

TP53 Genetic Variations In Human Cancers

© IARC TP53 Database 2019

Molecular Mechanisms and Biomarkers Group
International Agency for Research on Cancer Lyon, France

<http://p53.iarc.fr>

What Is TP53 ?

TP53 Is A Tumor Suppressor Gene



p53^{+/+}



% mice with tumor

1% at 18 months



p53^{+/-}



2% at 9 months



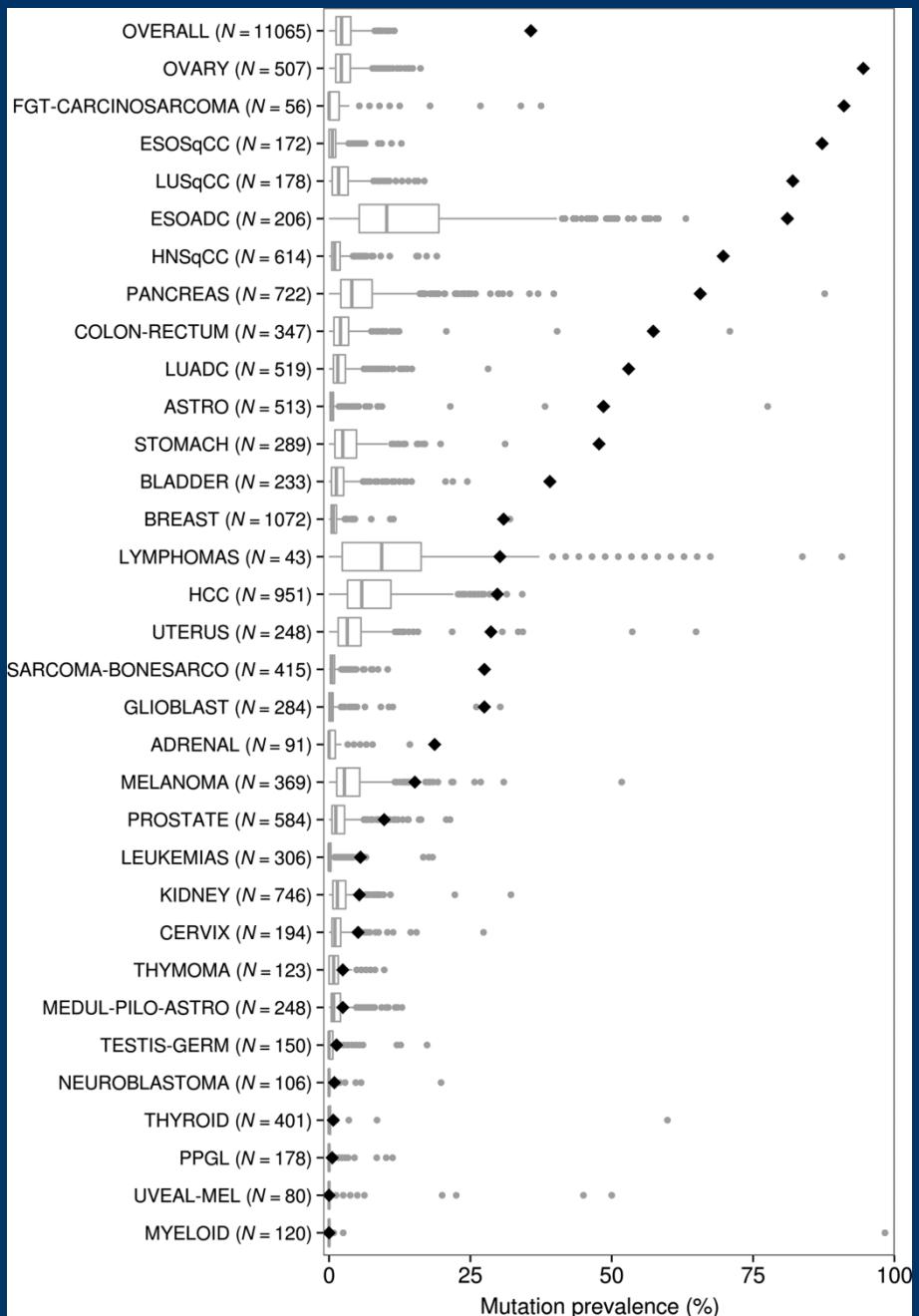
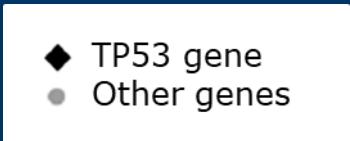
p53^{-/-}



75% at 6 months

Donehower et al. 1992

TP53 is the Most Frequently Mutated Gene in a Majority of Cancers

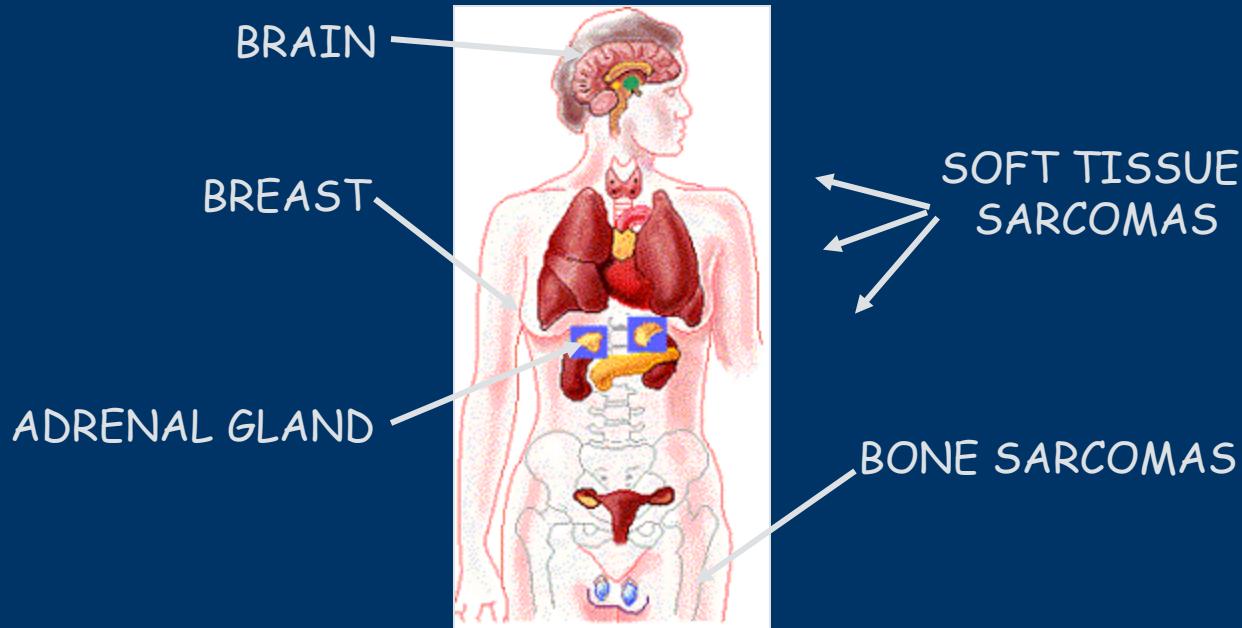


In Specific Types Of Cancers Where TP53 Mutations Are Unfrequent p53 Protein May Be Inactivated By Protein Interactions

Cancer	TP53 mutation frequency	Inactivating protein
Neuroblastoma	< 2%	Twist
Sarcomas	< 20%	Mdm2/Twist
Retinoblastoma Melanoma	< 1%	Mdm4
Cervical cancer	< 10%	E6 (HPV)

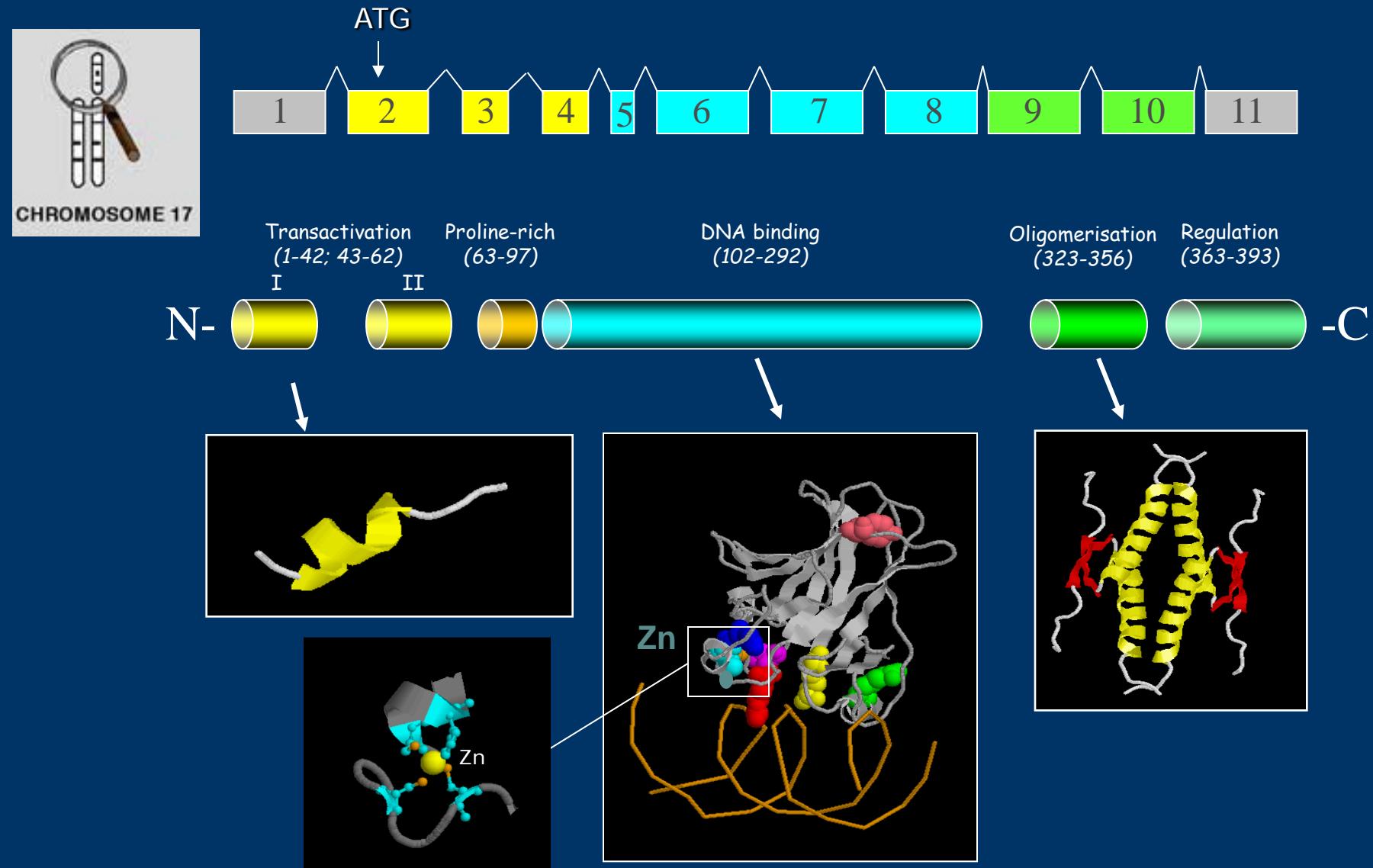
TP53 Germline Mutations Are Responsible For Li-Fraumeni Syndrome

The **Li-Fraumeni syndrome** (LFS, OMIM# 151623) is a rare autosomal disorder characterised by a familial clustering of early onset tumors (<45), with a predominance of sarcomas, breast cancers, brain tumors and adrenocortical carcinomas.

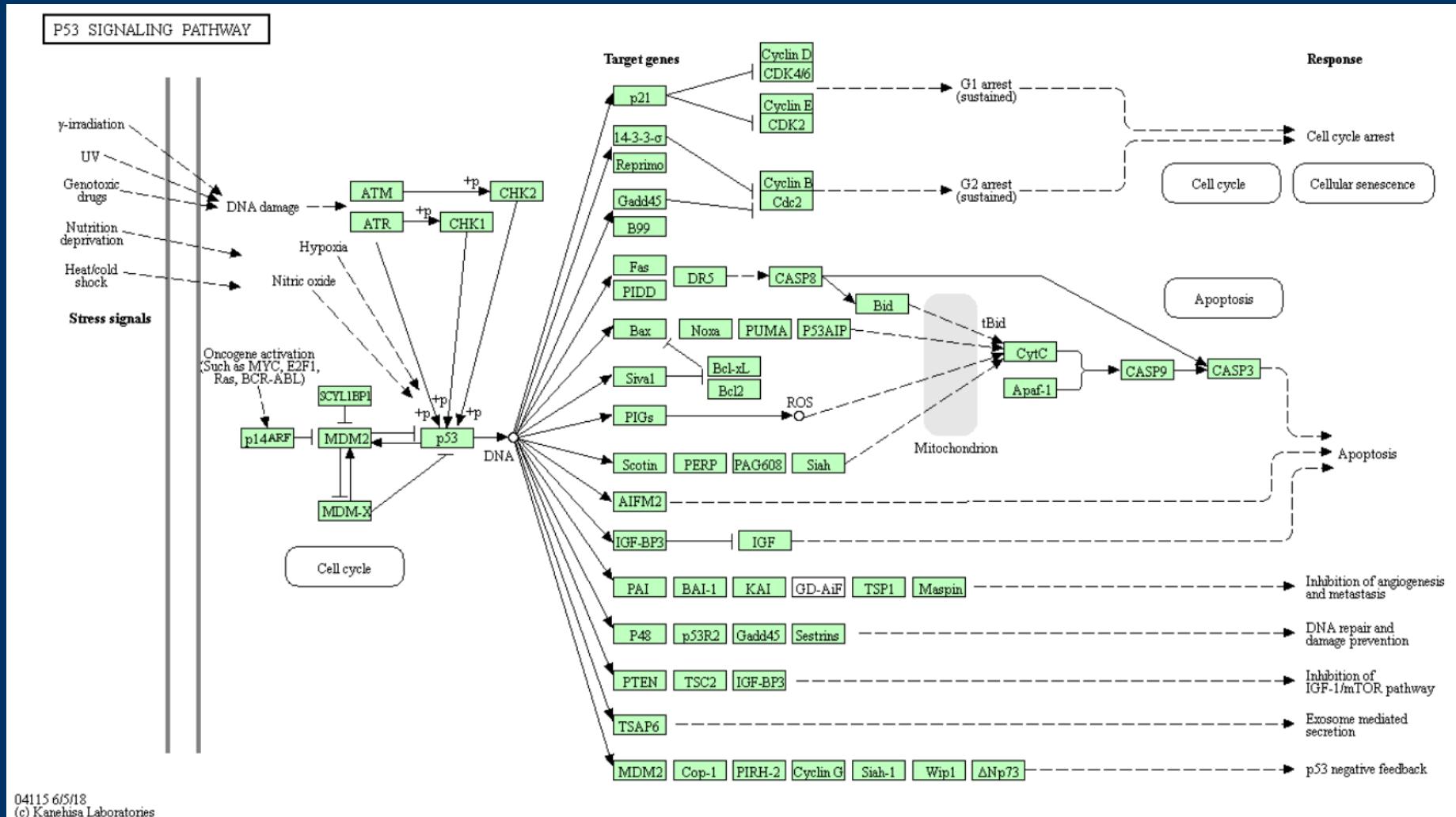


In 1990, Malkin et al. found that this syndrome may be caused by a germline mutation in the TP53 gene.

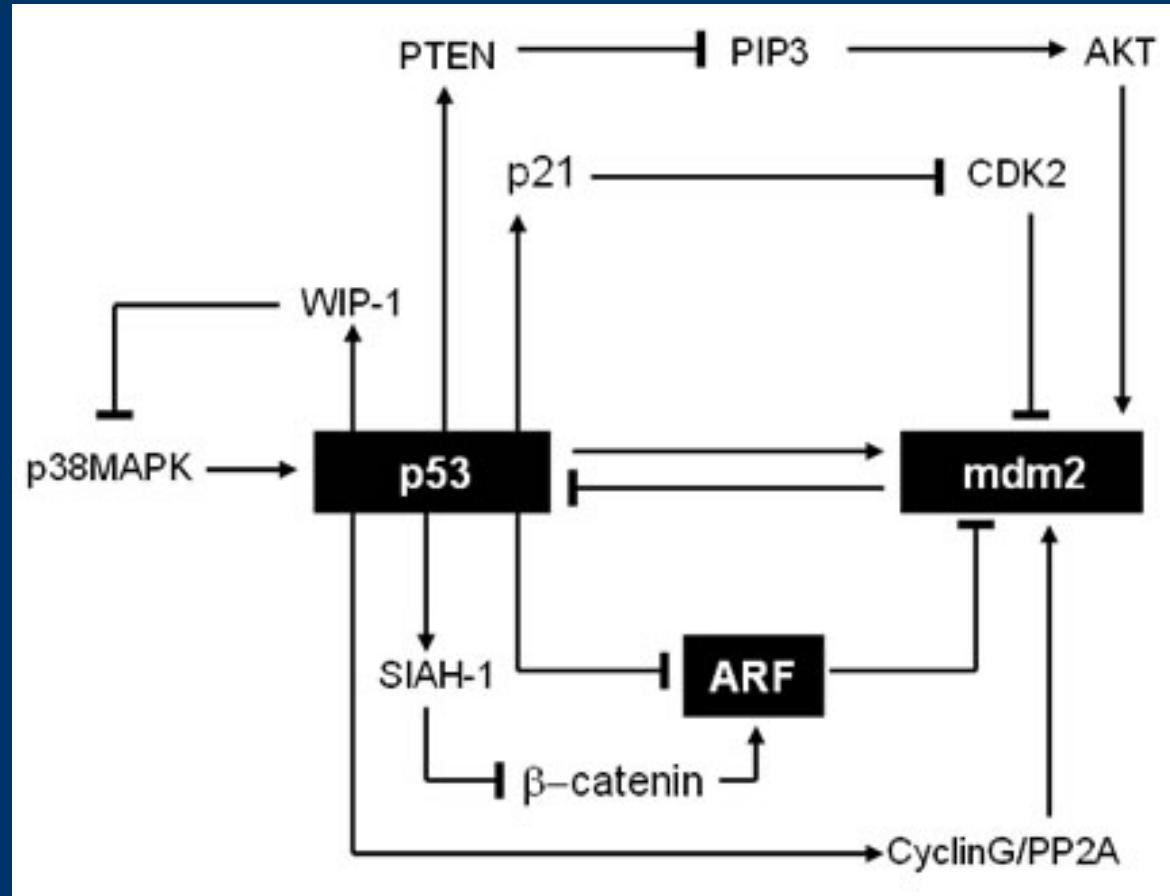
TP53 Encodes The p53 protein, A Transcription Factor



The p53 Pathway

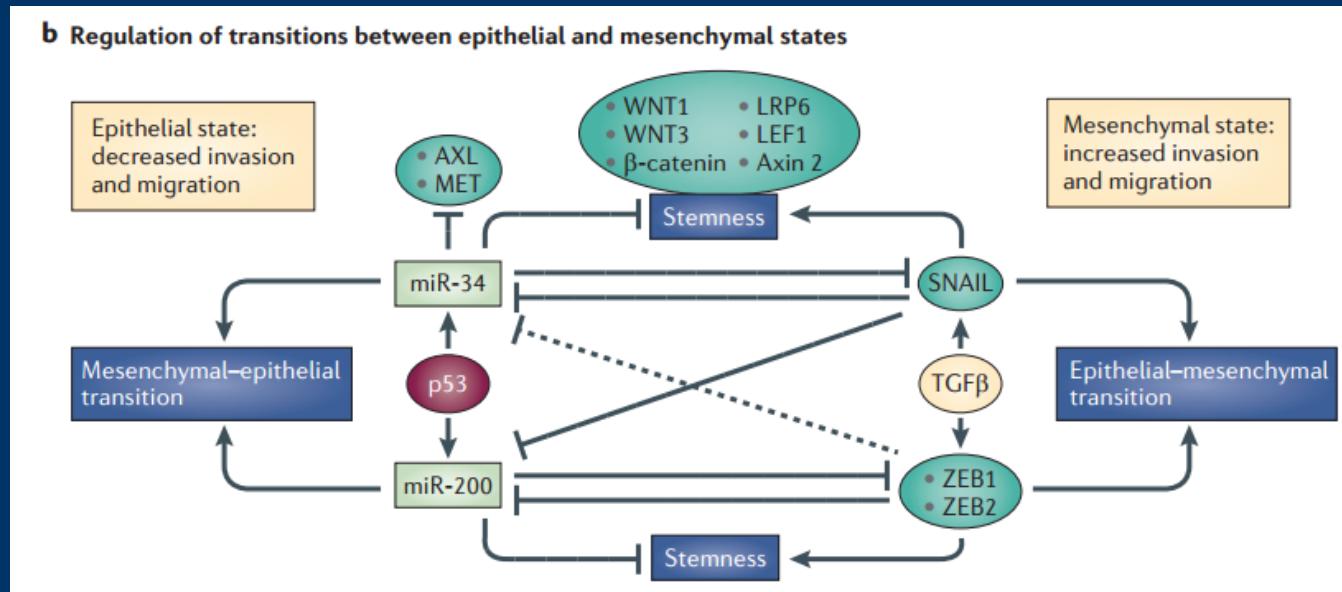
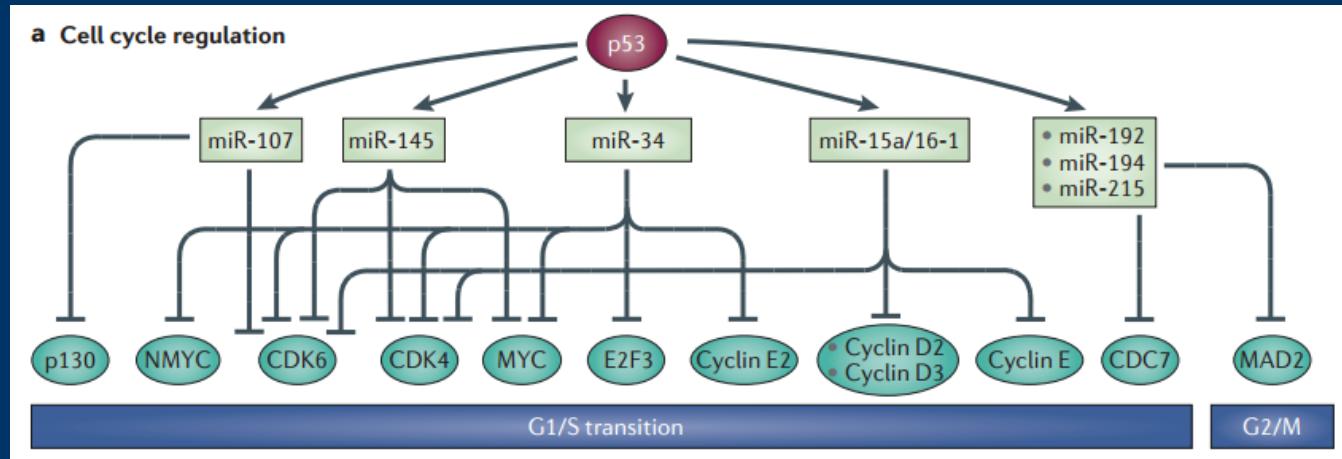


The p53 pathway: positive and negative feedback loops

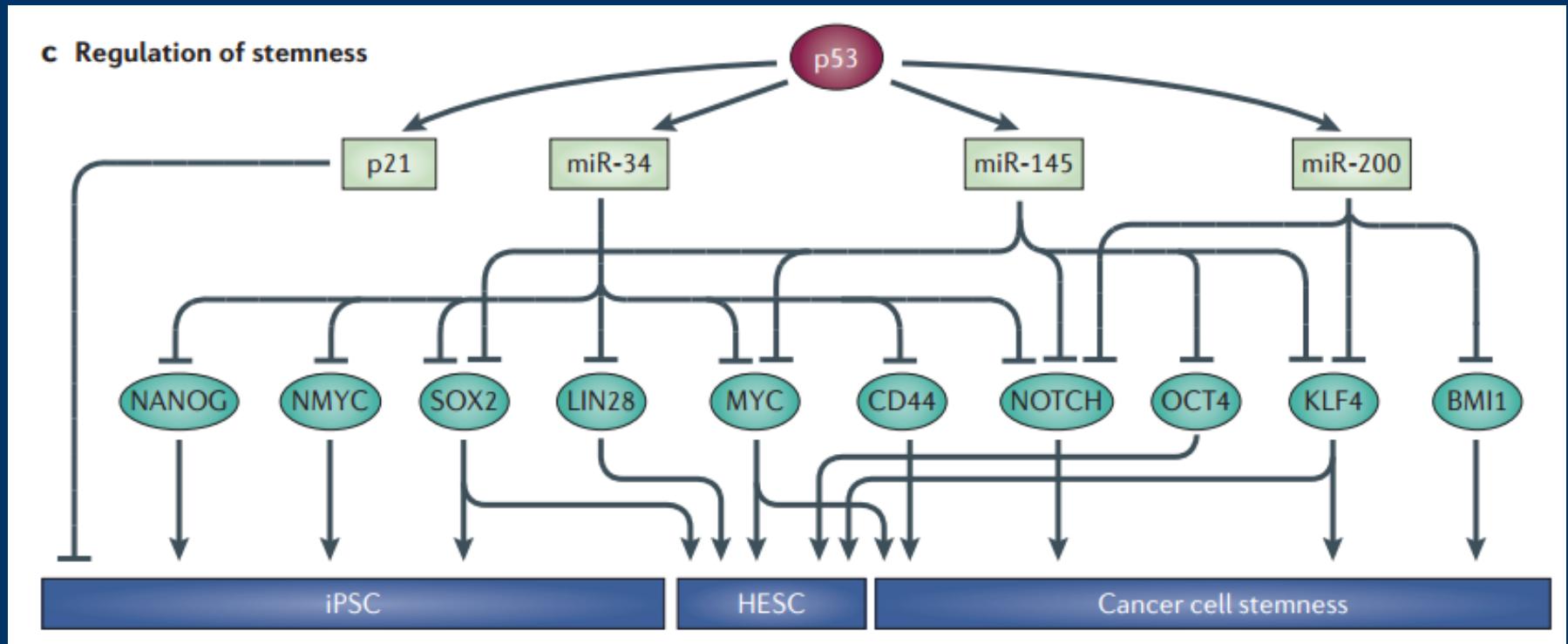


From Harris & Levine, 2005

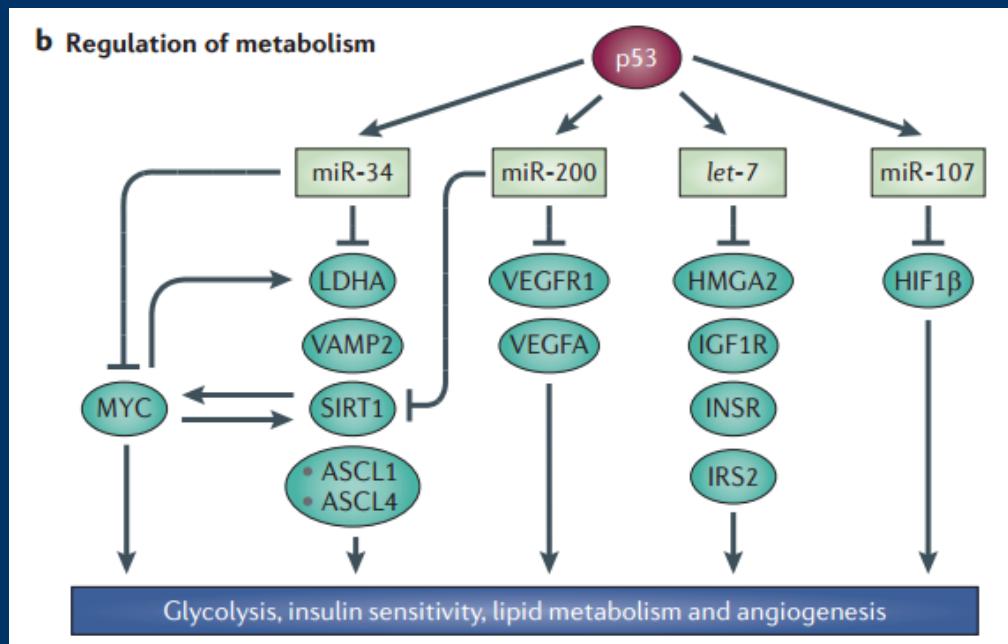
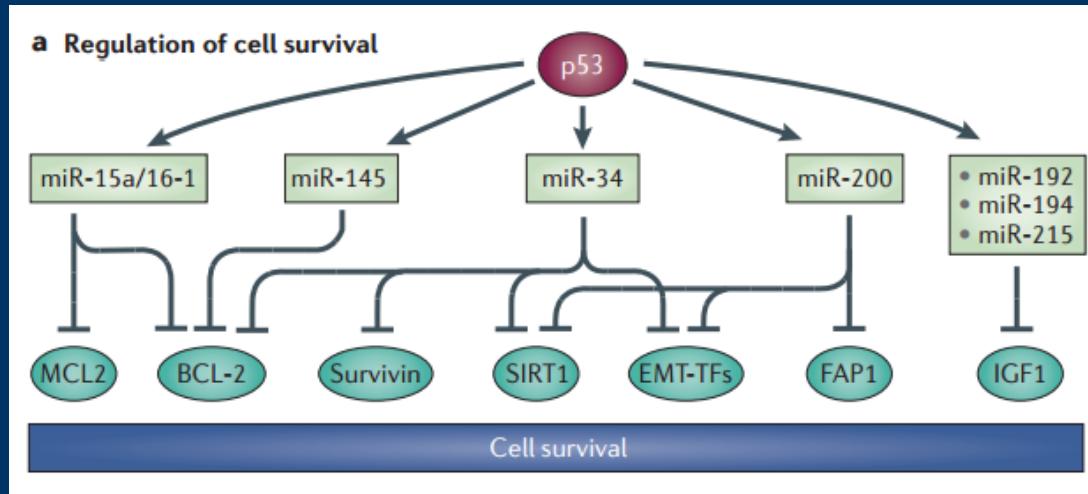
miRNA In The TP53 Pathway (1)



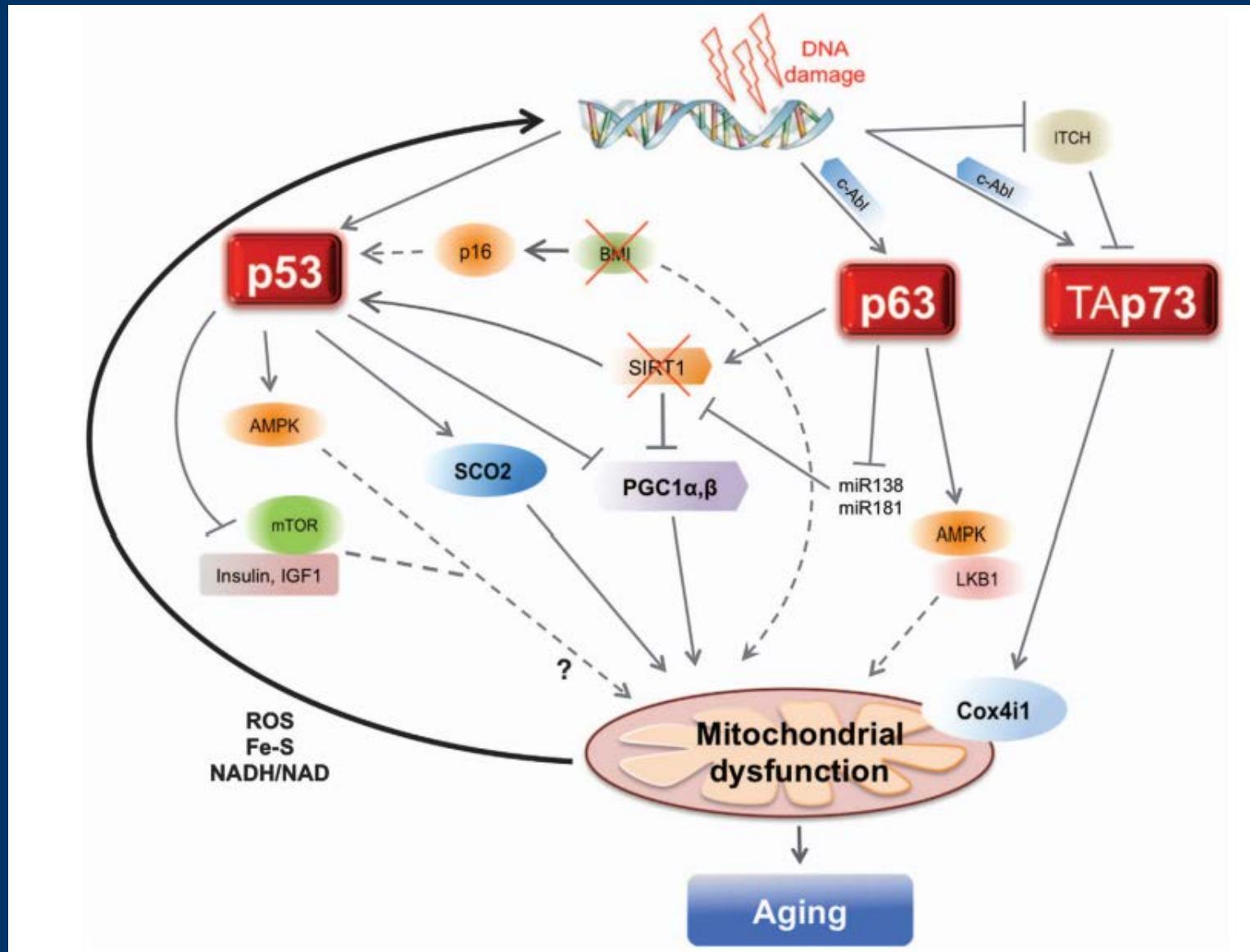
miRNA In The TP53 Pathway (2)



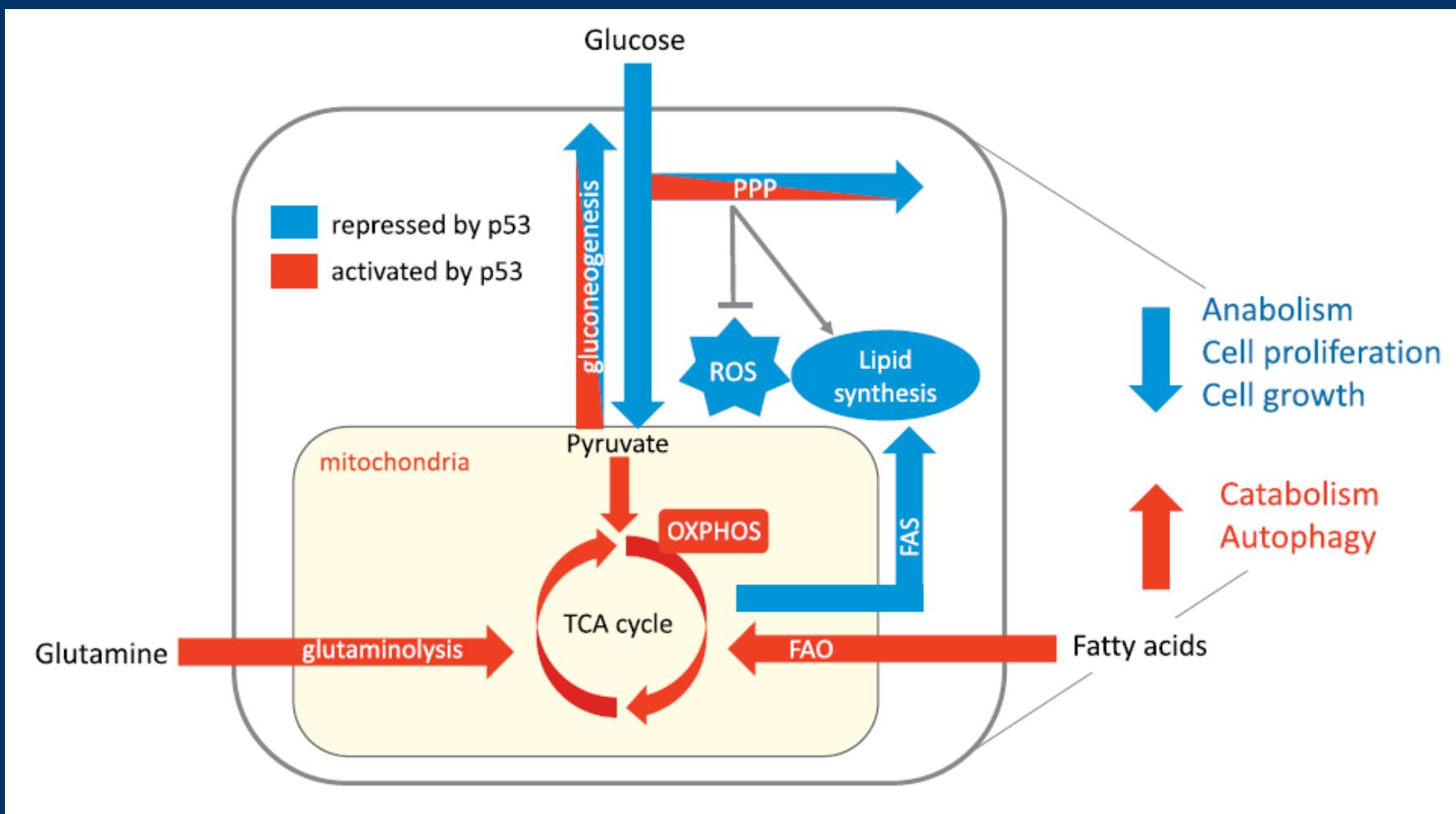
miRNA In The TP53 Pathway (3)



p53 and Ageing

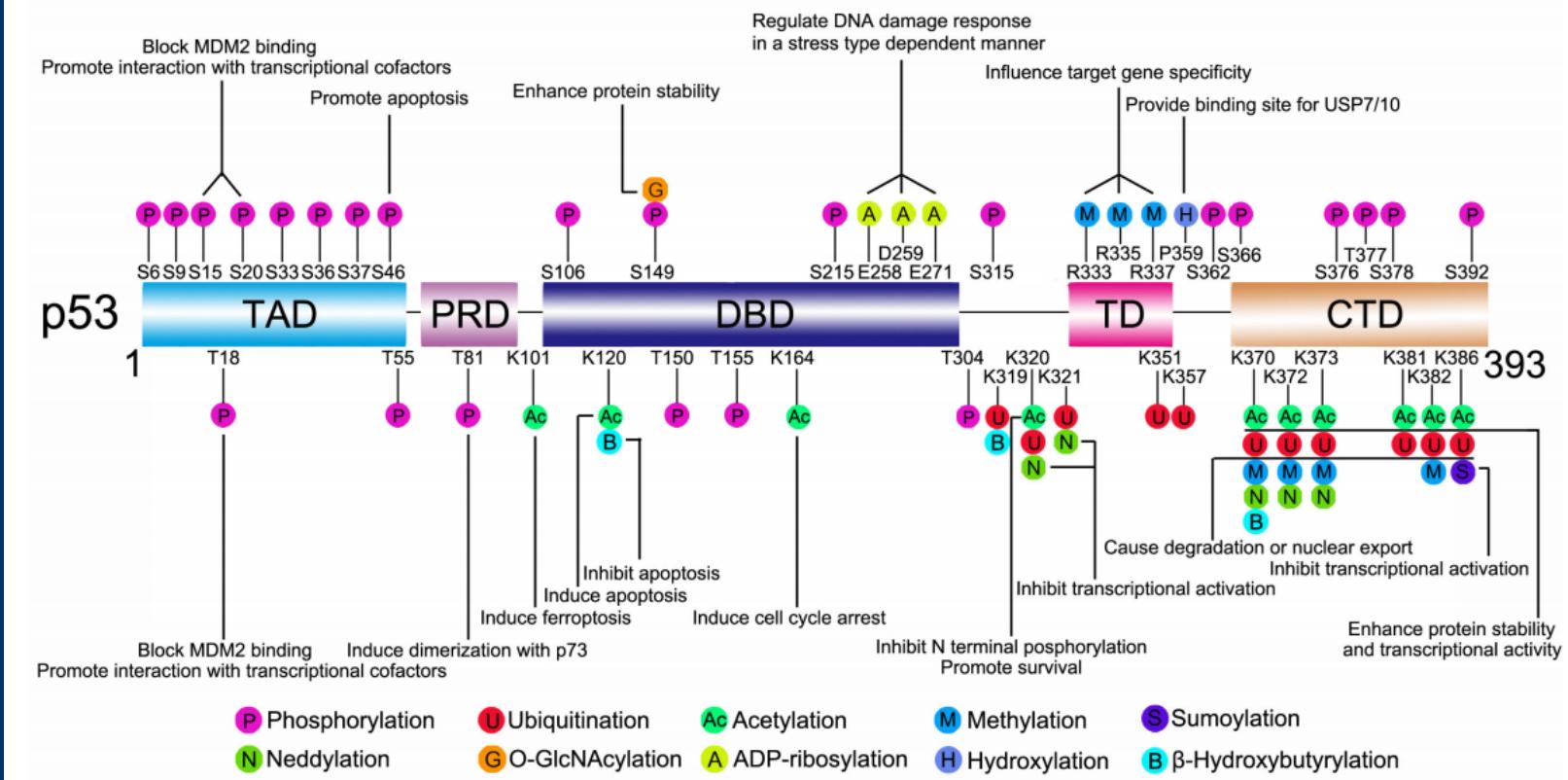


Regulation of energy metabolism by p53

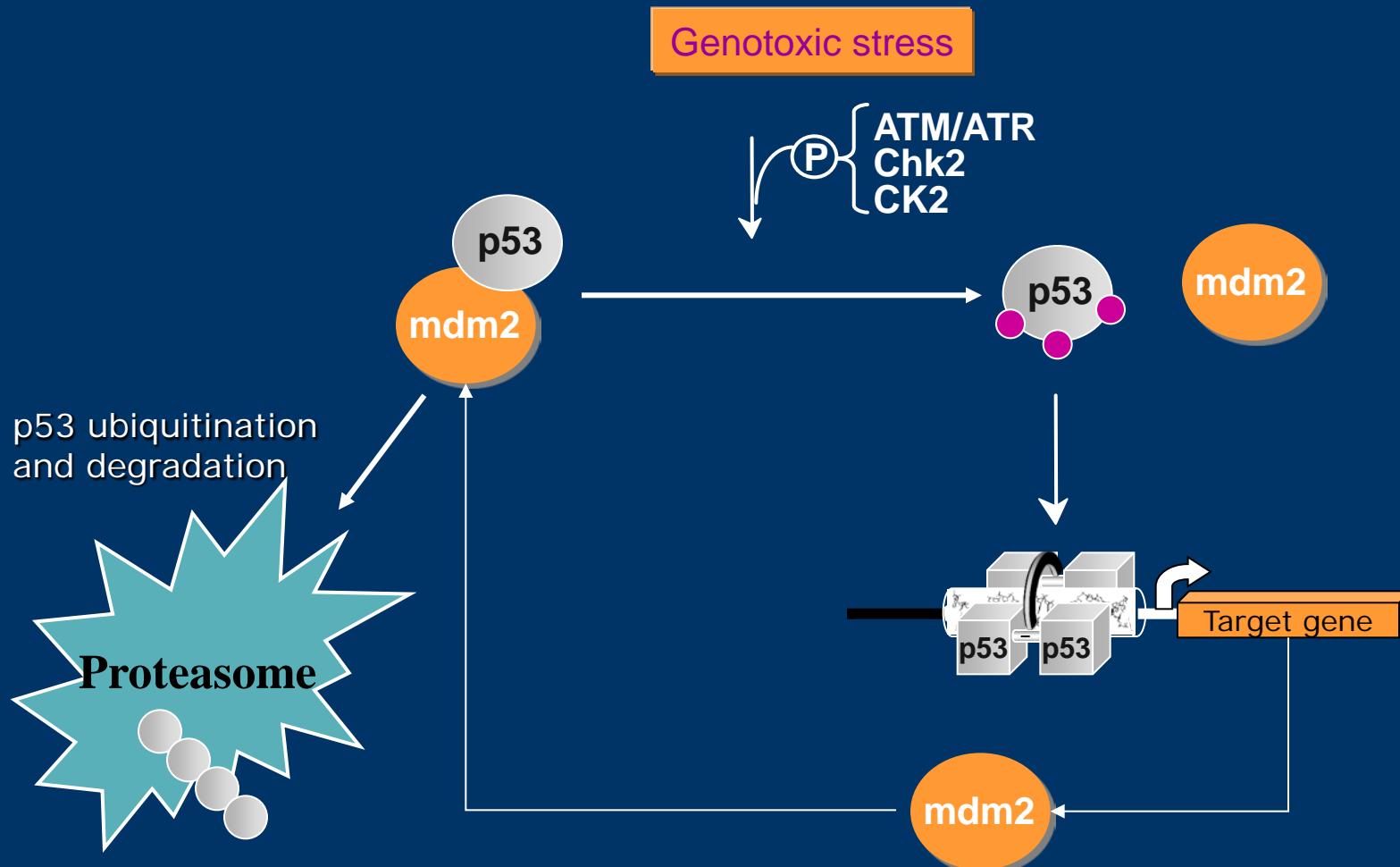


Several Post-Translational Modifications On p53 Regulate p53 Activities

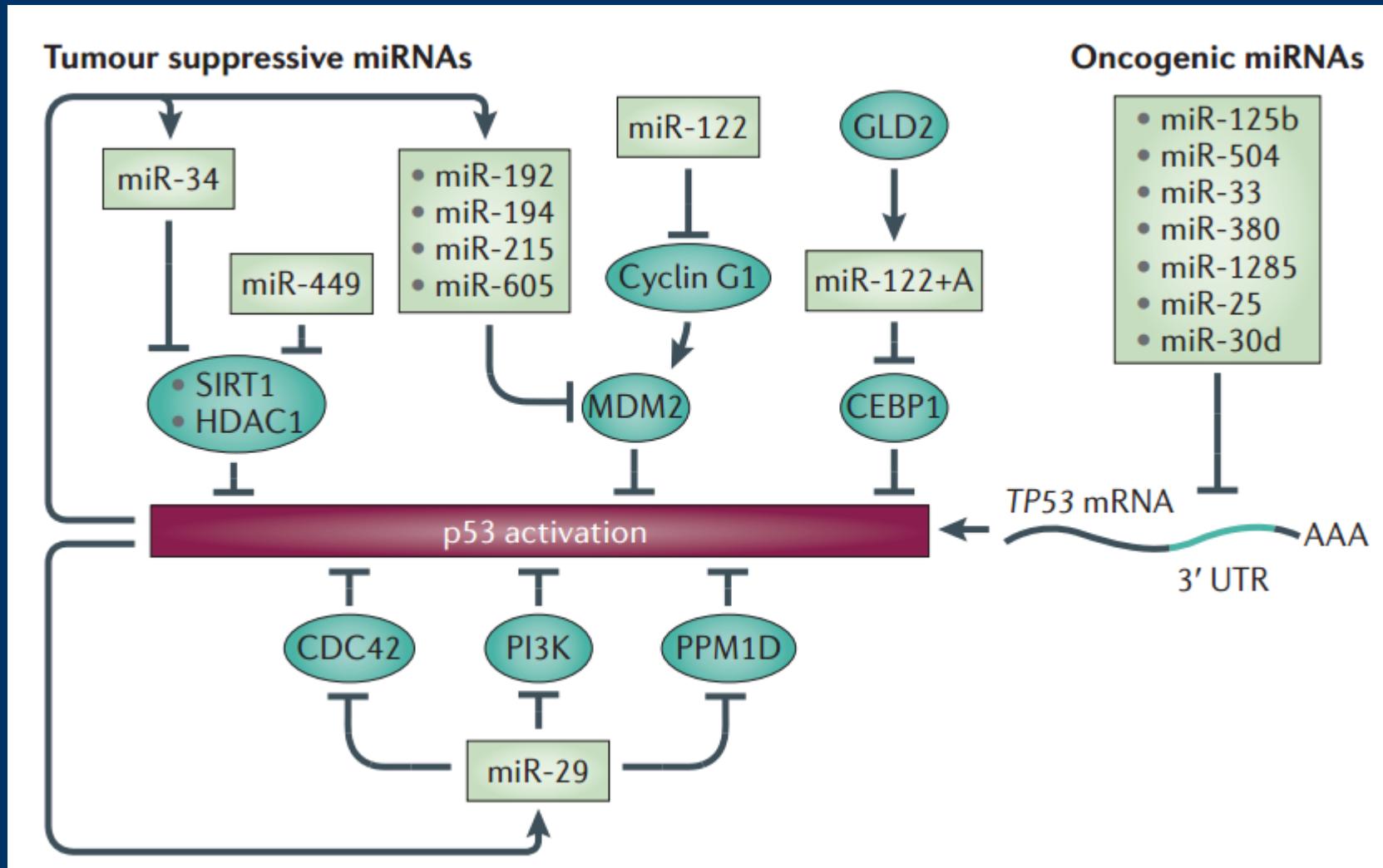
Figure 1 Overview of p53 post-translational modifications. The major sites for p53 modifications (phosphorylation, ubiquitination, sumoylation, neddylation, acetylation, methylation, O-GlcNAcylation, ADP-ribosylation, hydroxylation, and β -hydroxybutyrylation) are plotted. Different colors are used to differentiate distinct modification types. Representative functions of some modifications are indicated. The figure is mainly revised from Dai and Gu (2010) and Gu and Zhu (2012) and not drawn to scale.



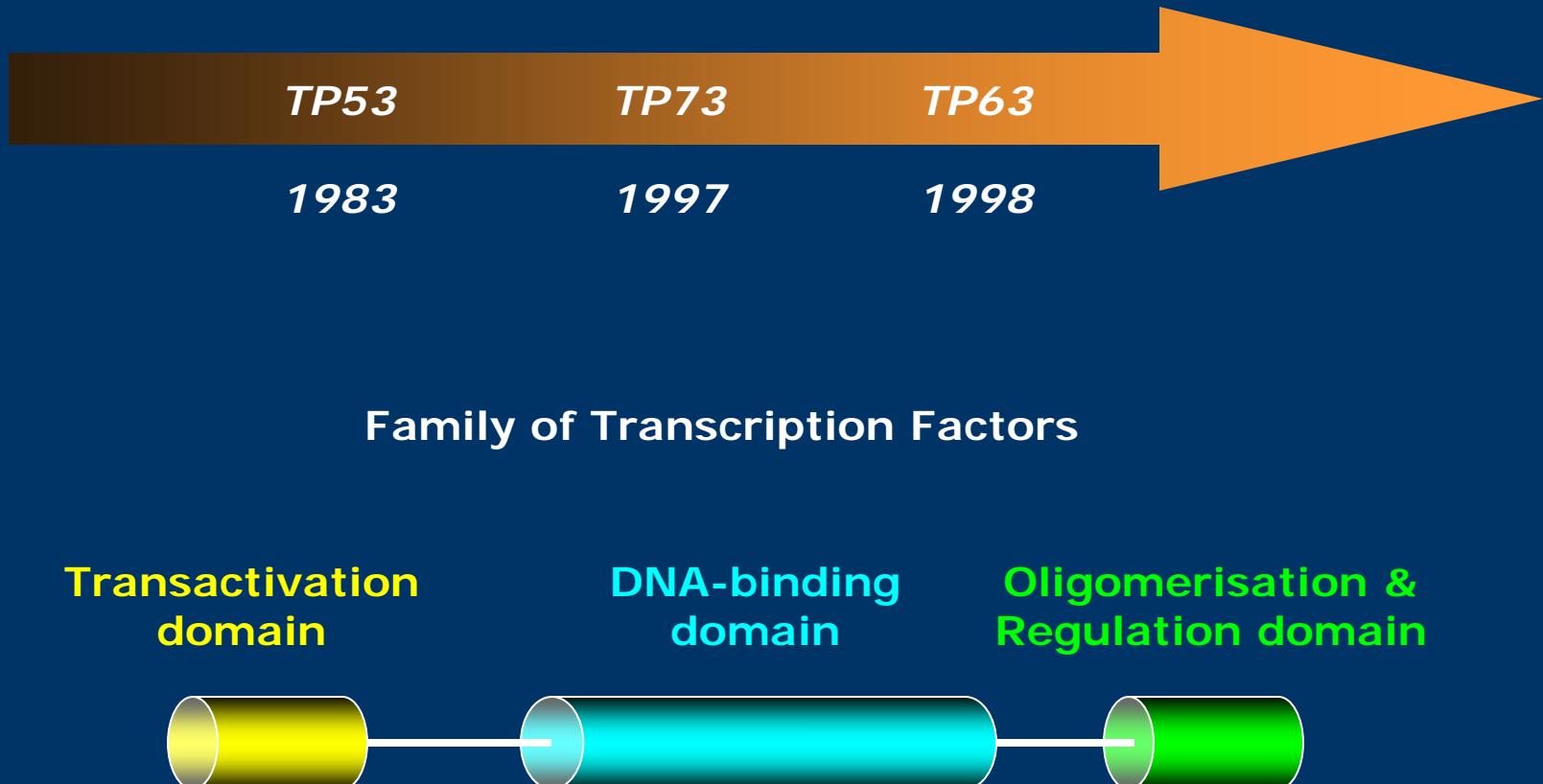
p53 Activation: Breaking p53-mdm2 Association



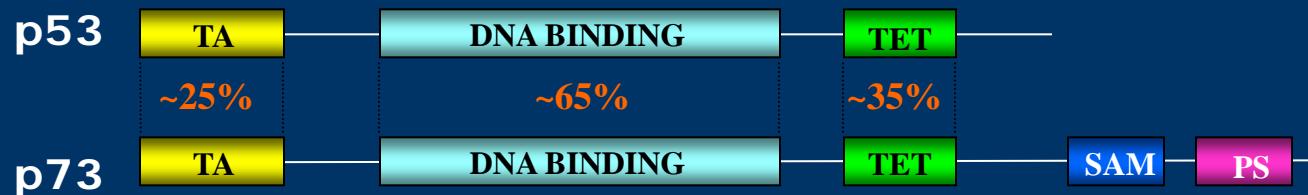
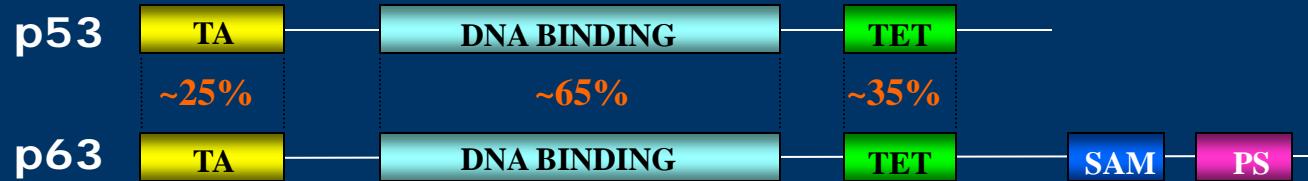
p53 Regulation by miRNA



TP53 Family Members: Similar Structure

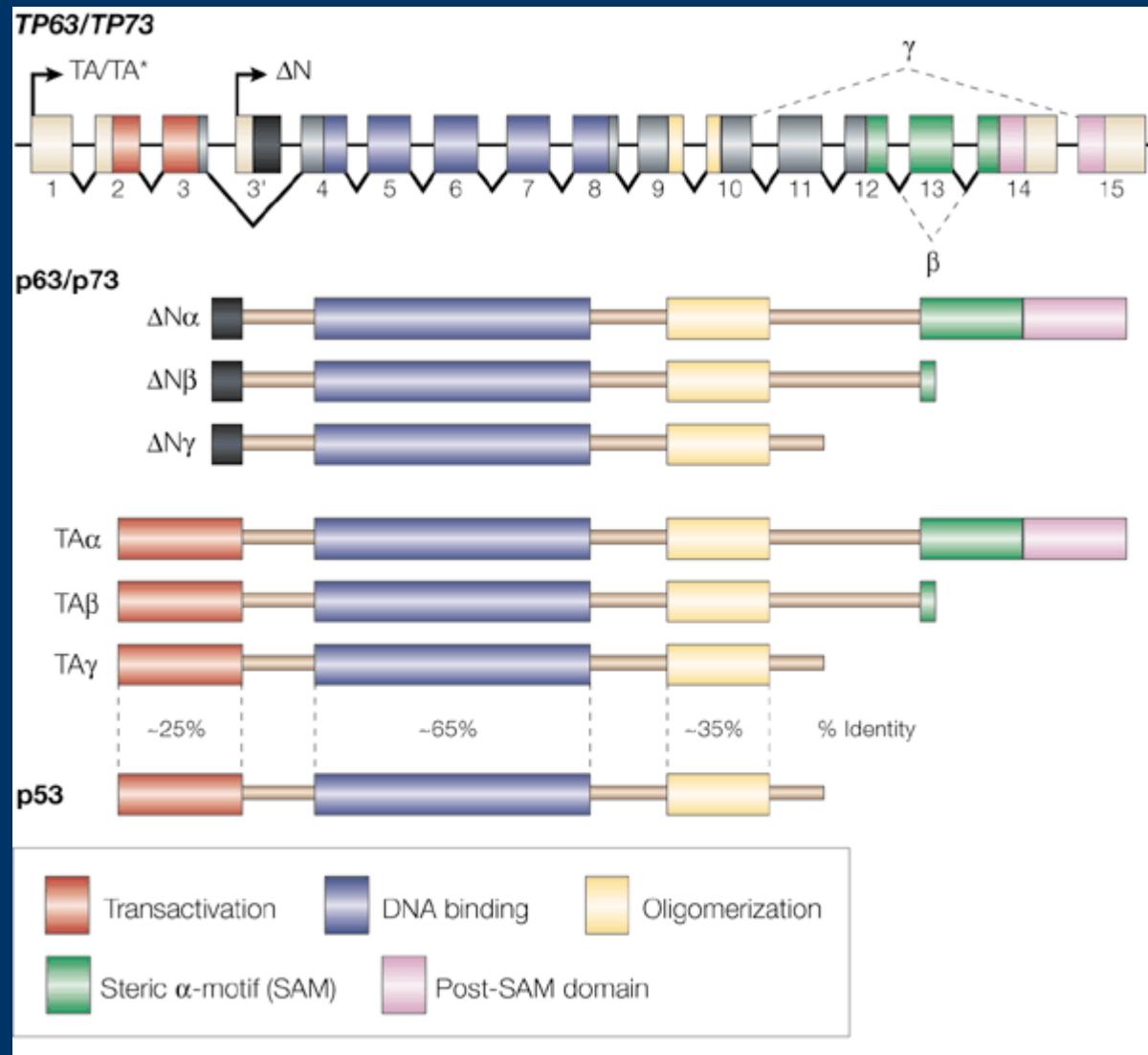


Sequence Identity Between p53, p63, p73 proteins

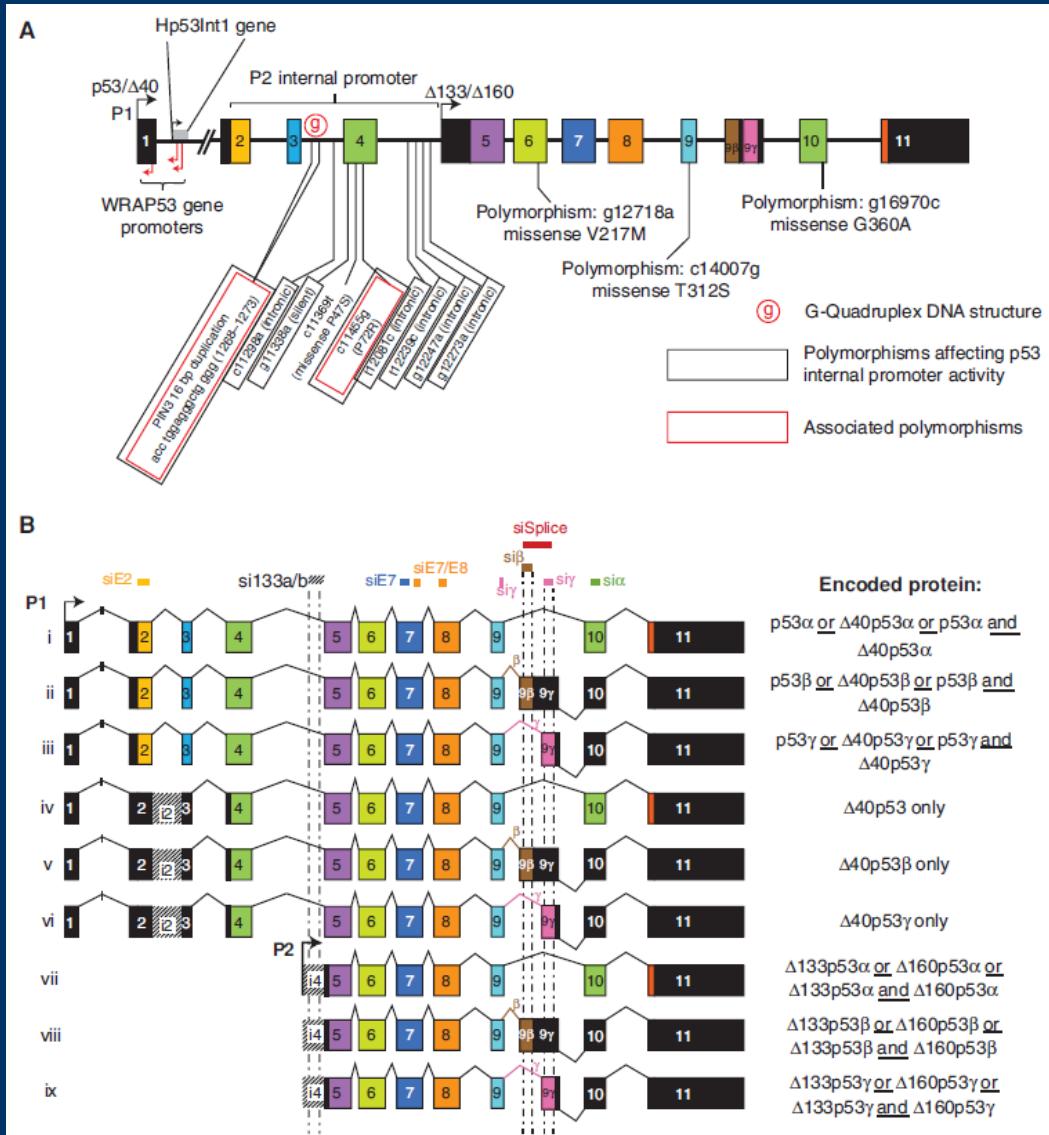


From Courtois et al., 2004

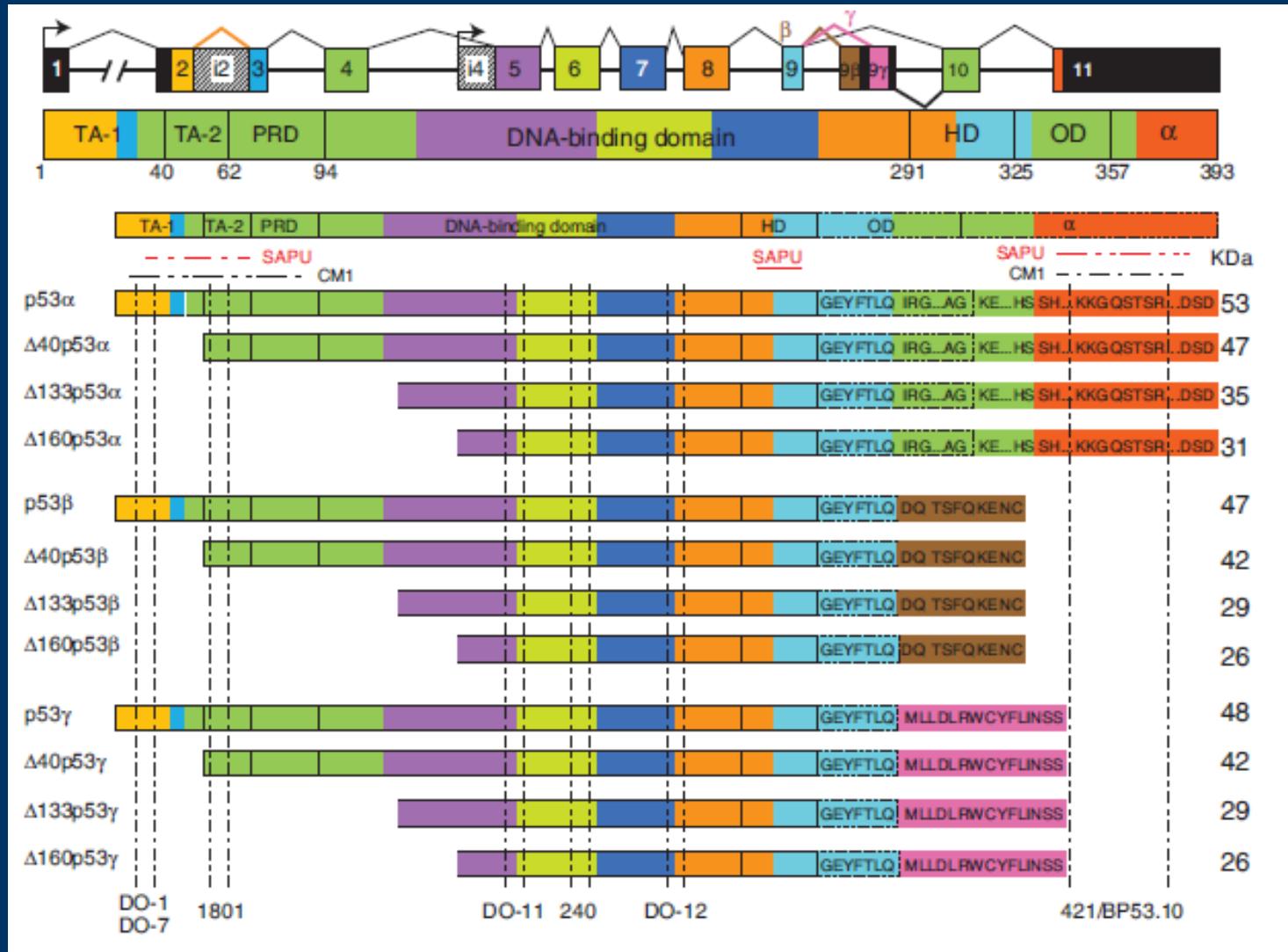
p63 & p73 Isoforms Are Generated By Alternative Splicing And Alternative Promoters



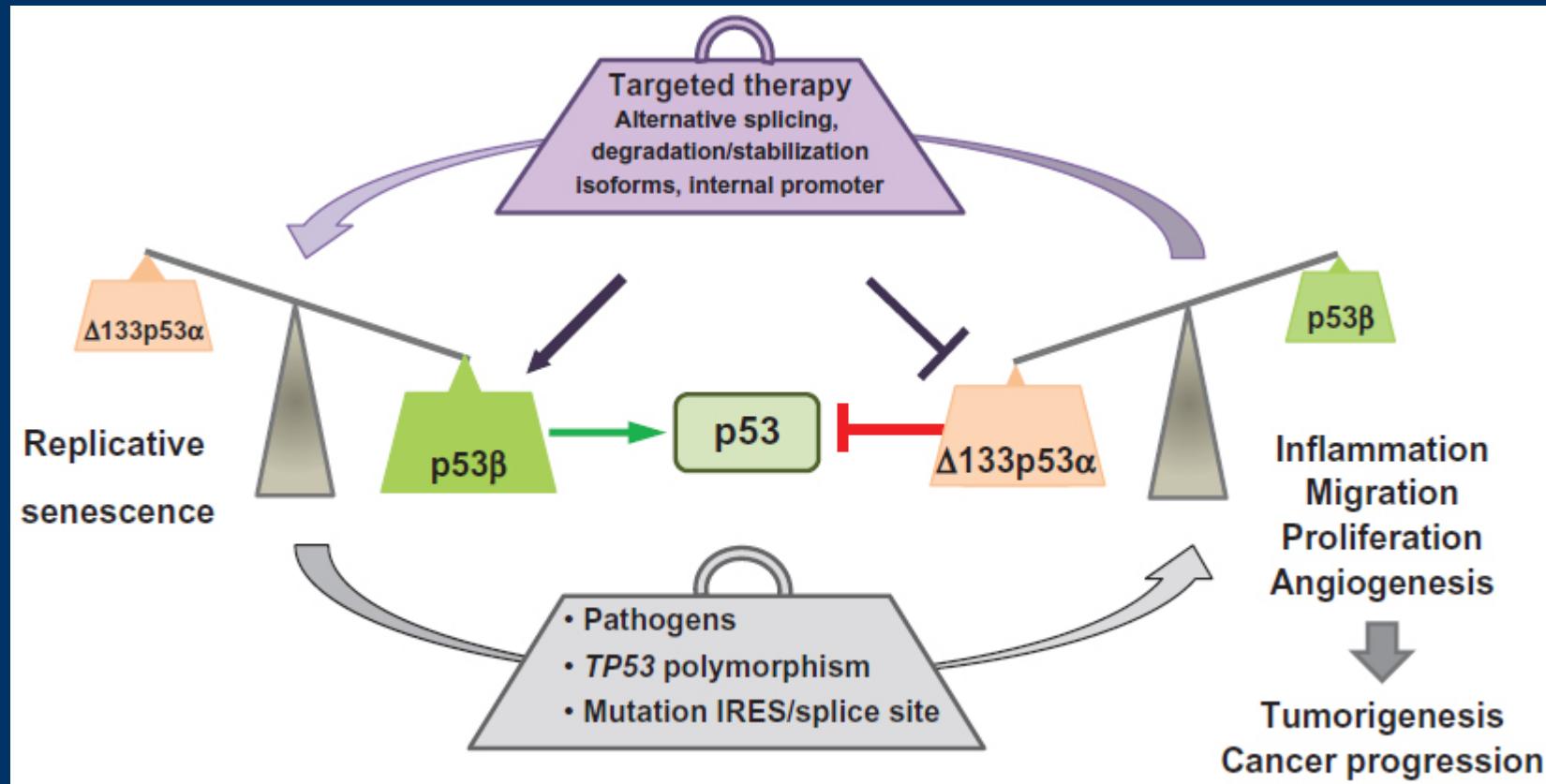
p53 locus and mRNA Isoforms



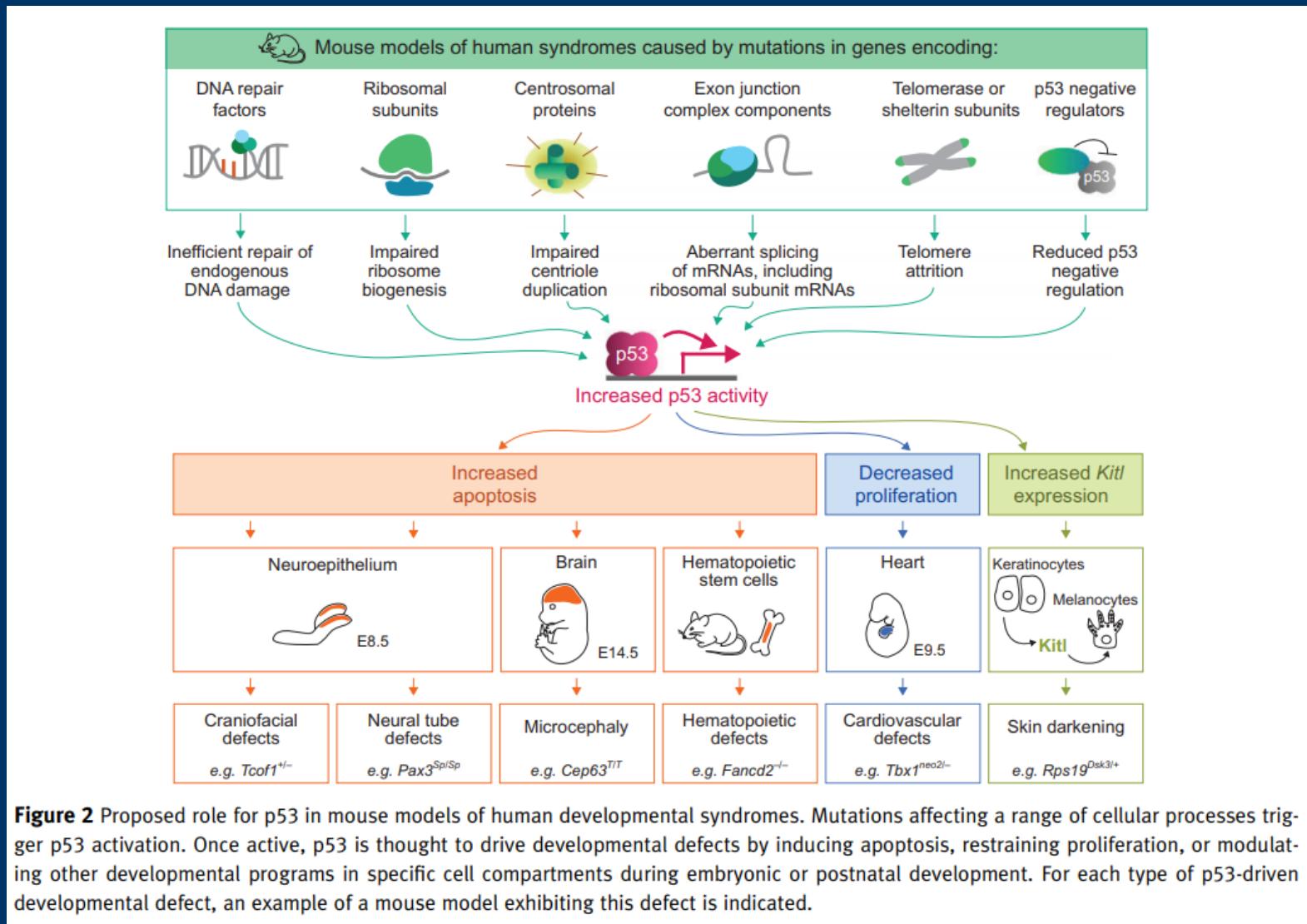
p53 Concensus Protein Isoforms In 2017



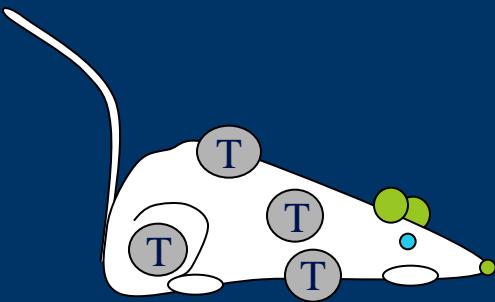
Role of p53 Splice Variants in Human Malignancy



The role of p53 in developmental syndromes



TP53 Family Members: Different Functions

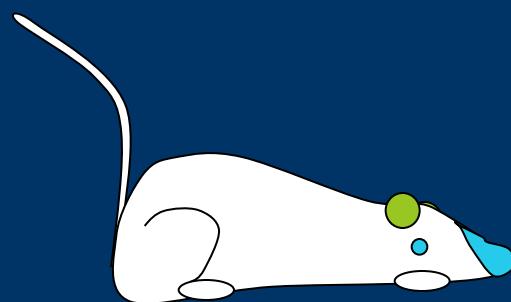


TP53

17p13(h)

23% female death by
exencephaly

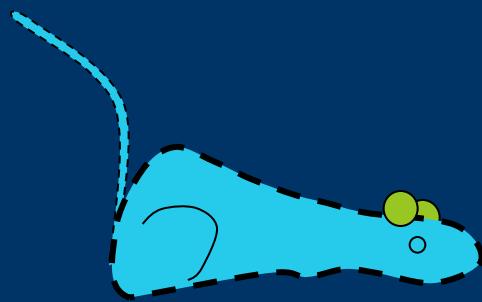
**High frequency of
tumor development**



TP73

1p36(h)

**hydrocephalus,
chronic infections,
inflammation,
abnormalities in
pheromone sensory
pathways**



TP63

3q27-28(h)

**Defects in the limb,
craniofacial and
epithelial development.**

No Skin!

TP53 Family Members: Mutations In Human Diseases



TP53

17p13(h)

Somatic mutations frequent in almost all cancer types

Germline mutations cause Li-Fraumeni syndrome

TP73

1p36(h)

LOH or isoforms overexpression in some tumor types, but no somatic mutation

No disease causing germline mutation

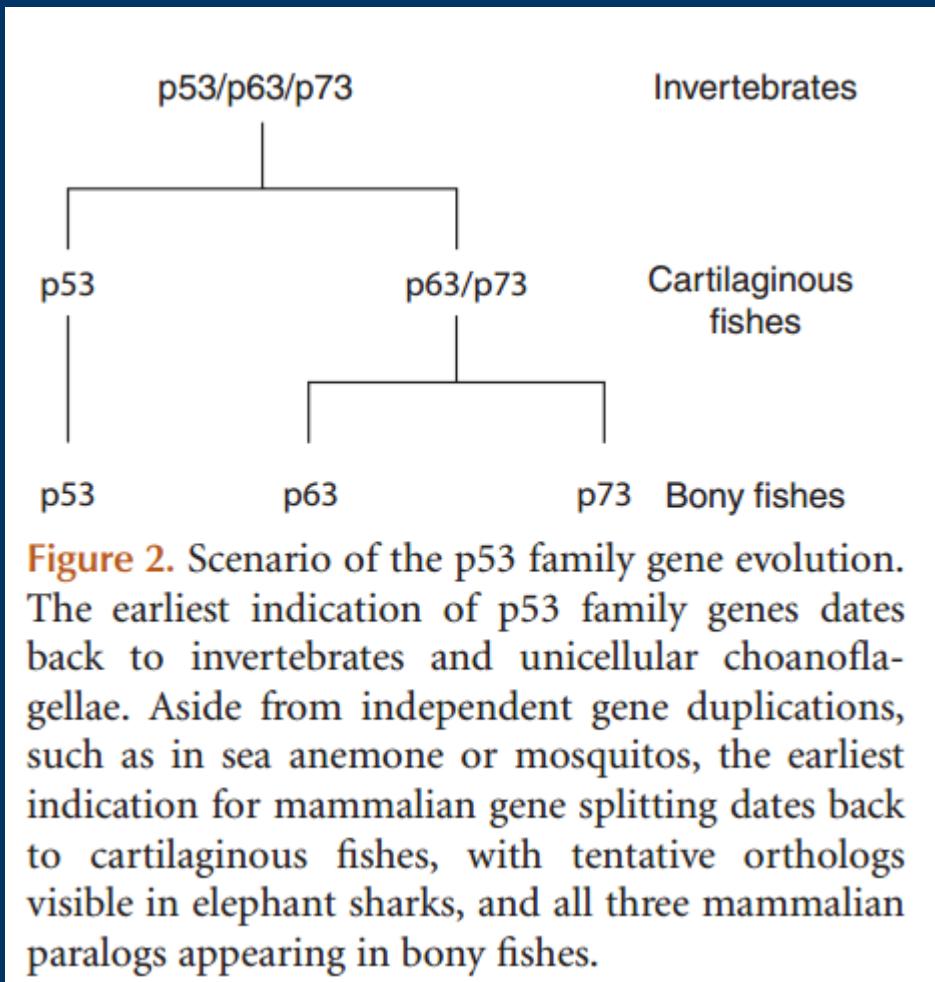
TP63

3q27-28(h)

Isoforms overexpression in some tumor types, but no somatic mutation

Germline mutations cause developmental disorders but not cancer

Origin and Evolution of TP53 Family

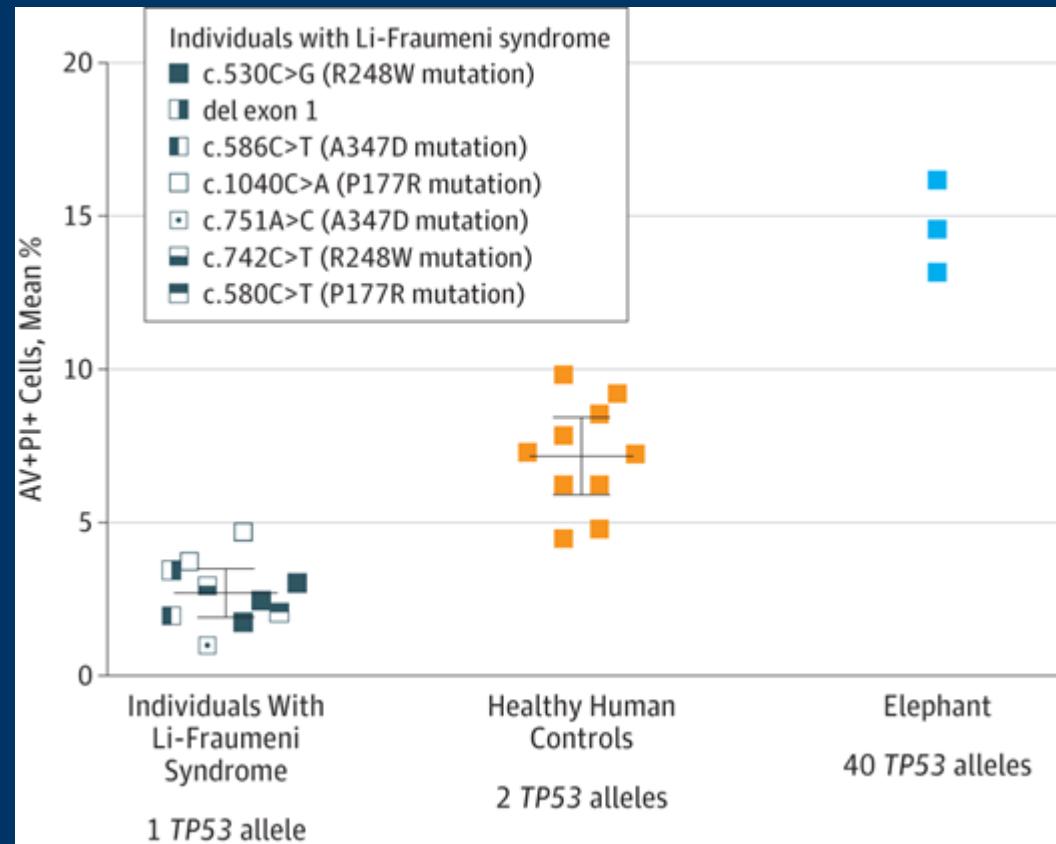


An Elephant in the Room!

Elephant cells have 40 copies of *TP53* gene

Compared with other mammalian species, elephants appeared to have a lower-than-expected rate of cancer.

Compared with human cells, elephant cells demonstrate increased apoptotic response following DNA damage.



Abegglen et al., JAMA, 2015

2009: 30 years of p53

- 1979: discovery
- 1983: defined as an oncogene
- 1985: cloning of the human gene
- 1989: the WT form is defined as a tumor suppressor
- 1989: LOH and first mutations identified in cancer
- 1990: TP53 is constitutively mutated in Li-Fraumeni syndrome
- 1990: p53 is a transcription factor
- 1991: participation of p53 in the cellular response to DNA damage
- 1991: p53 induces apoptosis
- 1991: selective G to T mutation of TP53 gene in HCC from Africa
- 1992: TP53^{-/-} mice develop tumors spontaneously
- 1993: p53 induces G1 arrest *via* p21Waf1
- 1993: TP53 mutation is associated with poor prognosis in breast cancer
- 1994: crystal structure of p53 in complex with DNA
- 1996: p53 is induced by hypoxia
- 1997: role of mdm2 in the regulation of p53 stability demonstrated in mice
- 1997: TP73, first TP53 related gene discovered
- 1999: 10,000 human mutations described
- 1999: p53 plays a role in DNA repair
- 2002: constitutive expression of p53 accelerates ageing in mice
- 2002: discovery of a N-terminally truncated variant of p53
- 2003: p53 plays a role in global chromatin remodelling
- 2004: wt p53 and mutant p53 are targeted for cancer therapy
- 2005: description of nine p53 protein isoforms
- 2006: p53 plays a direct role in cellular metabolism
- 2007: p53 regulation of microRNAs, a new layer of complexity in the p53 network
- 2008: a dual role for p53 in autophagy is described
- 2009: p53 deficiency help cellular reprogramming and stem cells production

TP53: the most popular gene ever!

THE TOP 10

The ten most studied genes of all time are described in more than 40,000 papers.

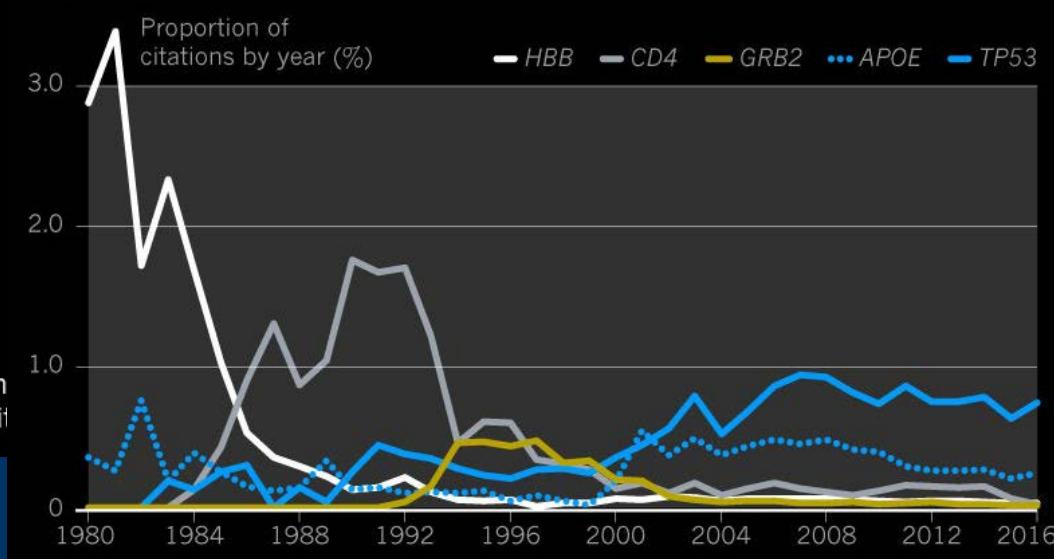
1	<i>TP53</i>	8,479 citations
2	<i>TNF</i>	5,314
3	<i>EGFR</i>	4,583
4	<i>VEGFA</i>	4,059
5	<i>APOE</i>	3,977
6	<i>IL6</i>	3,930
7	<i>TGFB1</i>	3,715
8	<i>MTHFR</i>	3,256
9	<i>ESR1</i>	2,864
10	<i>AKT1</i>	2,791

1 TP53

The tumour-suppressor p53 is mutated in up to half of all cancers.

616

Interleukin
in immuni



NEWS FEATURE • 22 NOVEMBER 2017

The most popular genes in the human genome

A tour through the most studied genes in biology reveals some surprises

The IARC TP53 Database

A Locus Specific Database To Study TP53 Gene Variations In Human Cancers

International Agency for Research on Cancer

World Health Organization

IARC TP53 Database

ABOUT DATA USER'S HELP DATABASE RESOURCES REFS CORNER LINKS

chr17:7571720-7590863 19,144 bp. TP53 (Homo sapiens tumor protein p53 (TP53), transcript variant go

QUICK LINKS

- Search mutation
- Search cell-line
- TP53 reference sequences
- Downloads
- User manual
- Protocols and tools

Why Study TP53 Mutations?

TP53 somatic mutations are frequent in most types of **sporadic human cancers** (frequencies vary from 5% to 70% depending on cancer type and stage).

TP53 mutations may also be inherited in families with a predisposition to multiple cancers, as in the **Li-Fraumeni syndrome** (LFS).

In several cancers, the nature of TP53 mutations and their distribution along the coding sequence have allowed the identification of **tumor-specific mutation spectra**, revealing clues on the mechanisms that might have caused the mutation.

Different types of mutation have different phenotypes.

The presence of a TP53 mutation may be **predictive** of the tumor response to treatment and patient survival.

The IARC Database: Information System For TP53 Mutations

- Extract TP53 mutation data from publications
- Organize and annotate data into a format that allows easy retrieval and analysis
- Provide a web-based tool to analyse TP53 mutation patterns in cancers

SCIENTIFIC LITERATURE – WEB
Data & Knowledge

- Extraction
- Annotation
- Integration

IARC TP53 DATABASE

- Interfacing

IARC TP53 WEBSITE
Public release of structured data and knowledge

Data Available

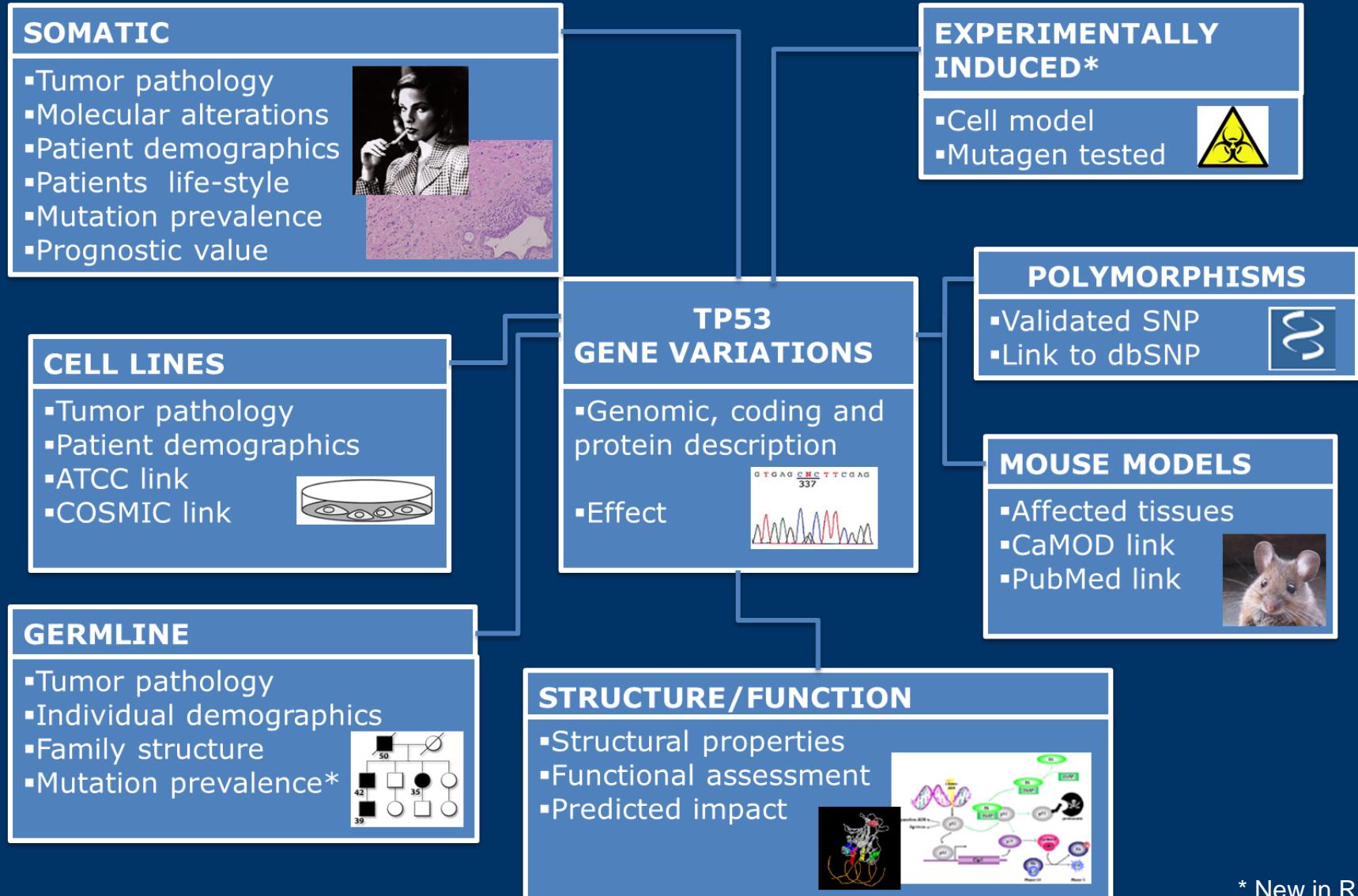
- Somatic mutations in human sporadic cancers
- Germline mutations and Li-Fraumeni syndrome
- Polymorphisms in human populations
- TP53 status of human cell-lines
- Functional assays of mutant proteins
- Structural properties of mutant proteins
- Mouse-models with engineered TP53 gene
- Experimentally-induced mutations

Criteria For Inclusion

- TP53 **somatic mutations** associated with human sporadic cancers that have been **identified by sequencing** and published in peer-reviewed literature. This includes mutations found in normal, pre-neoplastic and neoplastic tissues, including metastases, as well as in cell-lines derived from such tissues
- Human TP53 **germline mutations** (identified by sequencing and published in peer-reviewed literature) in individuals affected or not by a cancer
- p53 mutants that have been tested in human cells or yeast assay for **functional activities** such as specific DNA-binding, transcriptional activation, dominant-negative effects on the wild-type protein, gain of function...
- **Mouse-models** with engineered TP53 gene that are included in caMOD database or have been reported in peer-reviewed literature.
- **Experimentally-induced mutations** obtained in the Hupki mouse models or a yeast assay of mutagenesis

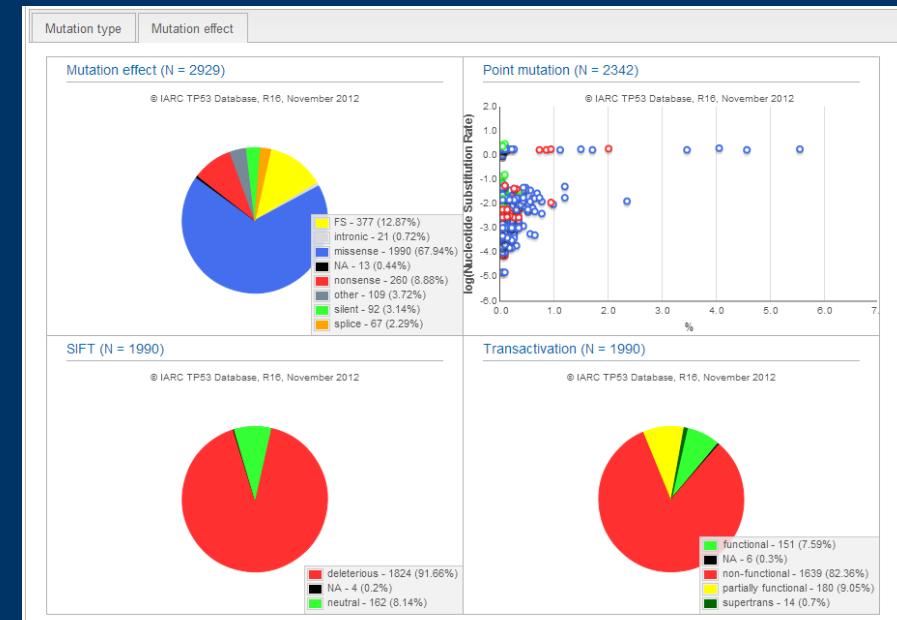
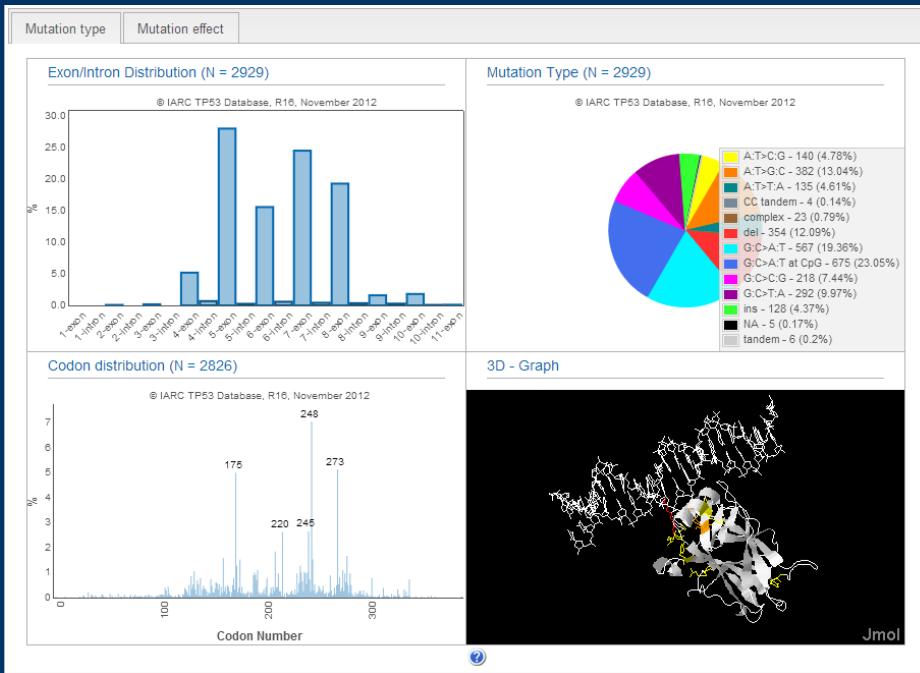
Database Structure And Contents

Detailed annotations and contents are available at <http://p53.iarc.fr/Manual.aspx>



* New in R17

Web Analysis Tools



Show 50 entries

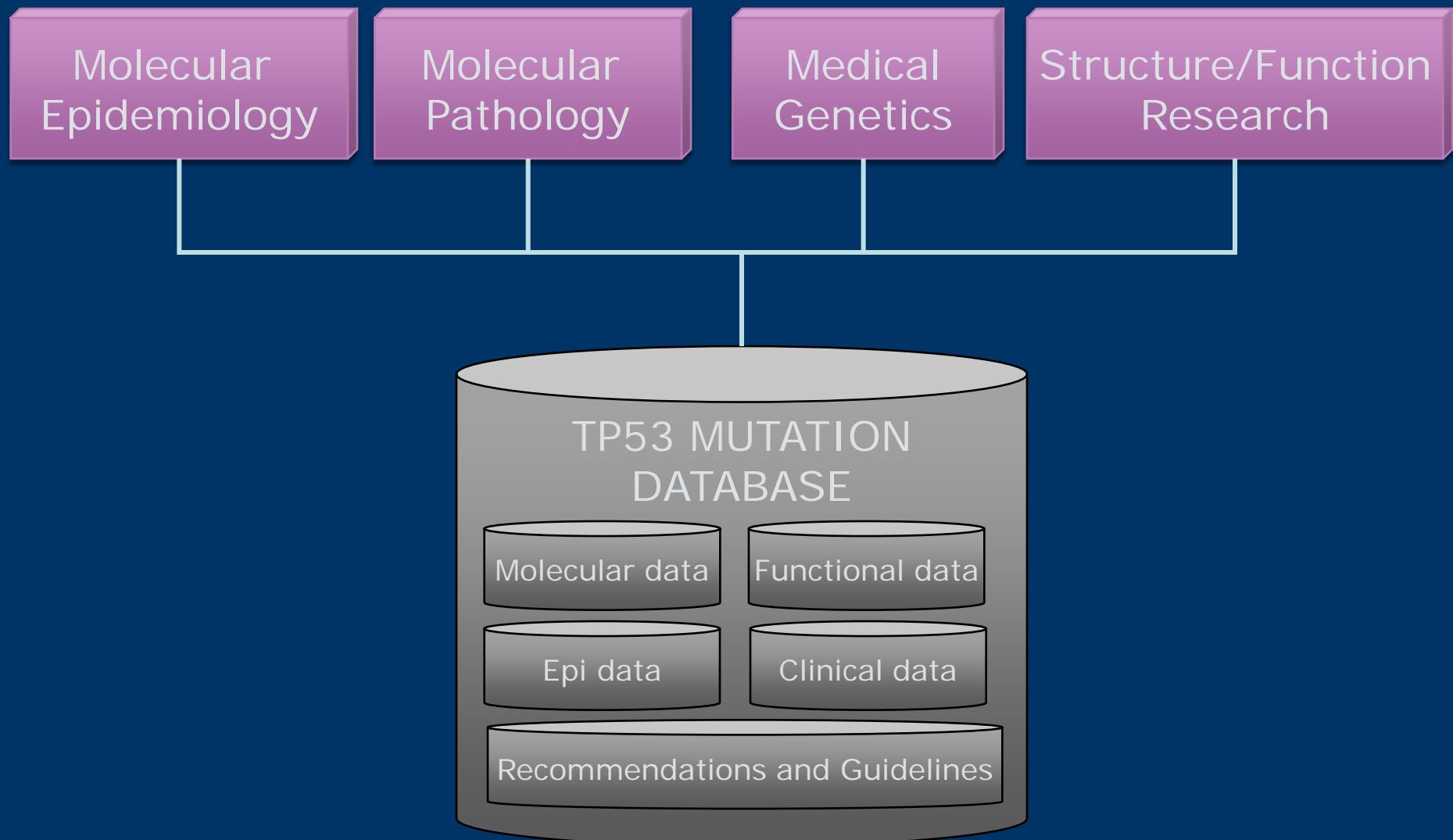
Search:

	Genomic description (hg38)	cDNA description	Protein description	Exon number	Effect	TA Class	Align-GVGD Class	Somatic count	Germline count	CellLine count	TCGA ICGC GENIE count	CLINVAR link	COSMIC link	Validated SNP	dbSNP link	gnomAD link
<input checked="" type="checkbox"/>	g.7675088C>T	c.524G>A	p.R175H	5-exon	missense	non-functional	C25	1216	59	79	1000	12374	10648	no	28934578	yes
<input checked="" type="checkbox"/>	g.7674220C>T	c.743G>A	p.R248Q	7-exon	missense	non-functional	C35	937	48	116	651	12356	10662	no	11540652	yes
<input checked="" type="checkbox"/>	g.7673802C>T	c.818G>A	p.R273H	8-exon	missense	non-functional	C25	858	51	83	635	12366	10660	no	28934576	yes
<input checked="" type="checkbox"/>	g.7674221G>A	c.742C>T	p.R248W	7-exon	missense	non-functional	C65	739	49	56	528	12347	10656	no	121912651	yes
<input checked="" type="checkbox"/>	g.7673803G>A	c.817C>T	p.R273C	8-exon	missense	non-functional	C65	707	27	59	665	43594	10659	no	121913343	yes
<input checked="" type="checkbox"/>	g.7673776G>A	c.844C>T	p.R282W	8-exon	missense	non-functional	C65	581	36	31	502	12364	10704	no	28934574	yes
<input checked="" type="checkbox"/>	g.7674230C>T	c.733G>A	p.G245S	7-exon	missense	non-functional	C55	456	45	31	288	12365	6932	no	28934575	yes
<input checked="" type="checkbox"/>	g.7674872T>C	c.659A>G	p.Y220C	6-exon	missense	non-functional	C65	402	17	26	329	127819	10758	no	121912666	yes
<input checked="" type="checkbox"/>	g.7674216C>A	c.747G>T	p.R249S	7-exon	missense	non-functional	C65	398	0	10	124	12352	10817	no	28934571	
<input checked="" type="checkbox"/>	g.7674894G>A	c.637C>T	p.R213*	6-exon	nonsense	NA	NA	329	19	25	430	43590	6503267	no	397516436	yes

Database Figures And Facts

- Database contents:
 - >29,000 somatic mutations
 - >1,500 germline mutations
 - >8,400 mutants with functional properties
 - >180 studies on TP53 mutation and clinical outcome
 - > Mouse models with engineered p53
 - > 900 experimentally-induced mutations linked to human exposures
 - Mutation occurrences in TCGA, ICGC and GENIE datasets
- Database usage
 - > 9,600 visits per month
 - > 700 downloads per month
 - > 6,300 citations in the scientific literature
 - Links with COSMIC, CLINVAR, dbSNP, gnomAD, ATCC, HGVS

IARC TP53 DATABASE: A Resource For Various Disciplines



TP53 Mutations In Human Cancers

Types Of Genetic Alterations In Cancer

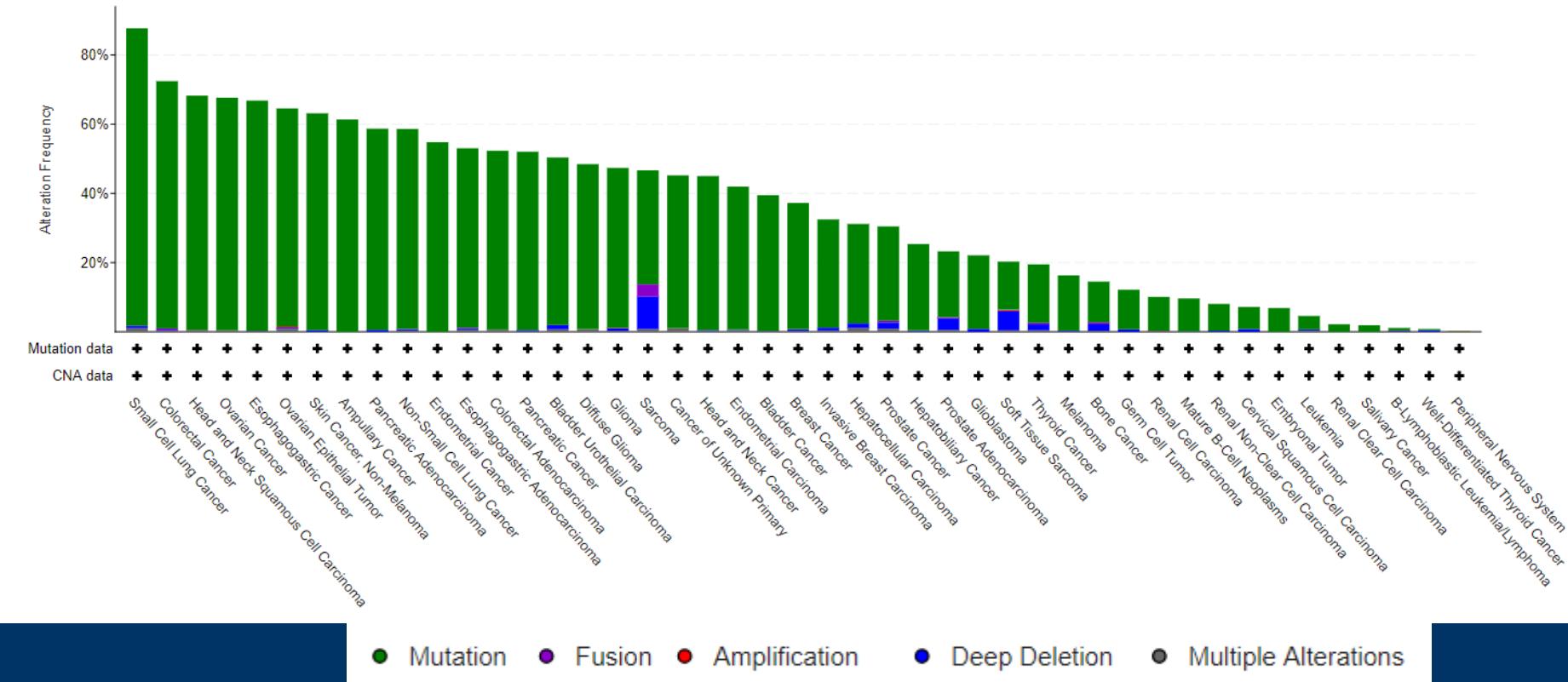
Somatic: Acquired during development and present only in cells undergoing clonal expansion

Inherited: present in the germline and detectable in both healthy and cancer cells

- Loss of parts or whole chromosomes
- Duplication of chromosomes
- Chromosome translocations
- Amplifications of chromosome fragments

- Intragenic deletions or insertions
- Recombination between adjacent genes
- Nonsense (Stop) mutations
- Missense mutations (substitutions)
- Methylation

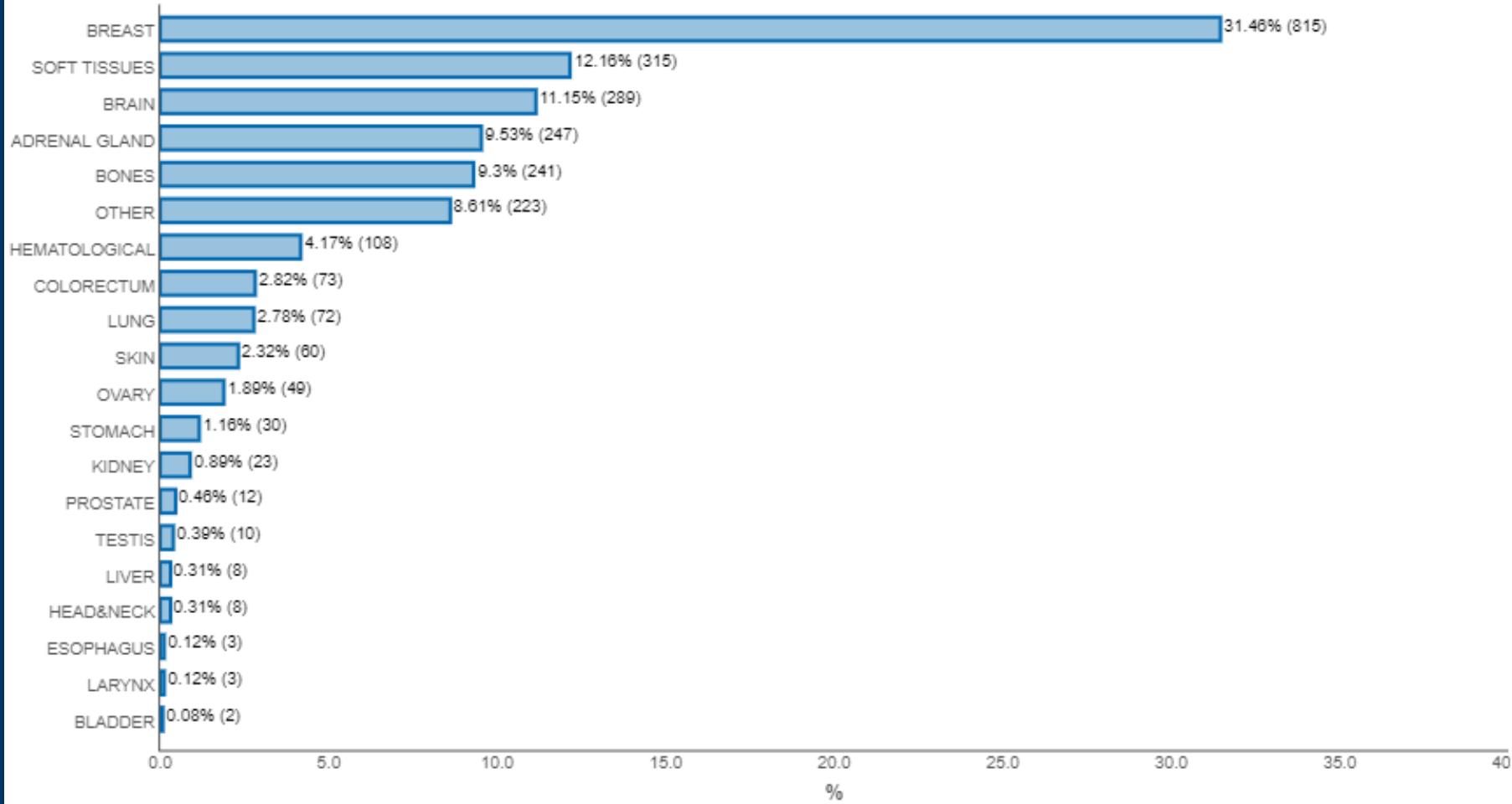
TP53 Somatic Alterations in Human Cancers: data from genomic studies



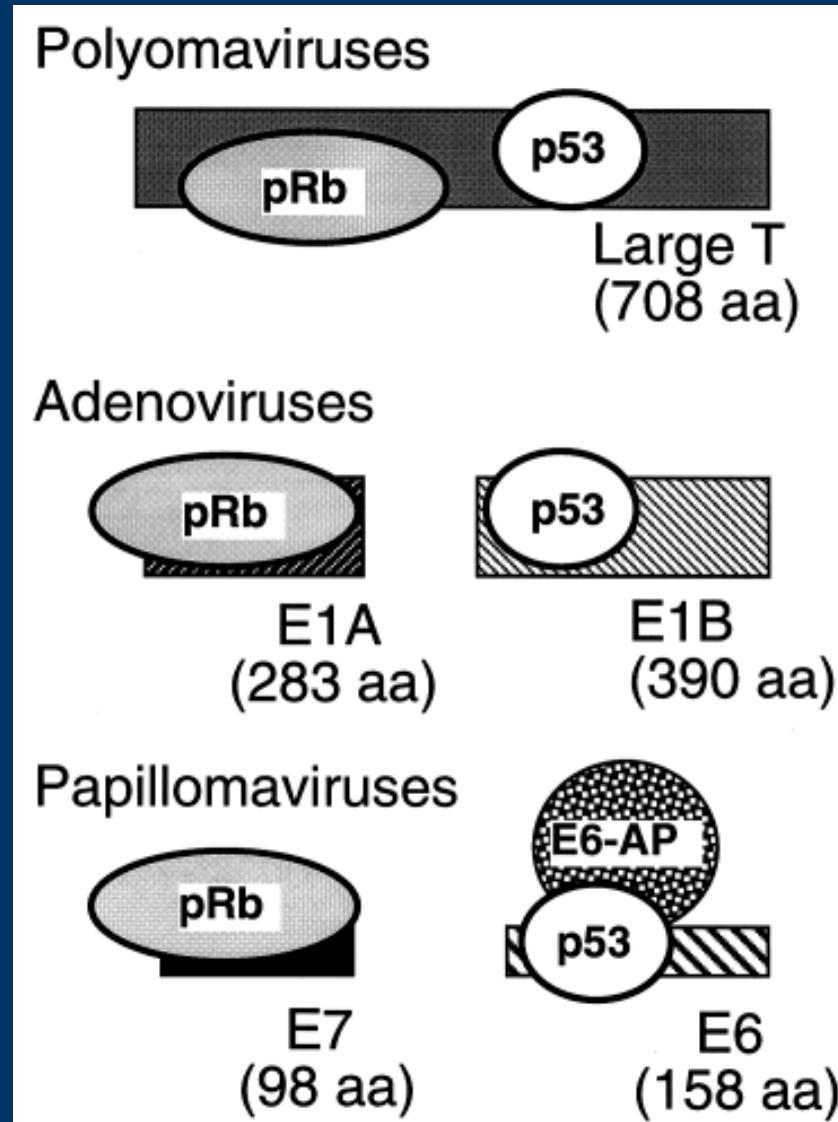
TP53 Germline Mutations Predispose To Several Types of Cancers

Tumors Associated with TP53 germline mutations (N = 2591)

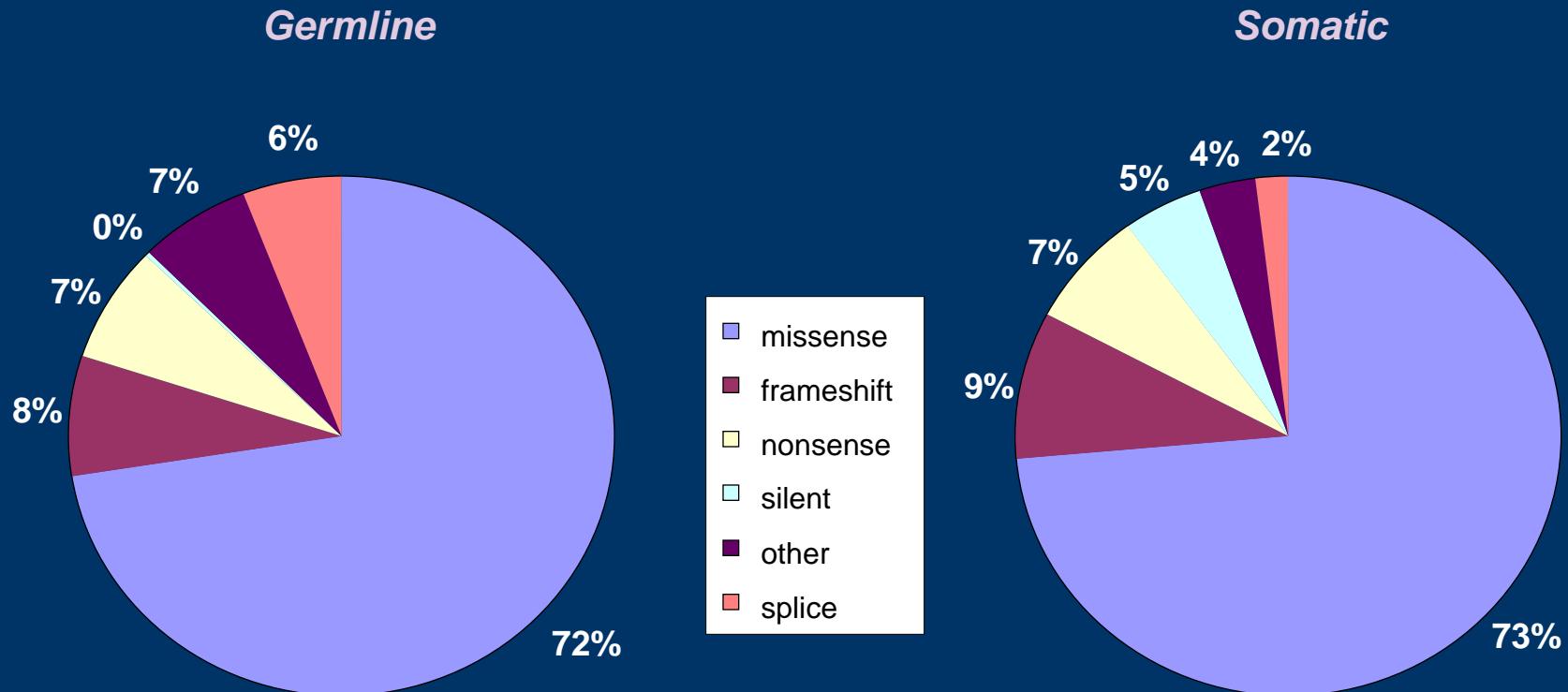
© IARC TP53 Database, R20.



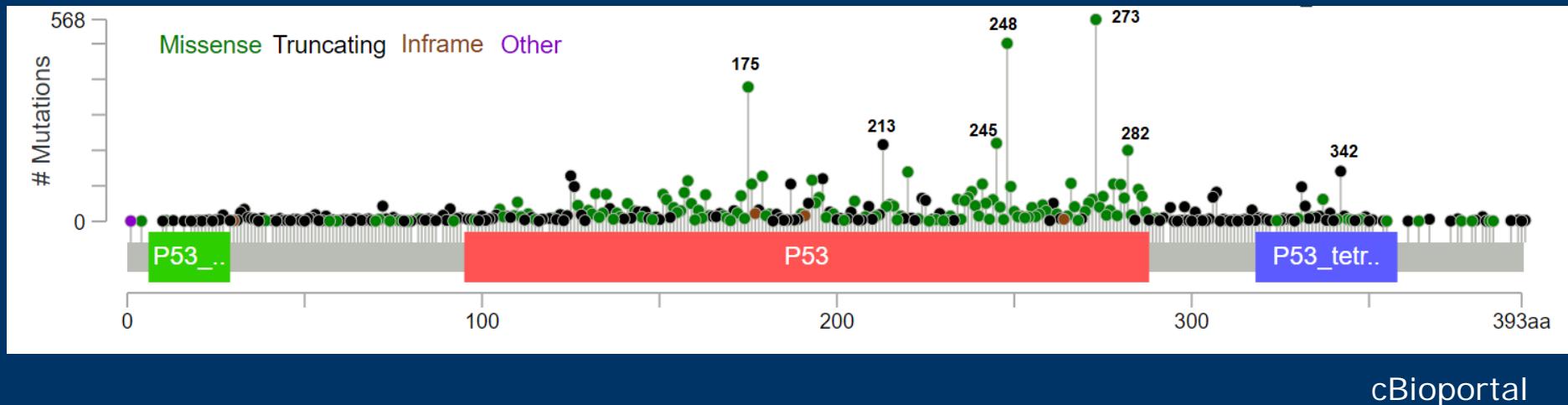
p53 Protein is Targeted by Viruses



The Majority Of TP53 Mutations Are Missense Mutations



Missense Mutations are Clustered in the DNA-binding Domain



cBioportal

Transactivation
(1-42; 43-62) Proline-rich
(65-97)

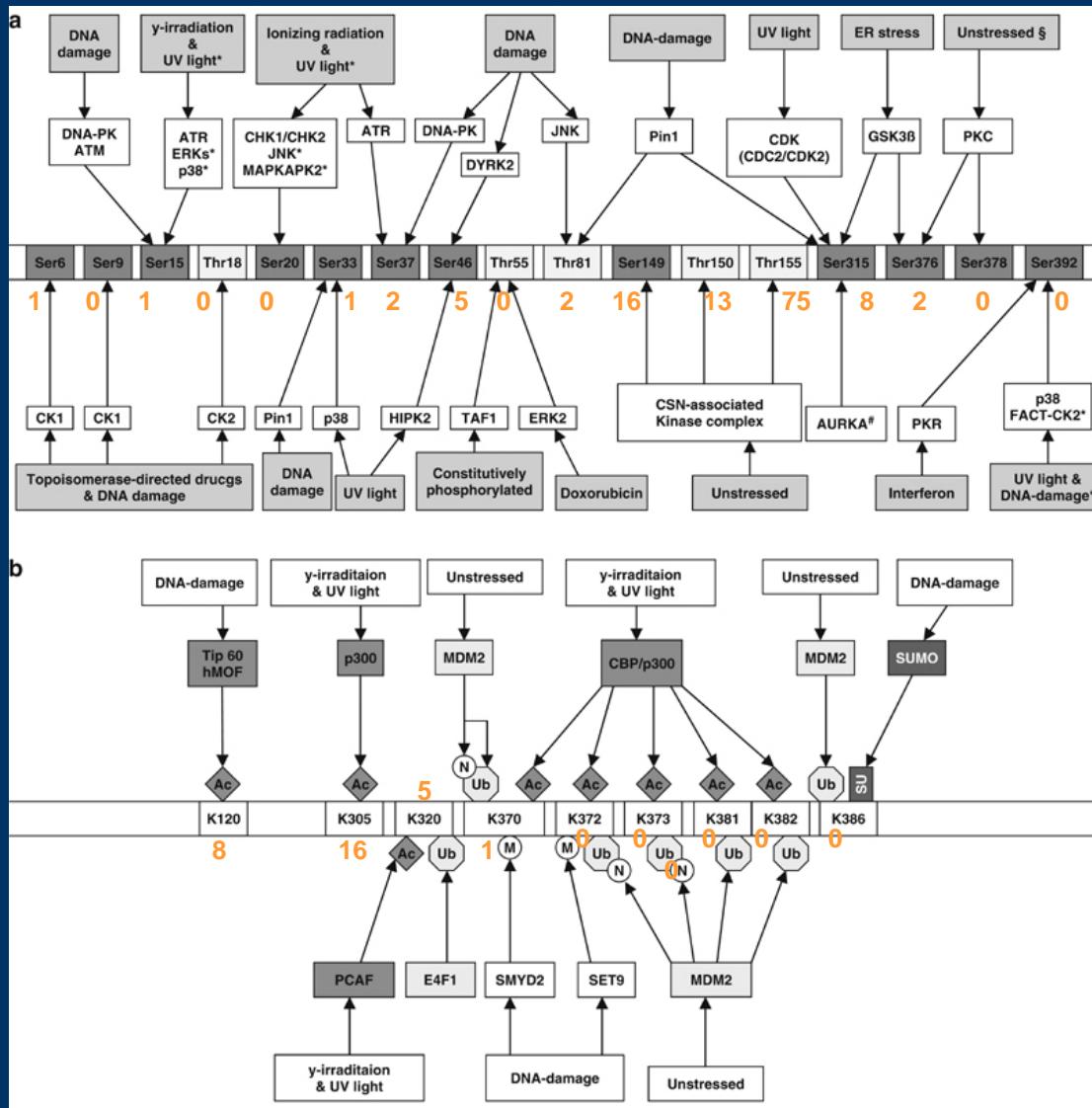
DNA binding
(102-292)

Oligomerisation
(323-356) Regulation
(363-393)

Mut. frequency	1 %	2.3 %	80 %	3.4 %	0.3%
Missense mut.	50.8 %	45.4 %	82.1 %	36.4 %	72.7 %

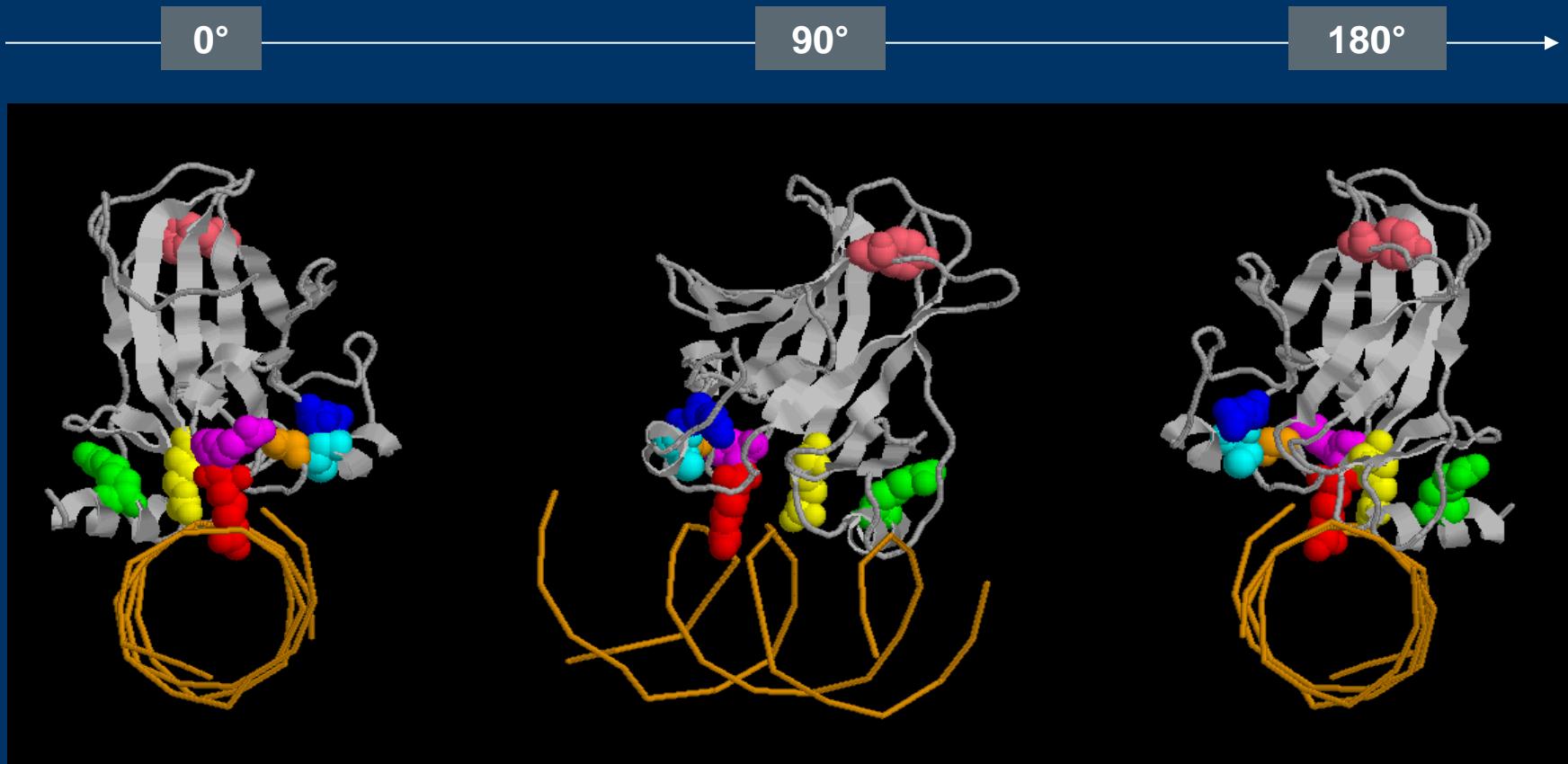
p53.iarc.fr

Post-Translational Modification Sites Are Rarely Mutated In Cancer



Number of missense mutations reported in sporadic cancers (IARC TP53 database, R12).

Most Frequent Mutations Are In The Loops That Make Contact With DNA



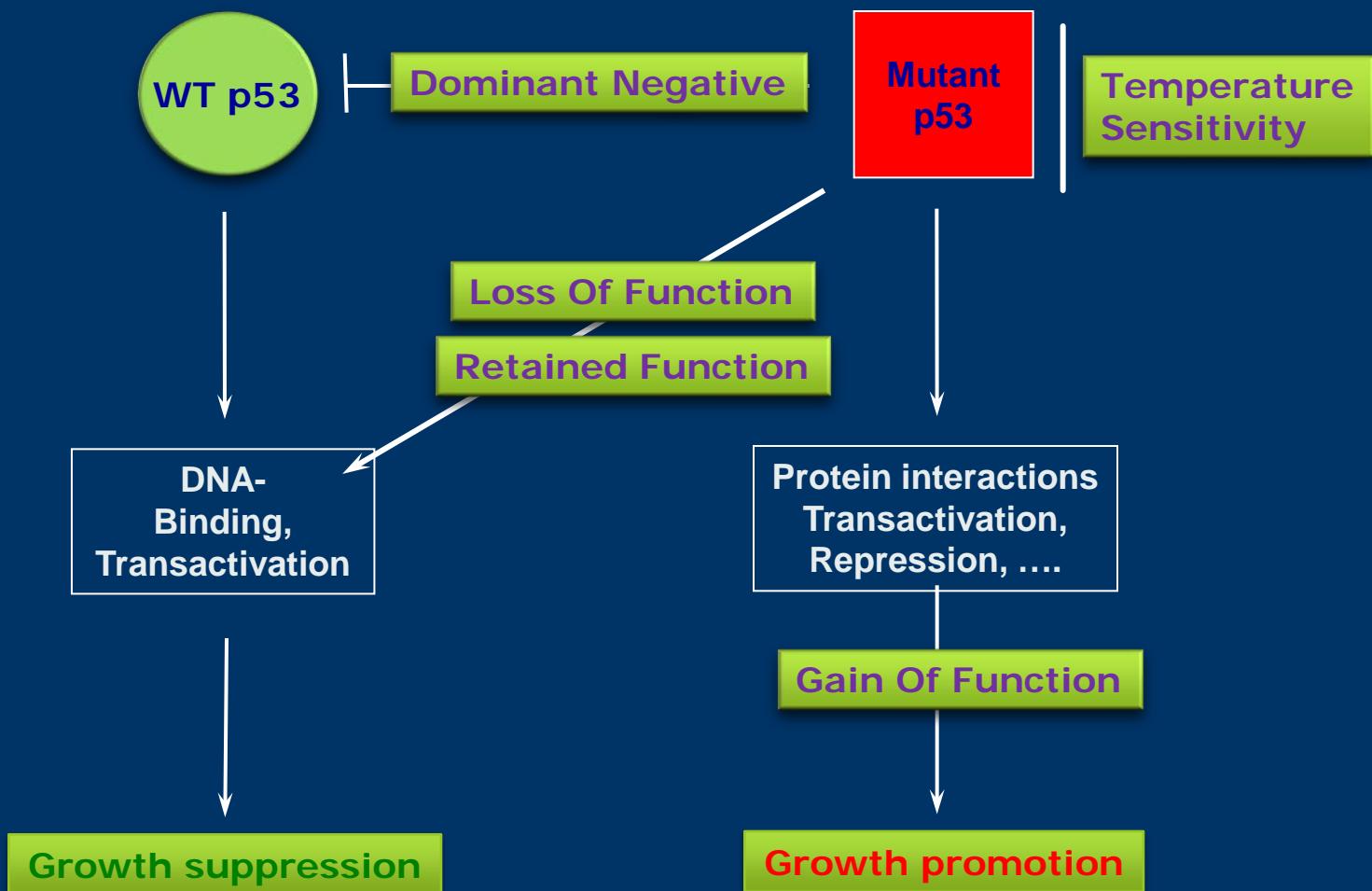
Codon: 175 > 248 > 273 > 282 > 249 > 245 > 220 > 176

Effects Of The Most Frequent TP53 Mutations

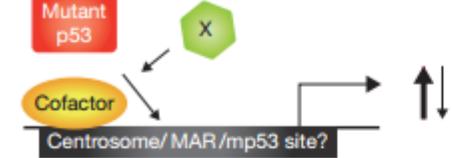
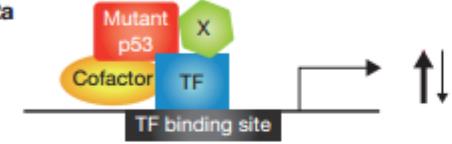
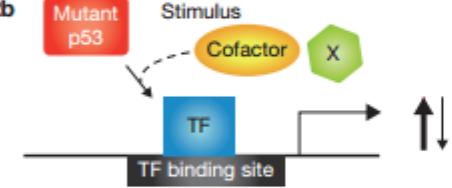
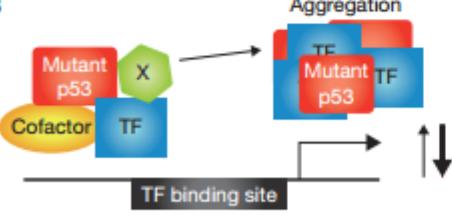
Mutations that represent about 20% of all mutations

Codon	Residue	Mutant	Effects on protein structure
175	Arg	His	Breaks crucial H-bond bridging loops L2 and L3
248	Arg	Gln	Breaks main contact with DNA in minor groove
273	Arg	His	Breaks main contact with DNA in major groove
248	Arg	Trp	Breaks main contact with DNA in minor groove
273	Arg	Cys	Breaks main contact with DNA in major groove
282	Arg	Trp	Destabilizes H2 helix and DNA binding in the major groove and breaks contacts on the β - hairpin

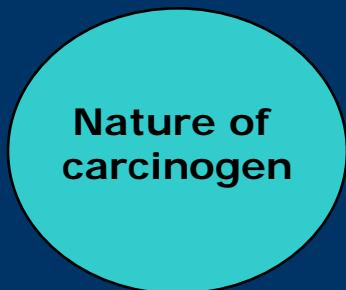
Biological Activities Of p53 Mutant Proteins



Models of Mechanisms Through Which p53 Mutants Function

Model	Description	Examples
1 	Mutant p53 interacts with DNA directly using mutant p53 binding elements or other regions on the DNA, including MARs, to regulate transcription. Transcriptional cofactors and other proteins can be involved.	● PML, EGR1, TOP1 ● p300
2a 	Mutant p53 enhances transcription by forming a complex with TFs that can include transcriptional cofactors and other proteins.	● EGR1, TopBP1, PIN1, VDR ■ ETS1, NF-κB, p63, p73, SP1, SREBP, NF-Y, ETS2 E2F1 ● p300, HDAC, CBP
2b 	In response to a stimulus, mutant p53 is recruited to a transcription regulatory complex that can include TFs, transcriptional cofactors and other proteins. This mostly results in activation of target gene expression.	● VDR, PLK2 ■ NF-Y, SP1 ● p300 stimulus: TPA, vitamin D, DNA damage
3 	Mutant p53 decreases transcription by binding TFs and/or transcriptional cofactors and other proteins, sometimes preventing their binding to DNA. This activity can also involve aggregation of mutant p53 with other proteins.	● TopBP1, ANKRD11, VDR, SMAD2 ■ p63, p73, SP1 ● p300
4 	Mutant p53 interacts with other proteins, not directly involved in transcriptional regulation, and enhances or blocks their function.	● NRD1, EFEMP2, TOP1, BTG2, MRE11

How to Interpret Mutation Patterns?



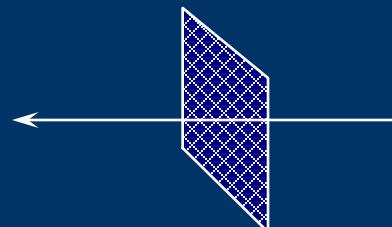
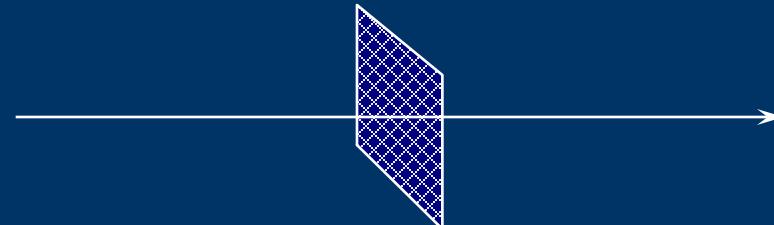
ADAPTATION

Effects of the mutation on cell behavior

Type of mutation
Position and sequence context
Strand bias/asymmetry

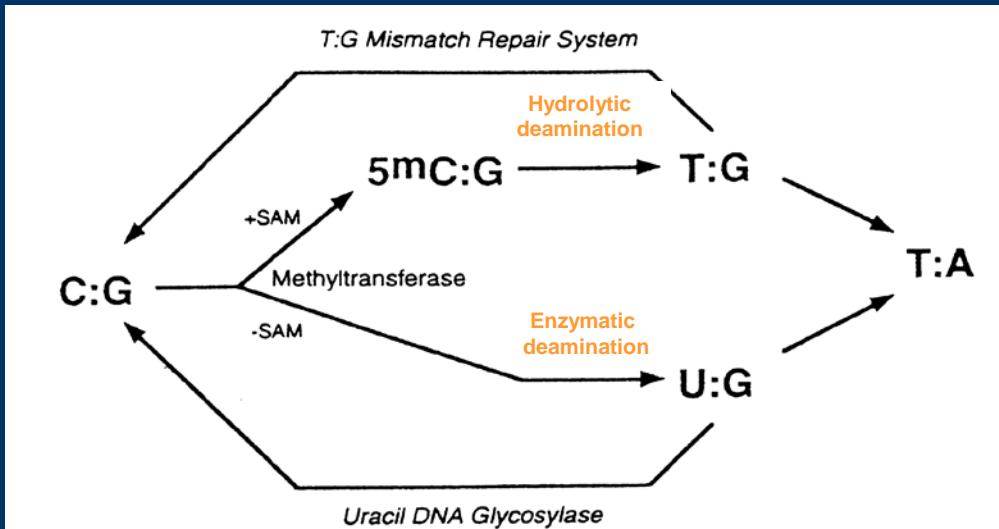
Metabolization and intracellular processing

Cellular strategies to cope with the lesion:
DNA repair



Sequence Context: CpG Mutations Are The Most Frequent Type Found In Human Cancers

C>T mutations occur frequently at CpG sites by endogenous mechanisms



Two possible pathways for C→T transition mutations.

From Yang et al., 1995

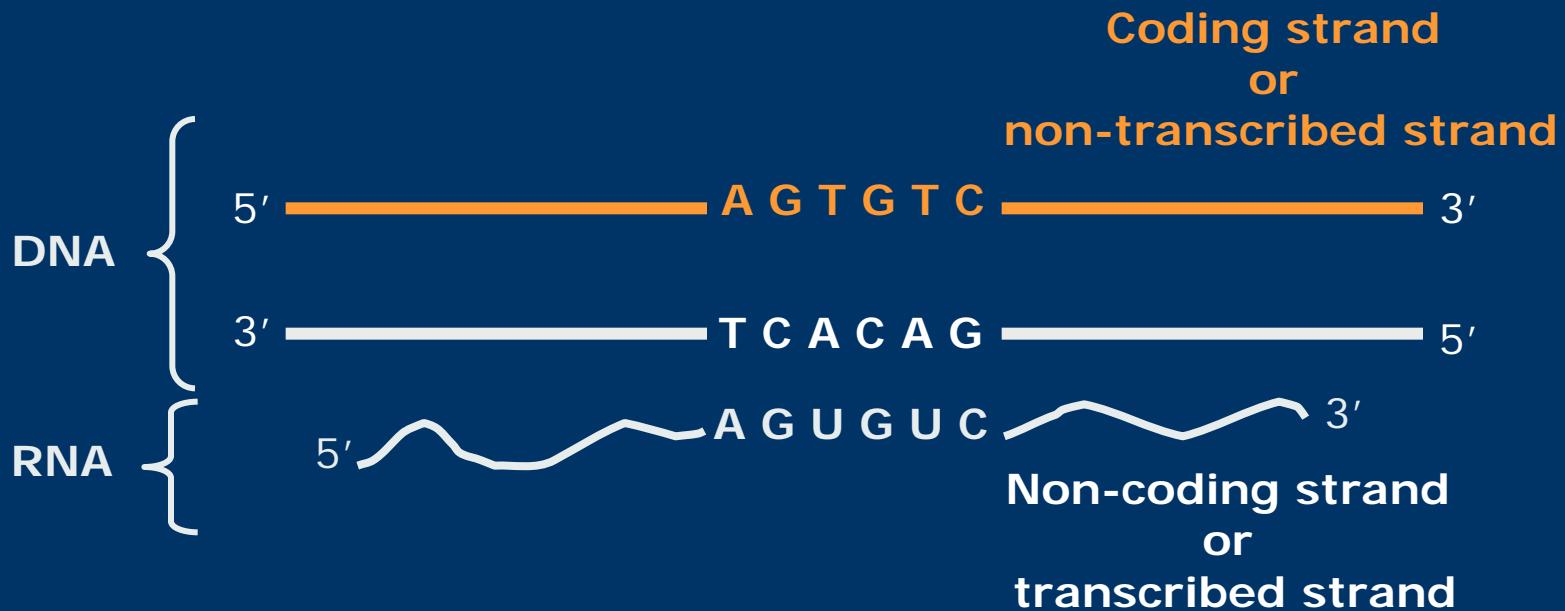
MUTATION PATTERN / 25715 mutations



Mutation Pattern	Count	Percentage
ins	709	2.75%
del	2214	8.60%
tandem	178	0.69%
CC tandem	180	0.69%
complex	138	0.53%
A:T>C:G	966	3.75%
A:T>G:C	2899	11.2%
A:T>T:A	1306	5.07%
G:C>A:T	5145	20.0%
G:C>A:T at CpG	6376	24.7%
G:C>C:G	1877	7.29%
G:C>T:A	3705	14.4%
NA	22	0.08%

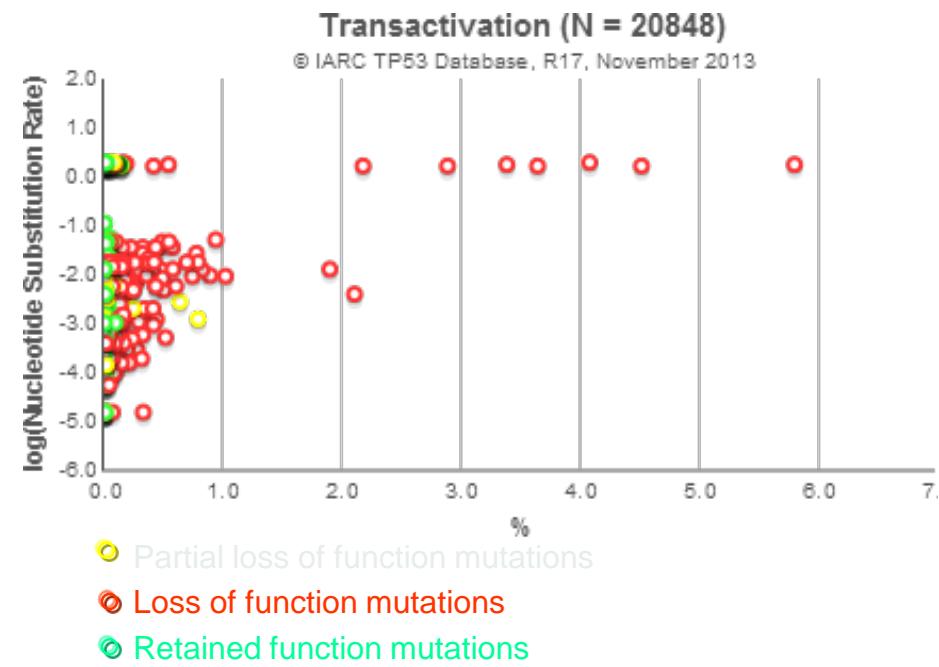
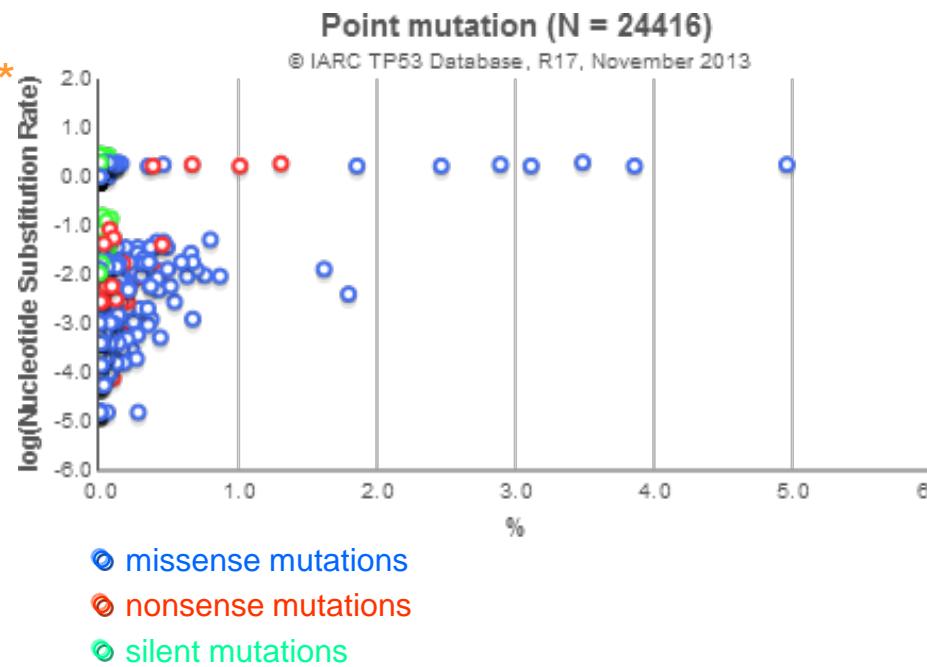
Strand Bias

There is a strand bias (or strand asymmetry) when a mutation event occurs preferentially on one strand of DNA



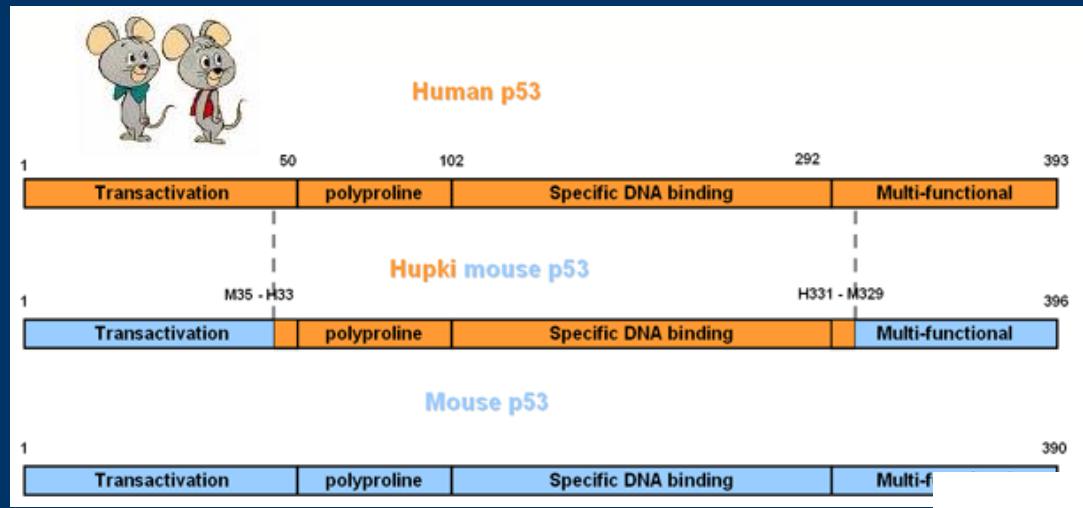
Interplay Between Mutagenesis And Biological Selection

Most frequent mutations are those arising from mutation events with high dinucleotide substitution rates and that produce non-functional proteins.



- * Substitution rates calculated according to dinucleotide substitution rates derived from human-mouse aligned sequences of chromosomes 21 and 10 ([Lunter and Hein 2004](#)) represent an estimate of the expected frequency of mutation events.

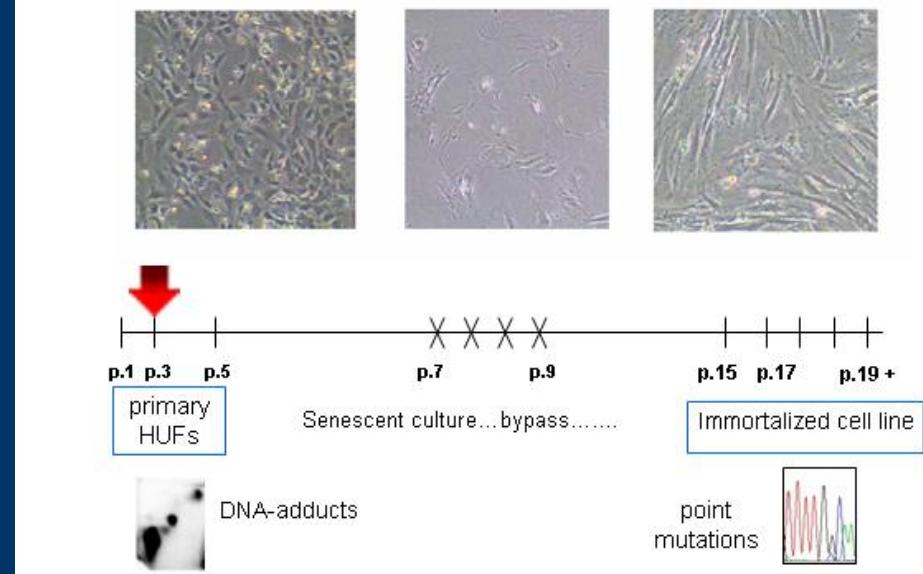
The Hupki Mouse And HUF Assay: New Tools To Investigate Human p53 Mutagenesis *In Vivo*



(Hupki) HUF Mutagenesis assay

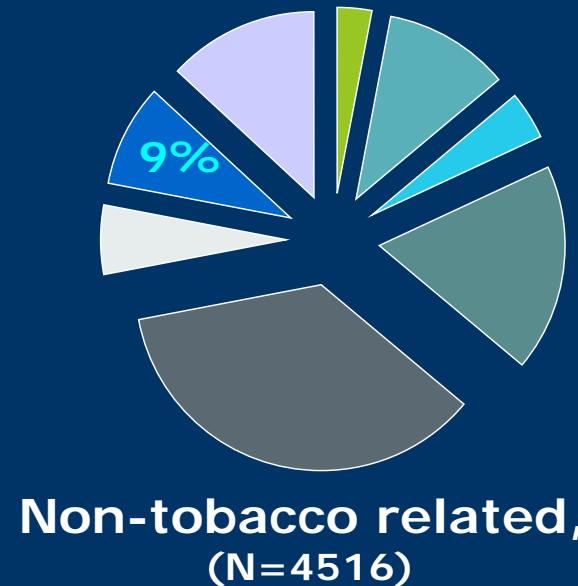
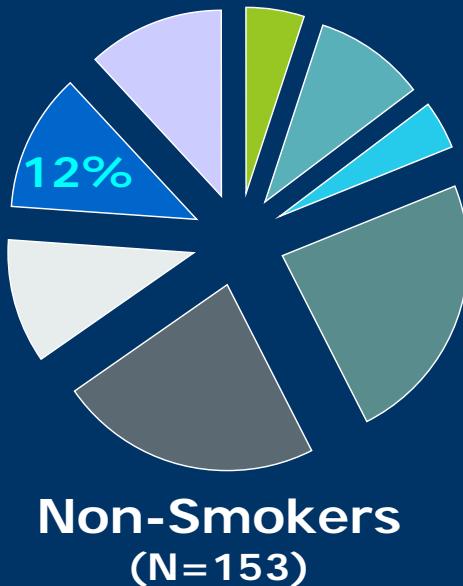
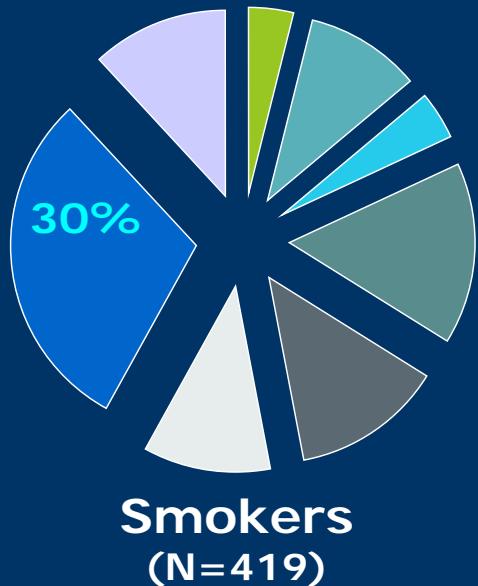
HUF is an embryonic fibroblast immortalization assay that uses cells from the Hupki mice, which can be used as an *in vitro* approximation of p53 gene mutagenesis in human cancer development.

Adapted from Hollstein



A Specific Mutation Pattern In Lung Cancer From Smokers

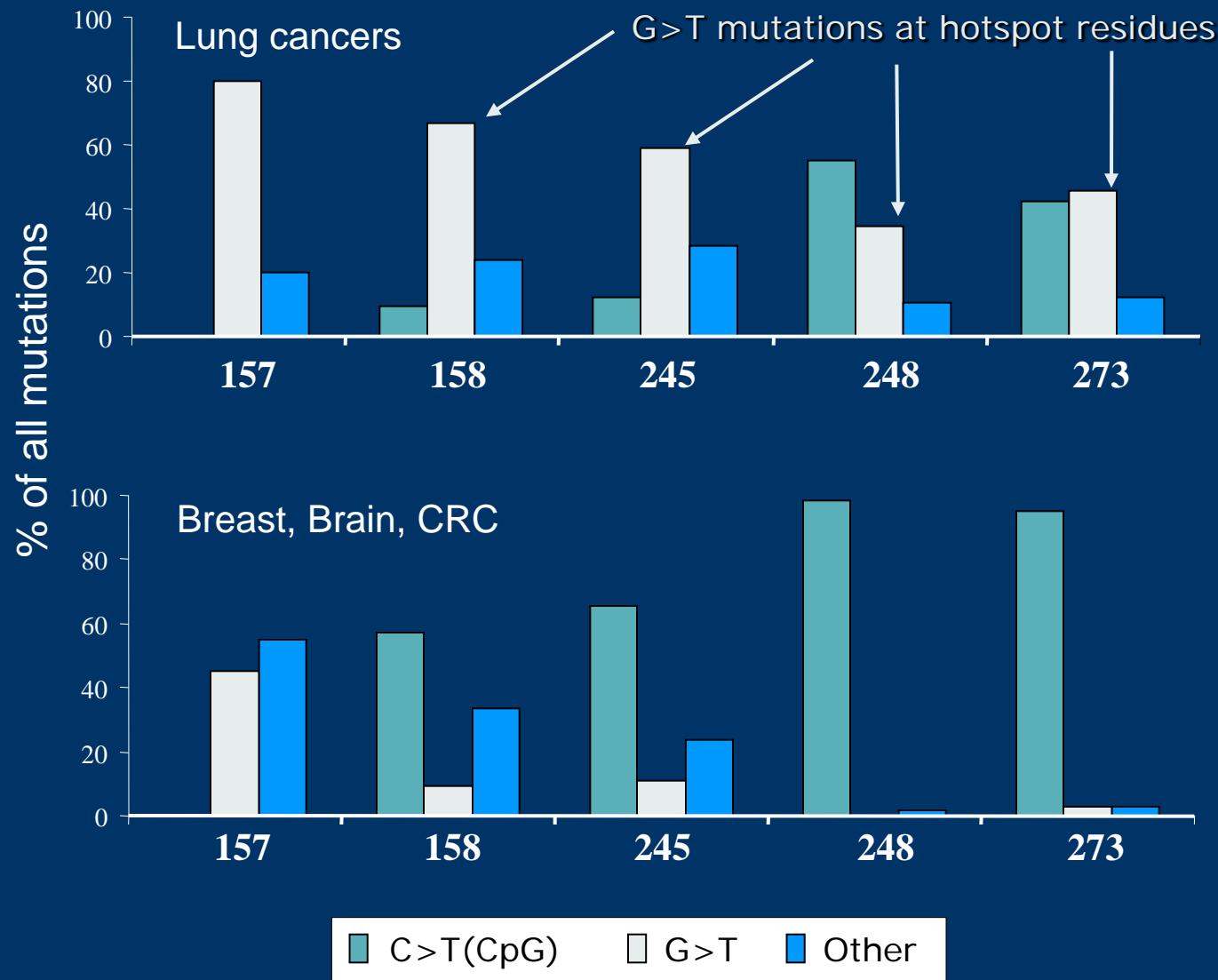
G:C>T:A



G>T mutations are more frequent in lung cancers from smokers than in non-tobacco related cancers.

Adapted from Pfeifer et al. Oncogene (2002)

Mutagenesis And Selection in Lung Cancer



Adapted from Pfeifer et al. Oncogene (2002)

Tobacco carcinogens



Enlarged view of air sacs (alveoli)



Damaged
air sacs
(alveoli)

Cigarettes contain many hazardous substances that damage the lungs when inhaled



4-Aminobiphenyl

2-Naphthylamine

Benzo(a)pyrene

Concentration/cigarette

15-40 mg

10-23 mg

100-600 mg

20-50 mg

0-200 ng

1.3-16 ng

20-70 ng

2.4-4.6 ng

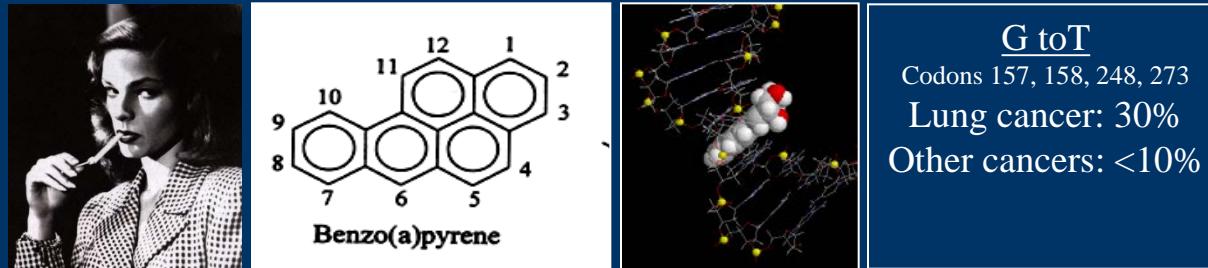
1.7-22 ng

20-40 ng

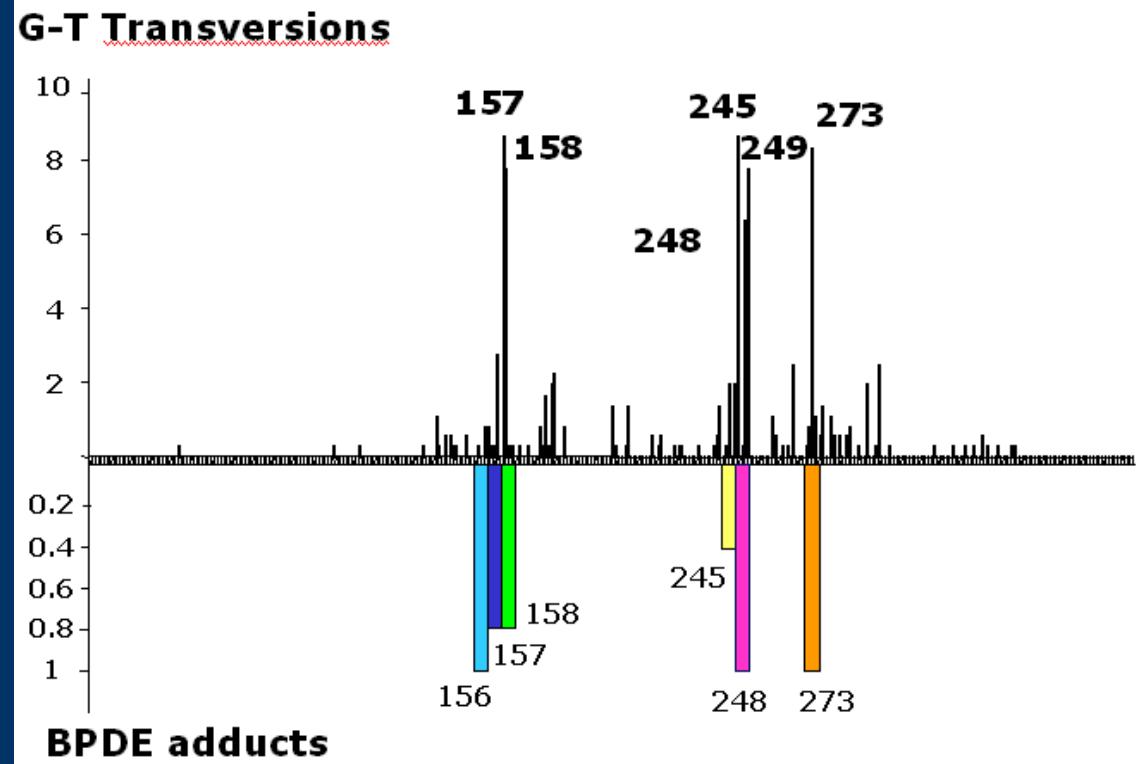
Source: IARC monograph vol38

TP53 Mutations Hotspots In Lung Tumors Of Smokers Coincide With Experimentally Induced B(a)P Adducts

**Benzo(a)
pyrene**

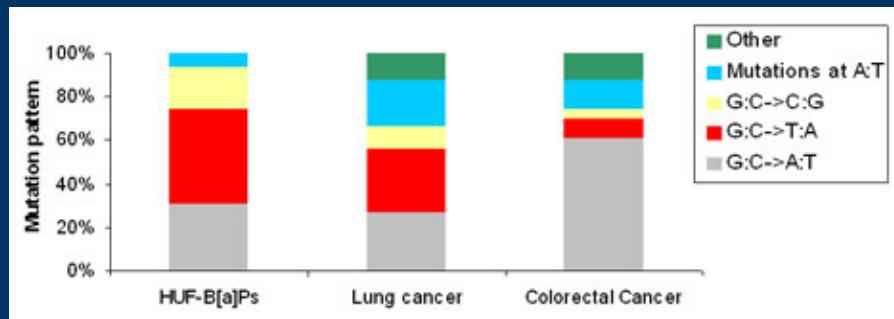


G to T
Codons 157, 158, 248, 273
Lung cancer: 30%
Other cancers: <10%



From Pfeifer et al.

TP53 Mutations Induced By B(a)P In the HUF assay Are Similar To The One Found In Lung Tumors Of Smokers



From Hollstein et al.

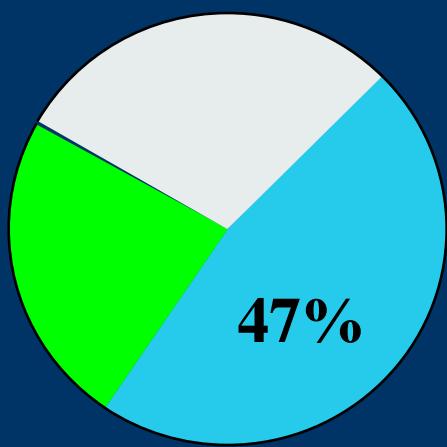
Table 1. *p53* gene mutations in HUF cell lines derived from BaP-exposed and untreated primary cells

Cell line	Base change*	Amino acid substitution	Lung cancer <i>p53</i> mutation [†] (rank) [‡]
Bap-treated[§]			
HUF-BaP-4	GCC to GGC (C to G)	A 138 G	
	GTC to GTT (C to T)	V 157 V	✓
	CGC to CCC (G to C)	R 158 P	✓
HUF-BaP-13	CGT to CAT (G to A)	R 273 H	✓
HUF-BaP-14	GGG to TGG (G to T)	G 117 W	
HUF-BaP-D14B	GTC to TTC (G to T)	V 157 F	(2nd)
HUF-BaP-15	g to t (G to T)	(intron 7) [¶]	✓
HUF-BaP-16	GAG to GAA (G to A)	E 224E [¶]	
HUF-BaP-20	g to c (G to C)	(intron 5) [¶]	
HUF-BaP-28	GTC to GTT (C to T)	V 157 V	✓
	CGC to CTC (G to T)	R 158 L	(1st)
	g to t (G to T)	(intron 5) [¶]	✓
	g to t (G to T)	(intron 5) [¶]	✓
HUF-BaP-48			
HUF-BaP-106	AGA to GGA (A to G)	R 280 G	✓
HUF-BaP-116	CCT to TCT (C to T)	P 278 S	✓
	GGG to TGG (G to T)	G 279 W	

TP53 Mutations In Skin Cancer: Effect Of UV Exposure

Repair defects:

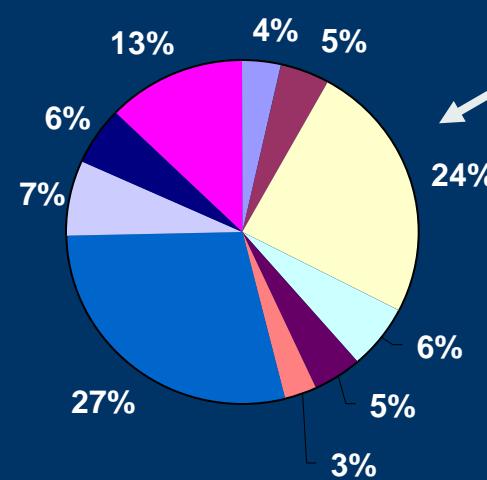
Skin SCC in XP patients



- CC > TT
- Insertion/deletion
- other

UV exposure:

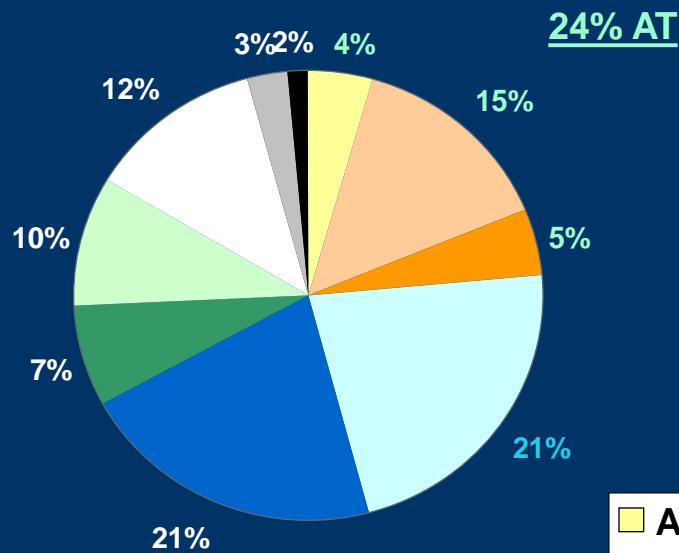
Sporadic Skin SCC



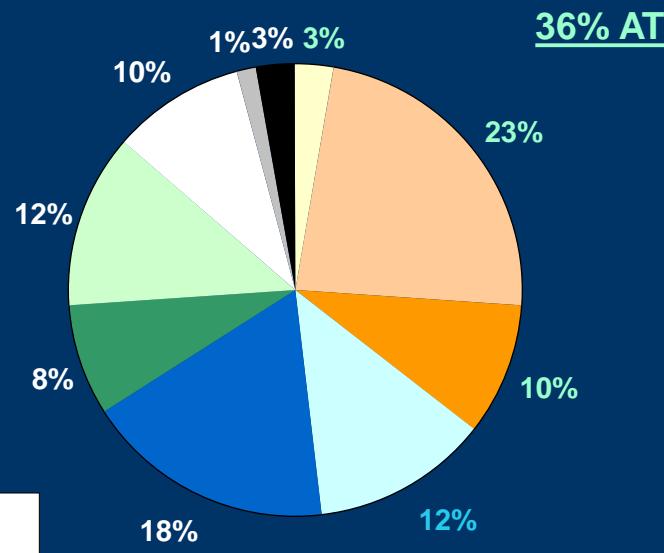
CC > TT =
UV-induced
mutations

TP53 Mutations In Breast Cancer: Effect Of Genetic Background

All Breast



BRCA1/2 carriers



- A:T>C:G
- A:T>G:C
- A:T>T:A
- G:C>A:T
- G:C>A:T at CpG
- G:C>C:G
- G:C>T:A
- del
- ins
- other

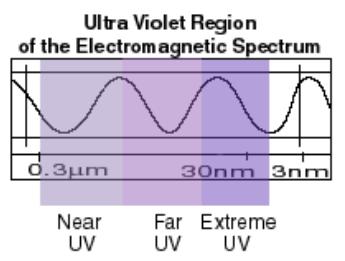
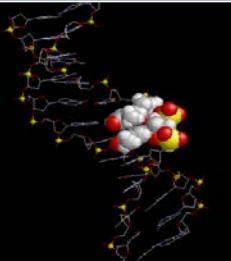
Mutations As "Carcinogen Fingerprints"

A mutation can be considered as a carcinogen fingerprint if there is:

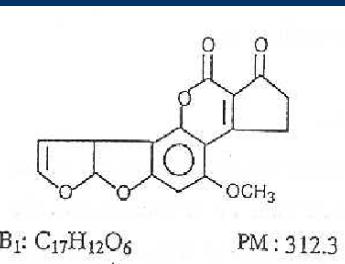
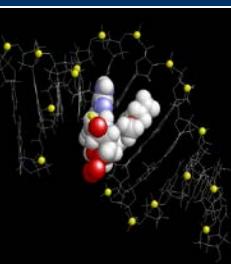
- ✓ Evidence that a **characteristic mutation pattern** is found in exposed compared with non-exposed individuals. This pattern should be distinct by at least one of the following criterion: type of mutations, site of mutations, strand bias.
- ✓ Evidence that the suspected carcinogen induces similar mutations in experimental model systems.
- ✓ Evidence that mutations occur **early** in tumor development.

Known TP53 Mutation Fingerprints

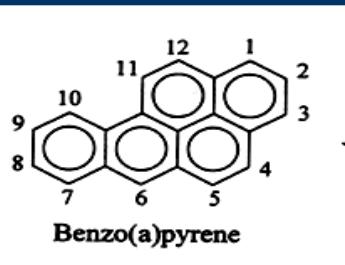
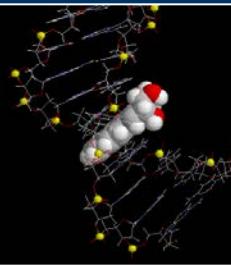
UV
radiations

Source	Mutagen	Adduct	TP53 mutations
	 		<p><u>CC to TT</u> Various codons</p> <p>Skin cancer: 15% Other cancers: <1%</p>

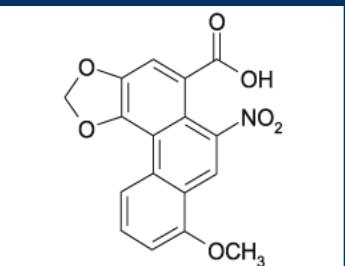
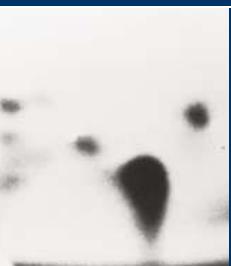
Aflatoxins

	  B ₁ : C ₁₇ H ₁₂ O ₆ MW : 312.3		<p><u>G to T</u> Codon 249</p> <p>Liver cancer: >30% Other cancers: <1%</p>
--	---	---	---

Tobacco
smoke

	  Benzo(a)pyrene		<p><u>G to T</u> Codons 157, 158, 248, 273</p> <p>Lung cancer: 30% Other cancers: <10%</p>
--	---	--	---

Aristolochic
acids

	 		<p><u>A to T</u> Codon 131</p> <p>Urothelial cancer</p>
--	---	---	---

Clinical Applications Of TP53 Mutations

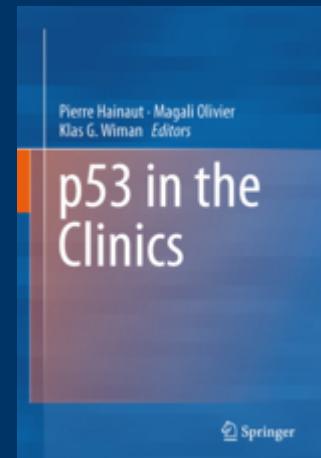
From Early Detection To Gene Therapy

- Cancer diagnosis
 - Early detection of cancerous lesion
 - Identification of cancer type
 - Marker of clonality
- Cancer aetiology
 - Identification of cause/exposure
- Patient outcome
 - Predict patient survival
 - Surveillance of recurrence
- Cancer treatment
 - Prediction of treatment response, treatment selection
 - Gene therapy
 - Re-activating TP53 in mutated cells

Prognostic Value Of TP53 Mutations

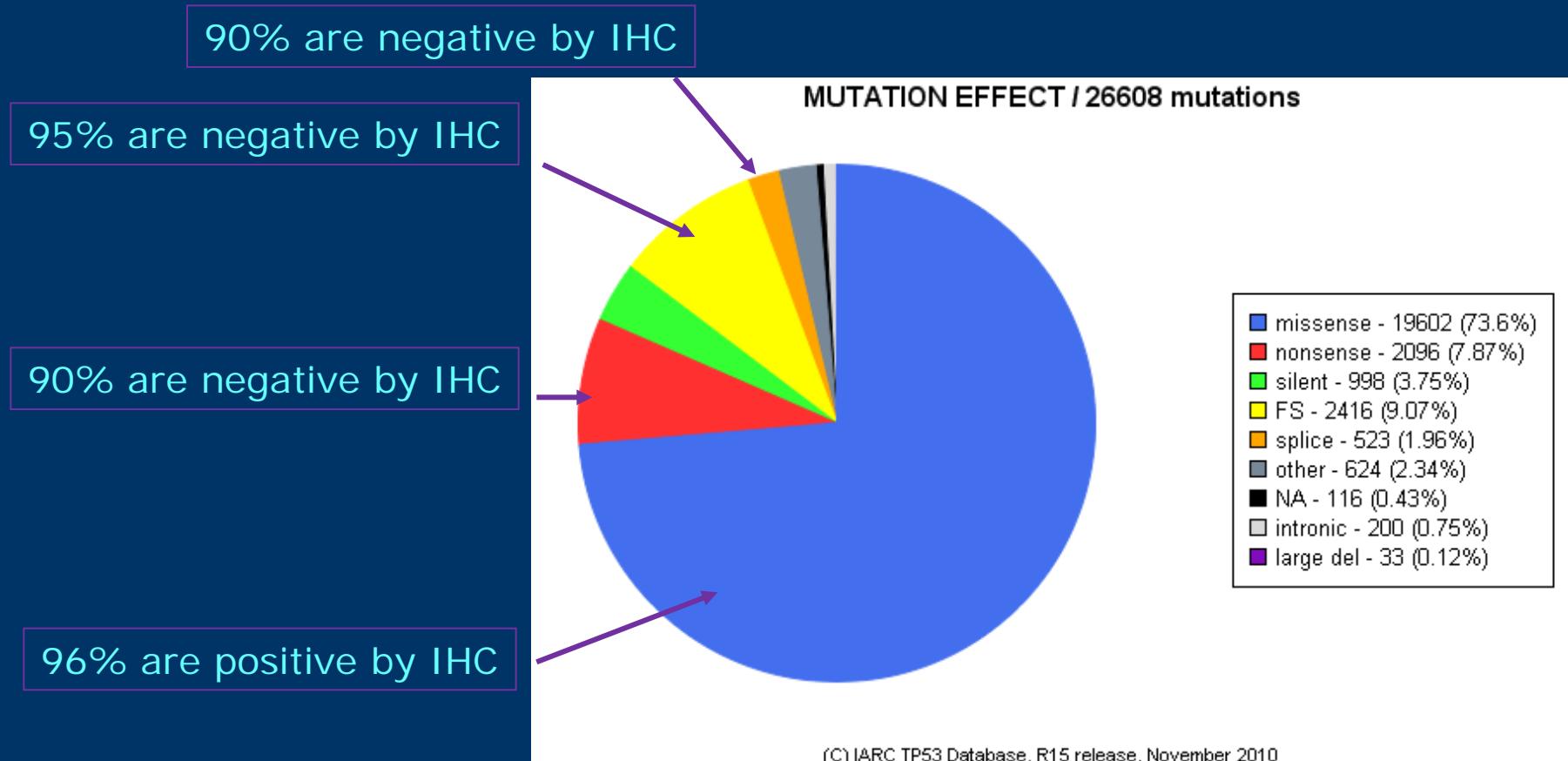
TUMOR SITE	Number of studies* reporting that TP53 mutations are :		
	Related to bad prognosis	Related to good prognosis	Not related to prognosis
Bladder	4	-	3
Bones	1	-	1
Brain	3	2	4
Breast	28	1	5
Colorectum	16	-	8
Esophagus	2	-	2
Head & Neck	7	-	2
Hematol.	12	-	-
Larynx	-	-	1
Liver	3	-	-
Lung	8	-	6
Ovary	7	1	2
Pancreas	1	1	1
Prostate	1	-	1
Soft tissues	2	-	-
Stomach	1	-	2
Renal pelvis	1	-	-

© IARC TP53 Database 2012



Chapter 8: TP53 Somatic Mutations: Prognostic and Predictive Value in Human Cancers

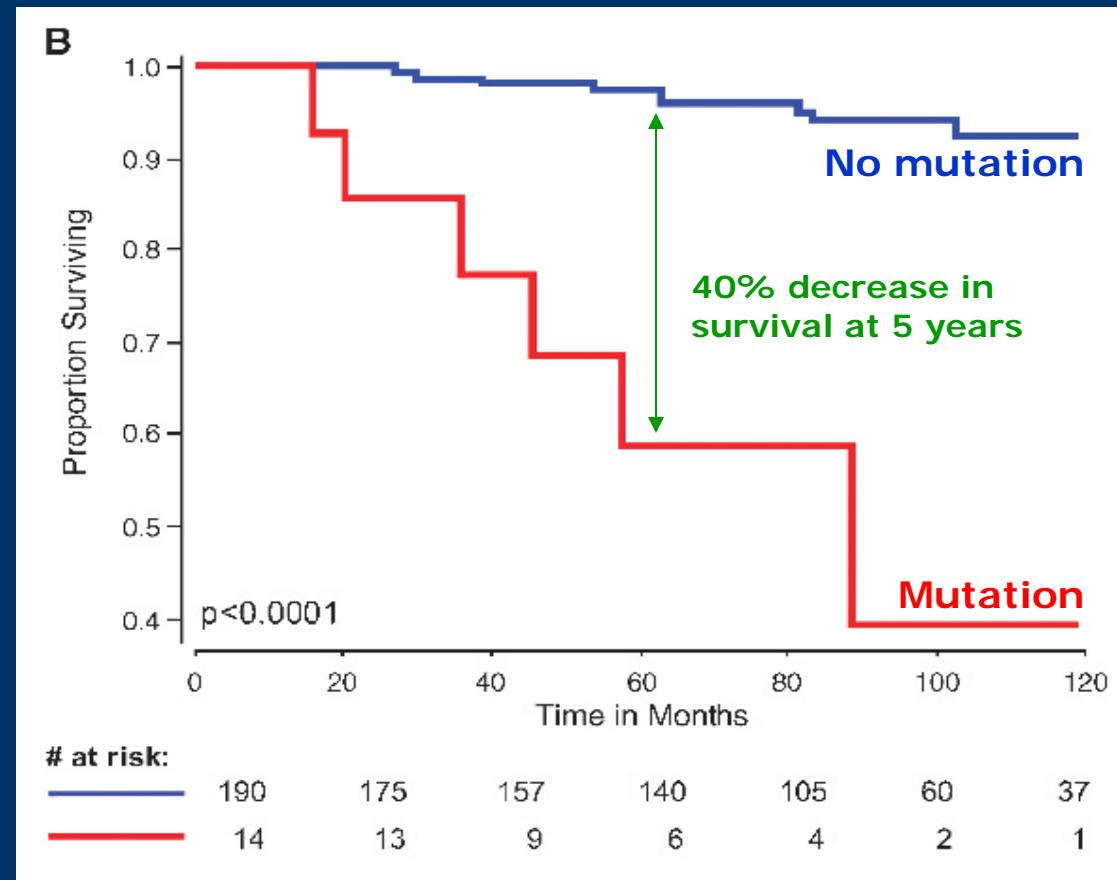
Assessing p53 status: Protein Accumulation vs Mutation



- 23% of cases with mutations may stain negative
- Studies using IHC to investigate p53 prognostic value have yielded inconsistent results
- IHC alone is not suitable for assessing TP53 mutation status

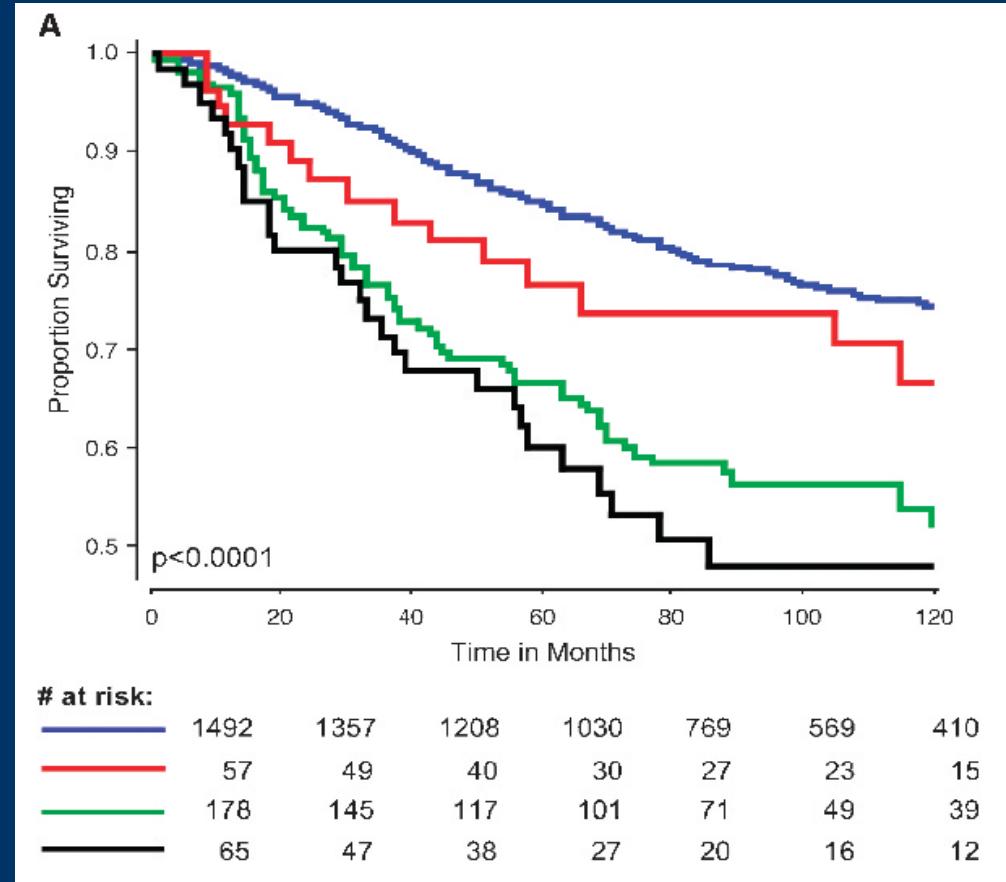
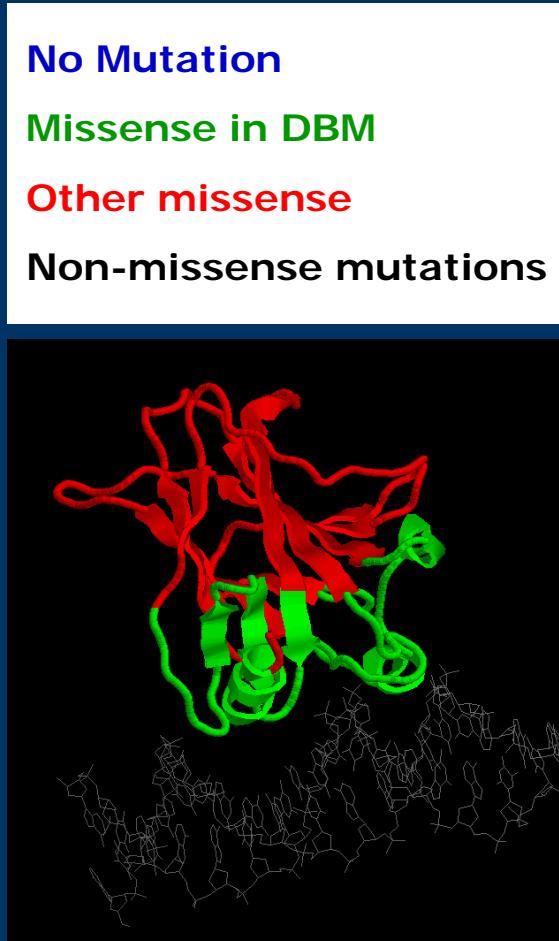
TP53 Mutations Are Associated With Shorter Survival in Breast Cancer Independently Of Stage, Grade And Hormone Receptors Status

Tumor grade <3, tumor size <5 cm, node negative and ER or PR positive cases
(204 patients)



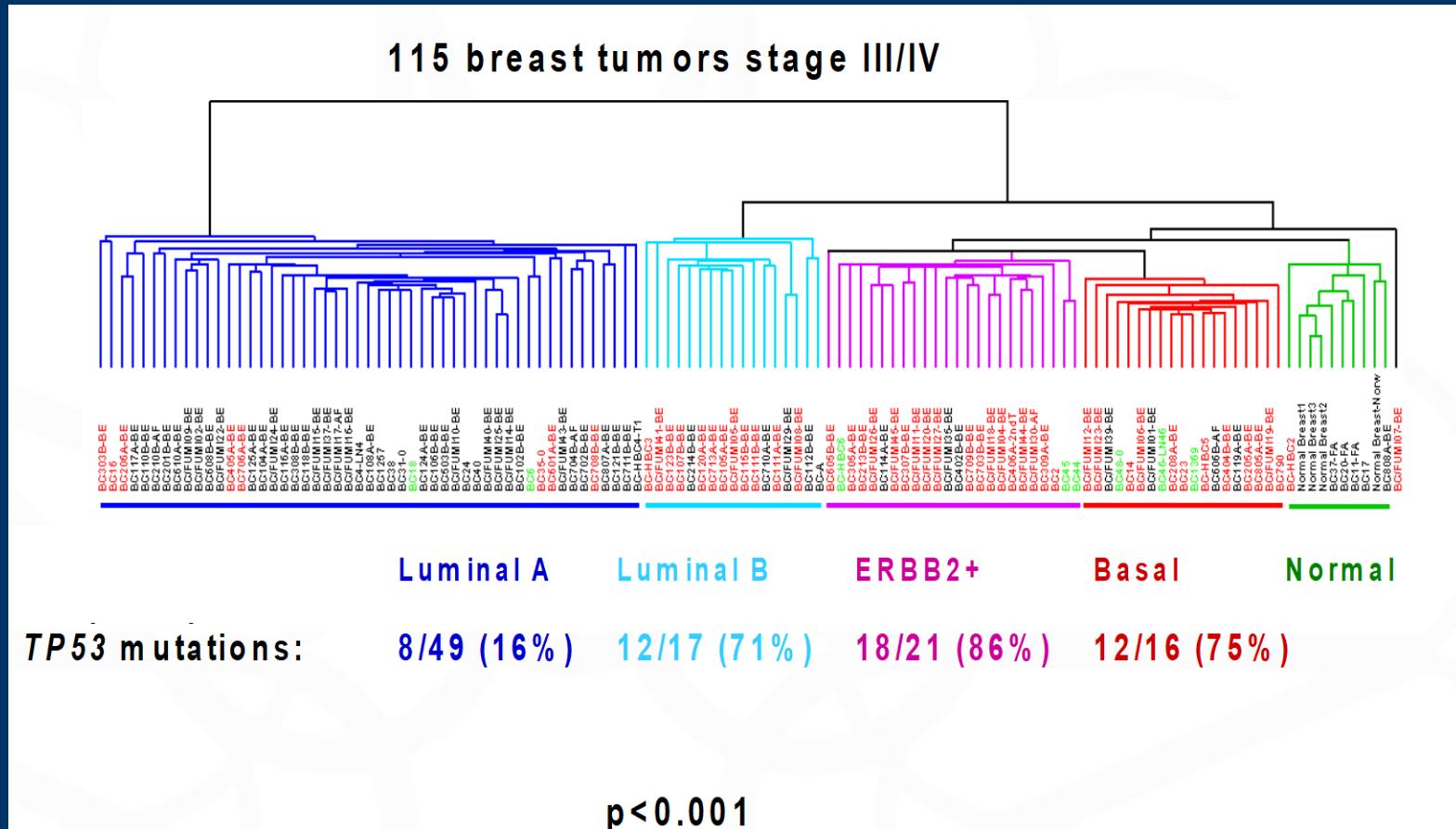
Olivier et al., Clin Cancer Res, 2006

TP53 Missense Mutations Within The DNA-binding Loops And Non-Missense Mutations Are Associated With The Worst Prognosis In Breast Cancer



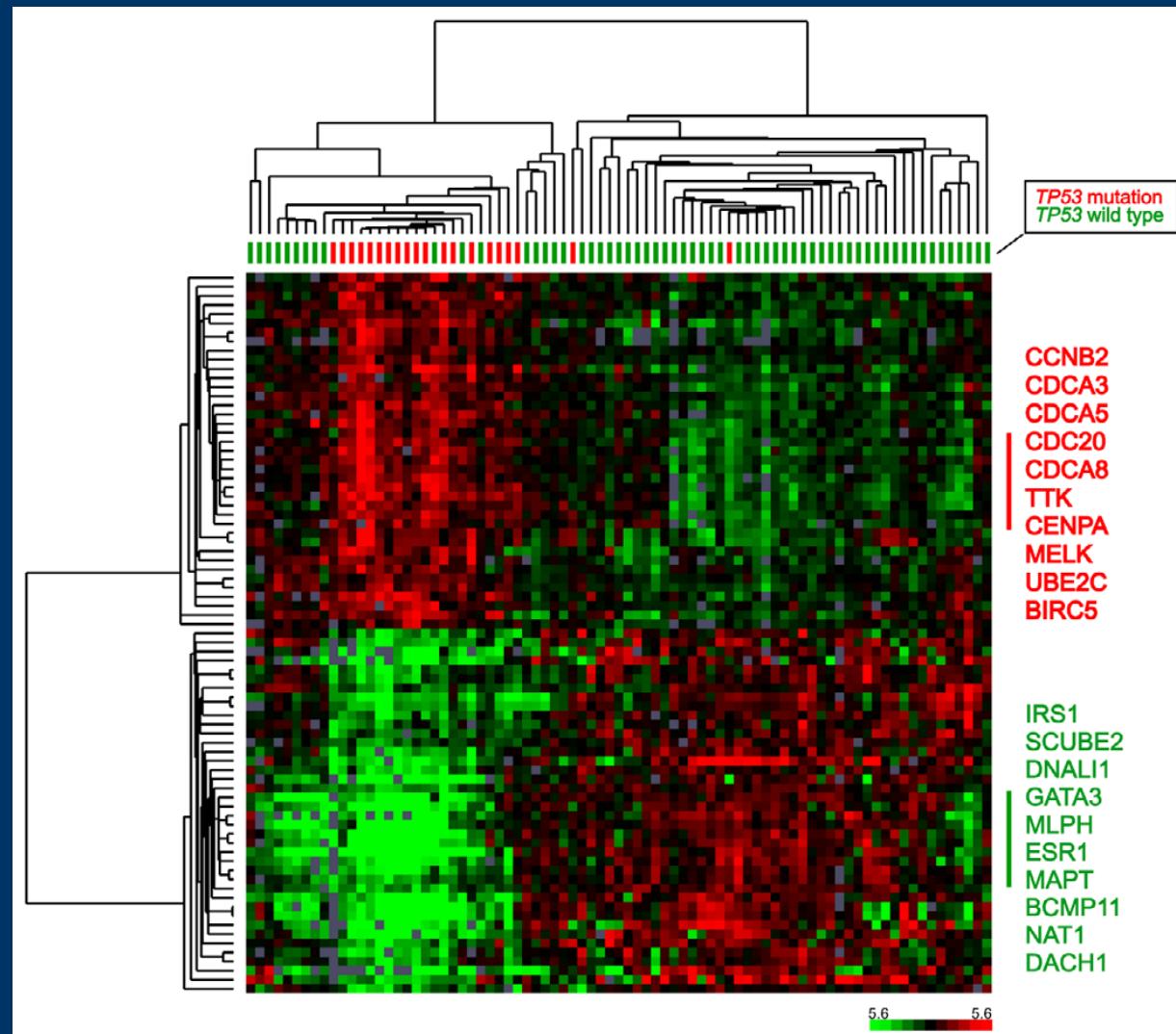
Olivier et al., Clin Cancer Res, 2006

TP53 Mutations Are Unevenly Distributed Across Molecular Subtypes



From Langerod et al., Breast Cancer Res, 2007 & Sorlie et al., PNAS, 2002

Gene Expression Signature Of TP53 Status

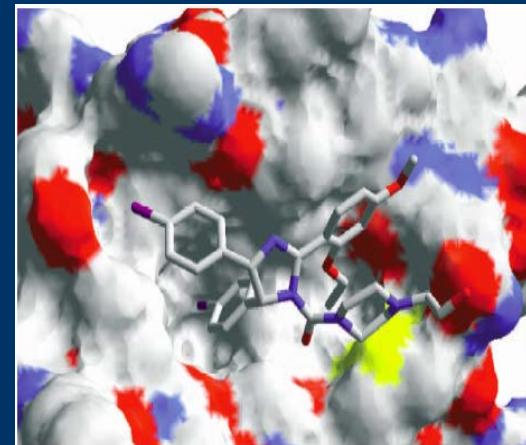


Strategies for Efficient Cancer Therapy: Virus-based Therapies

- ONYX-015
 - Is an attenuated chimeric human group C adenovirus, that has been developed to preferentially replicates in and lyses tumor cells that are p53 negative (McCormick, *Cancer Biol Ther.* 2003).
- Advexin (Ad5CMV-p53)
 - Is a non-replicating, non-integrating adenoviral vector that carries the p53 gene (Gabrilovich, *Expert Opin Biol Ther.*, 2006).

Strategies for Efficient Cancer Therapy: Small Molecules That Target p53

- Inhibition of mdm2/p53 interaction (*Nutlin-3, RITA*)
 - Kill cancer cells with WT p53
- Reactivation of mutant p53 (*PRIMA-1, CP31398, WR1065, MIRA-1, STIMA-1, RETRA*)
 - Kill cancer cells with MUT p53



Further Information

Human Mutation Variation, Informatics, and Disease

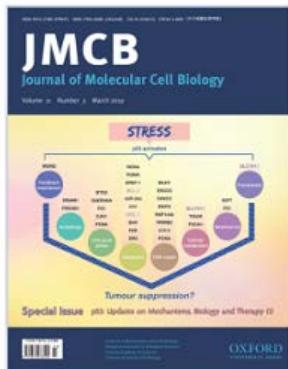


Databases

TP53 Variations in Human Cancers: New Lessons from the IARC TP53 Database and Genomics Data

Liacine Bouaoun, Dmitriy Sonkin, Maude Ardin, Monica Hollstein, Graham Byrnes, Jiri Zavadil, Magali Olivier

First published: 22 June 2016 | <https://doi.org/10.1002/humu.23035> | Cited by: 44



Volume 11, Issue 3, March 2019

Special Issue:
p53: Updates on Mechanisms, Biology and Therapy (I)

Cell Death & Differentiation

[« Previous Issue](#) | [Volume 25](#) | [Next Issue »](#)

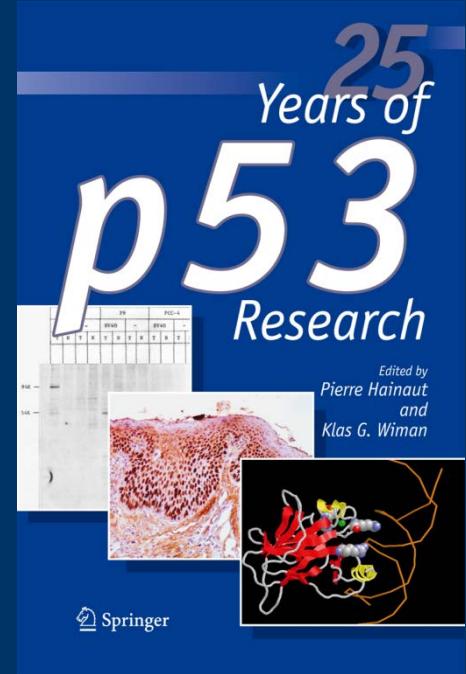
Volume 25 Issue 1, January 2018

Editorials

[Editorial](#) | 11 December 2017

[Reviewing the future of the P53 field](#)

Arnold J Levine



Pierre Hainaut · Magali Olivier
Klas G. Wiman *Editors*

p53 in the Clinics

Springer

Selected references and other resources links at:
<http://p53.iarc.fr/>