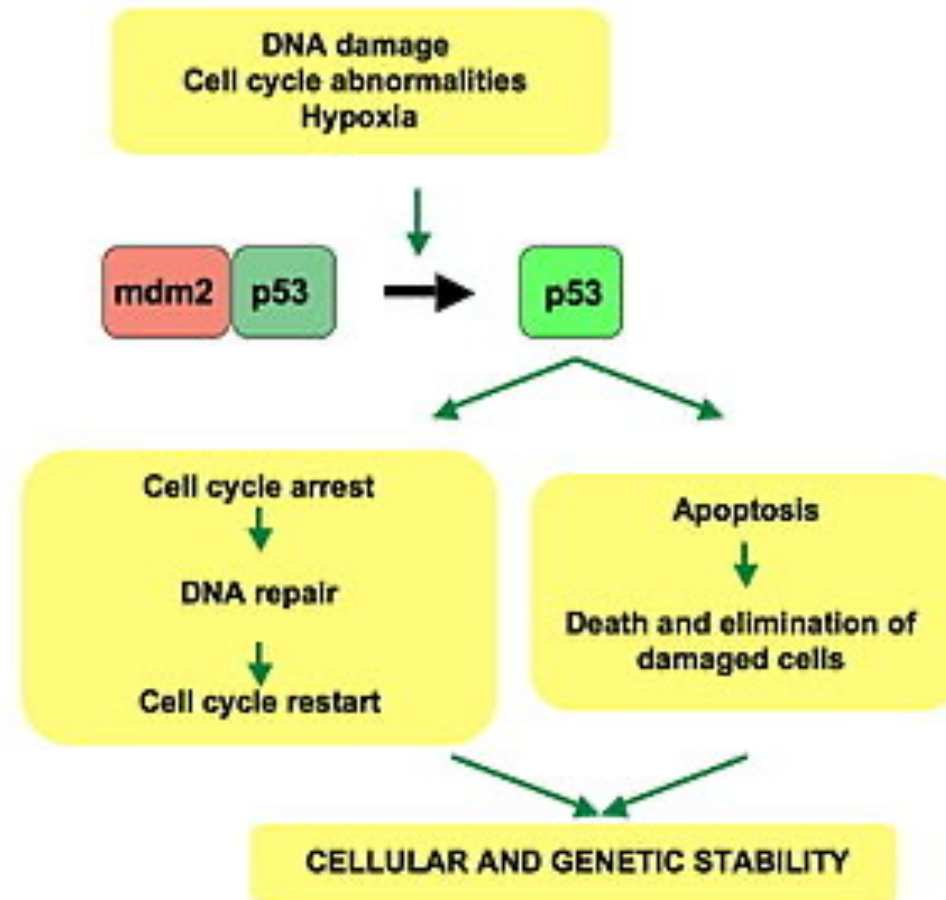
Mutations leading to Cancer



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- B) Loss of function in tumor suppressors genes cannot occur due to non-mutational processes like promoter methylation.
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- D) Mutation in tumor suppressors genes can only be somatic, and they don't occur in the germline.

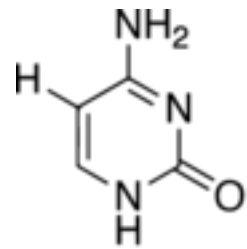
TP53 as an example of a tumor suppressor



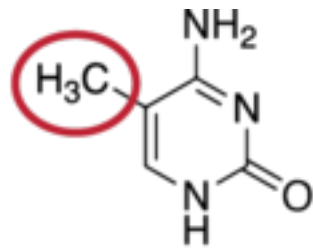
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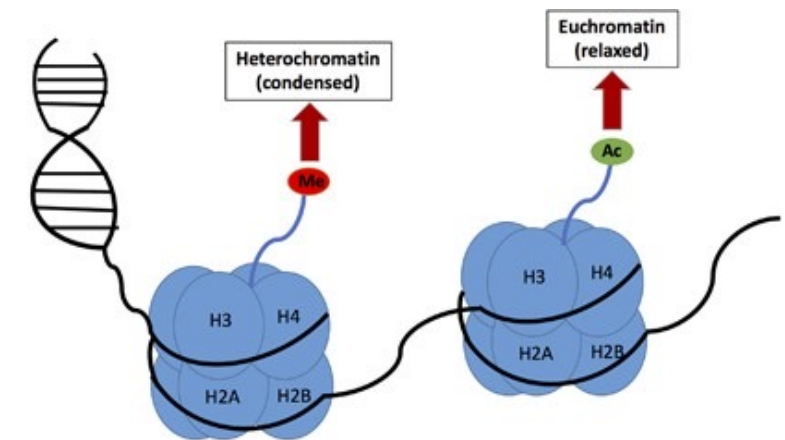
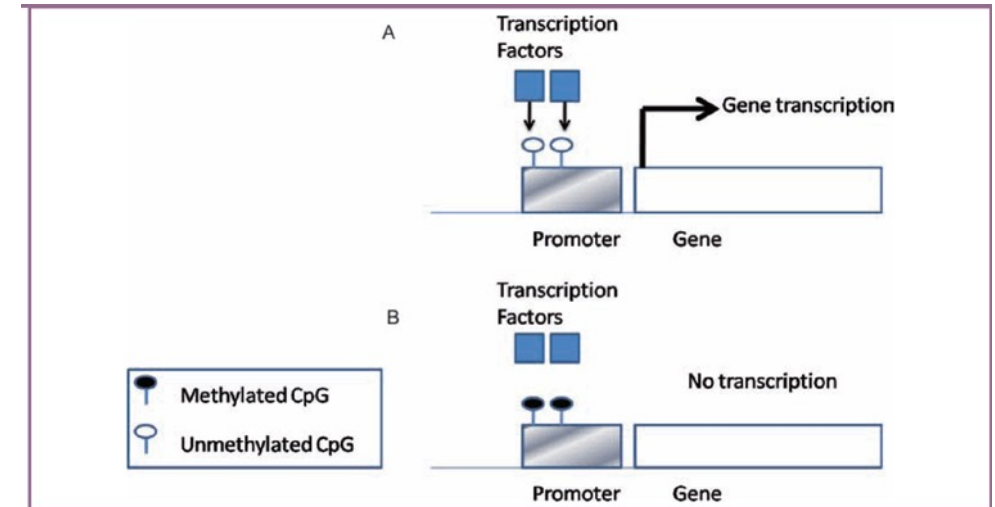
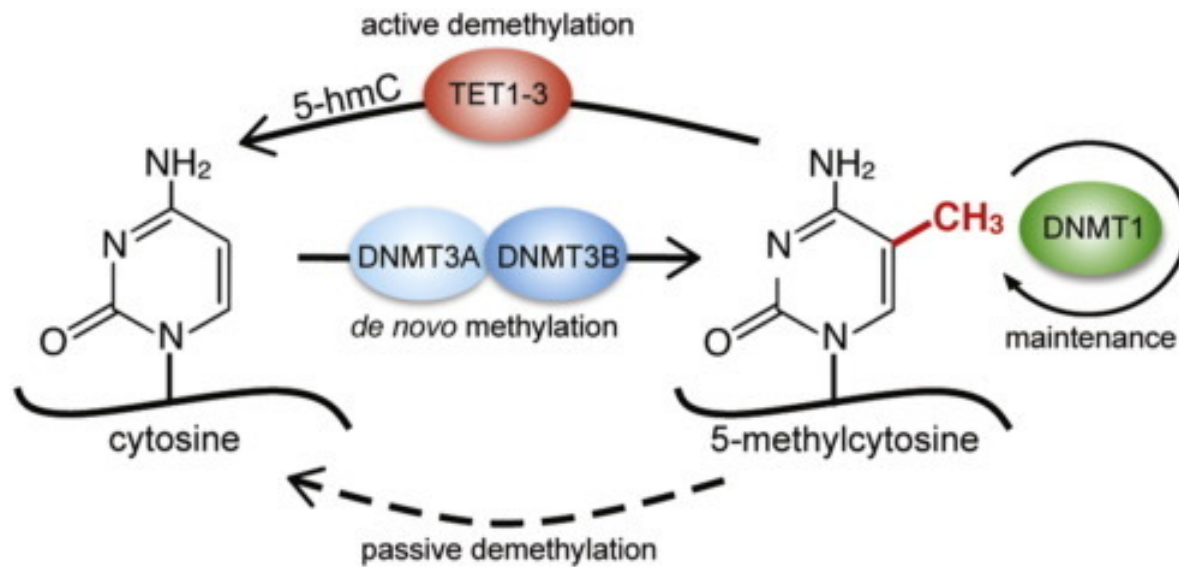
Epigenetics: Methylation as an example of an epigenetic modification



Cytosine



5-methylcytosine

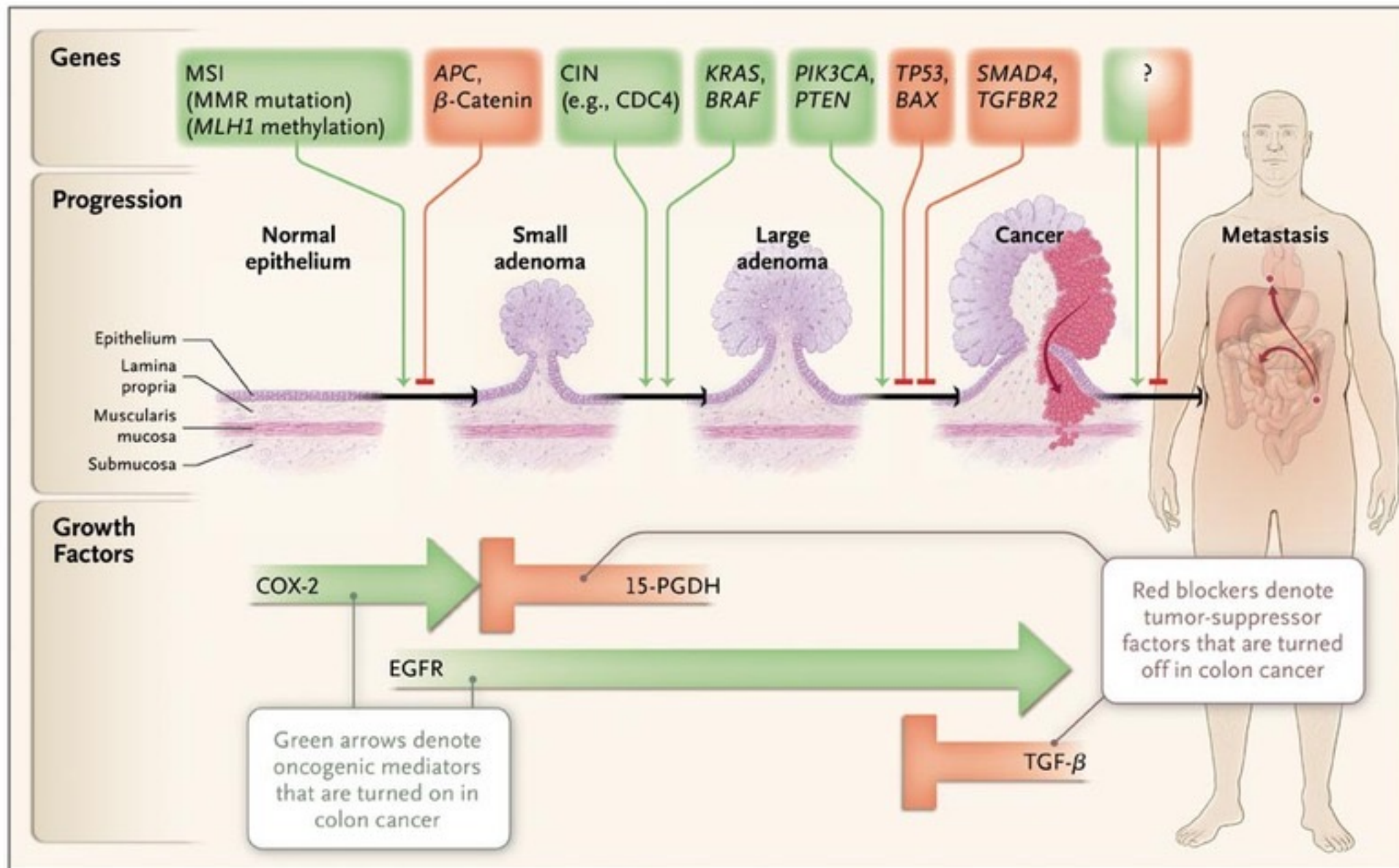


● Histones ● Ac Acetylation
 ● Me Methylation — Histone amino-terminal tail

Wikicommons
 Ambrosi JMB 2017
 Kim EMM 2017
 Lim TOG 2011

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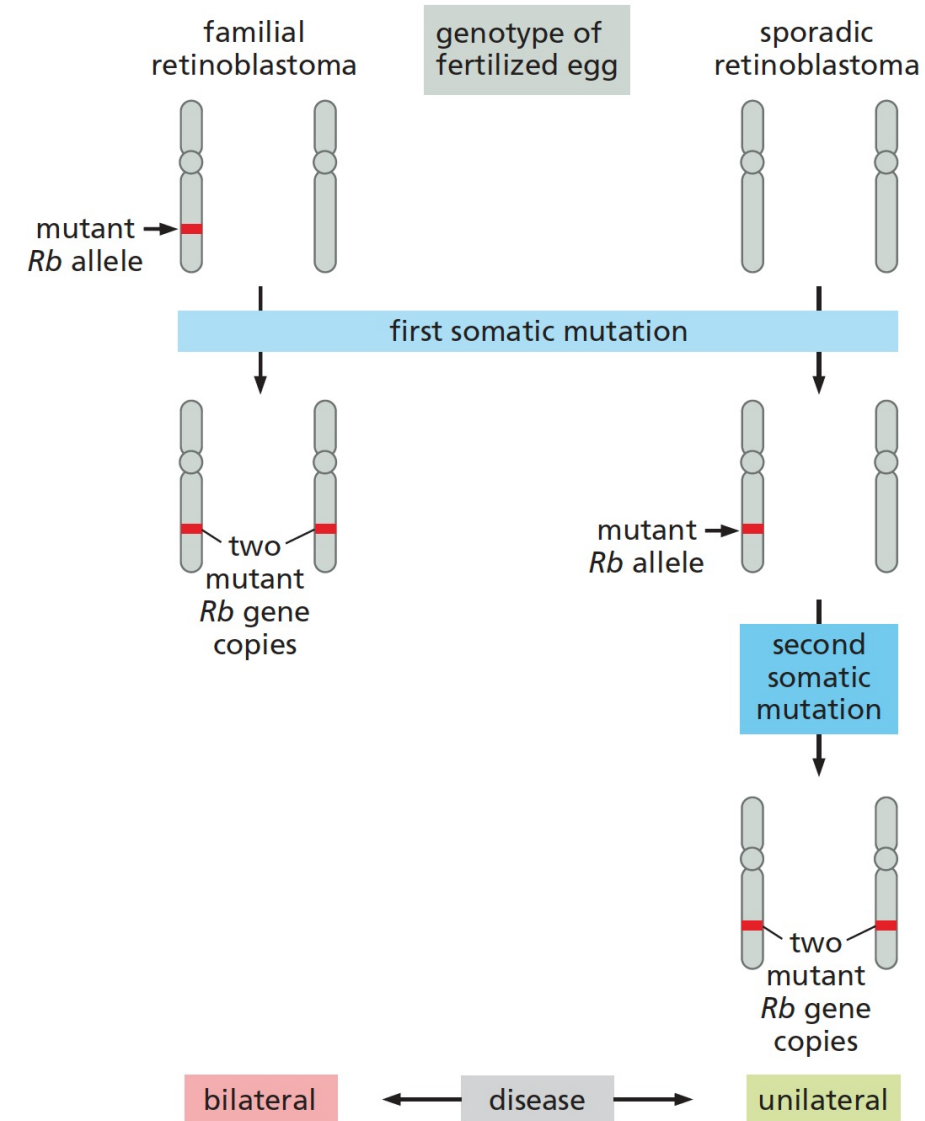
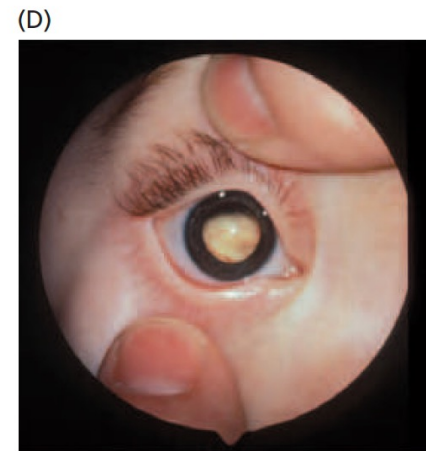
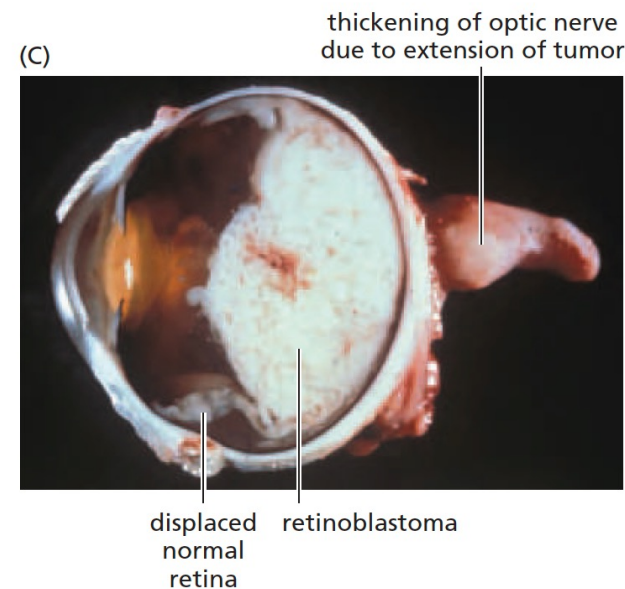
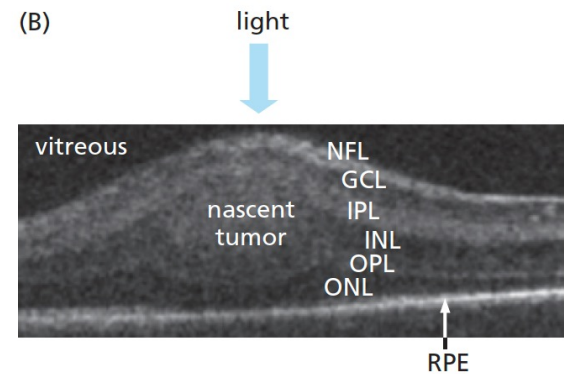
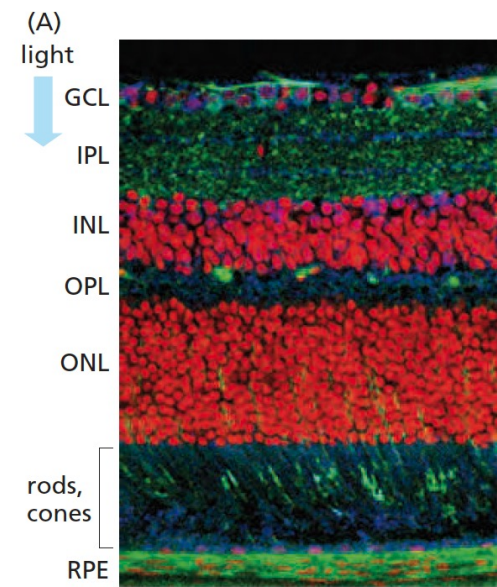
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RB (Retinoblastoma) as an example of a tumor suppressor with somatic and germline mutations



Understanding Cancer Classification and Modelling of Tumor Suppressors

Pablo Sánchez Vela, MD.

HOPP SEP

03/02/22

Recommended reads:

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After acknowledging the importance of TP53 as a tumor suppressor, you are interested in understanding the effect of other tumor suppressors. Which of the following genes is not a tumor suppressor?

- A) RB, a gene involved in controlling the pass through a cell cycle checkpoint..
- B) APC, a gene involved in downregulating the expression of beta-catenin, a known proto-oncogene.
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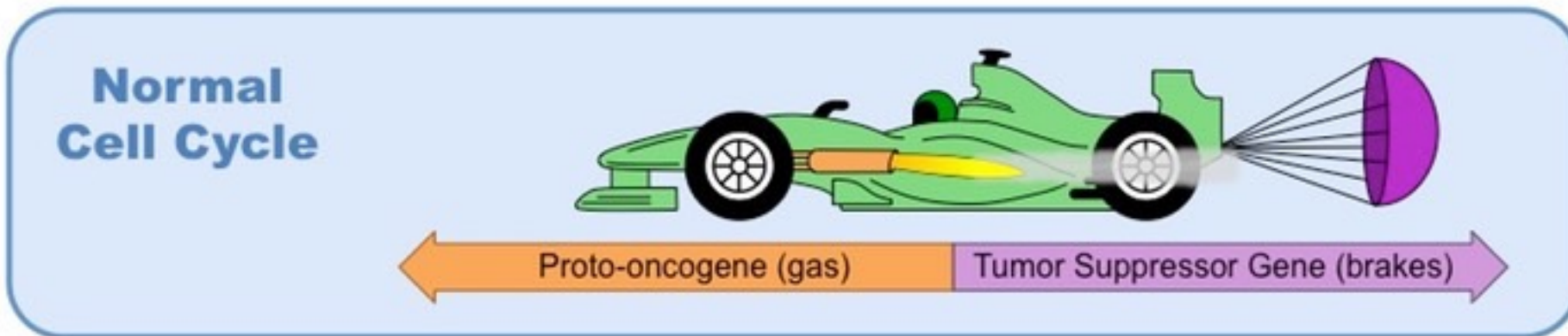
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