NÚCLEO DE QUITO

Programa de Certificación Oncológica para Enfermería

Paola E. Leone, PhD, Acad

Biología y Genética del Cáncer

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DPTO. APOYO DIAGNÓSTICO LABORATORIO DE GENÉTICA

Coordinadora, Laboratorio de Genética – SOLCA Núcleo de Quito

SOCIEDAD ECUATORIANA DE BIOLOGÍA

Presidente, Sociedad Ecuatoriana de Biología

Ex Presidente, Sociedad Ecuatoriana de Genética Humana

Ex Presidente, Academia de Ciencias del Ecuador

REDIMM Red Iberoamericana para la Investigación de Mieloma Múltiple

RIALCYTED Red Iberoamericana de Linfomas

Coordinadora General y de Nodo de Redes Iberoamericanas de Mieloma y Linfomas

90 artículos Scopus, 50 artículos Latindex, 11 libros, 19 capítulos libros (Ecuador, España)

No hay conflictos de interés por declarar

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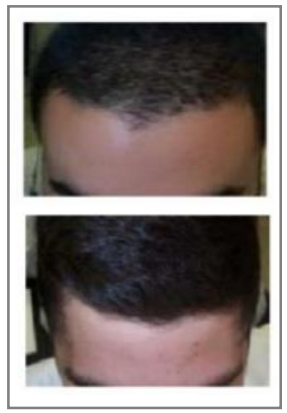
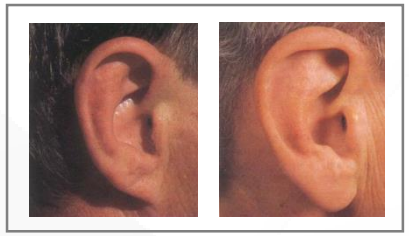
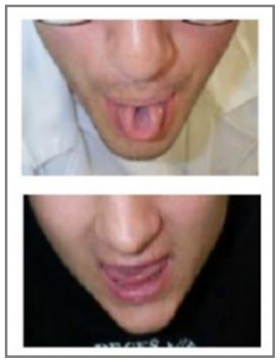
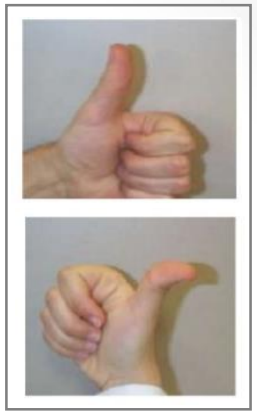
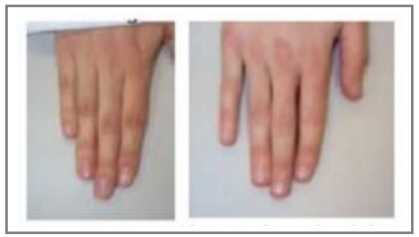
Características físicas de la población ecuatoriana

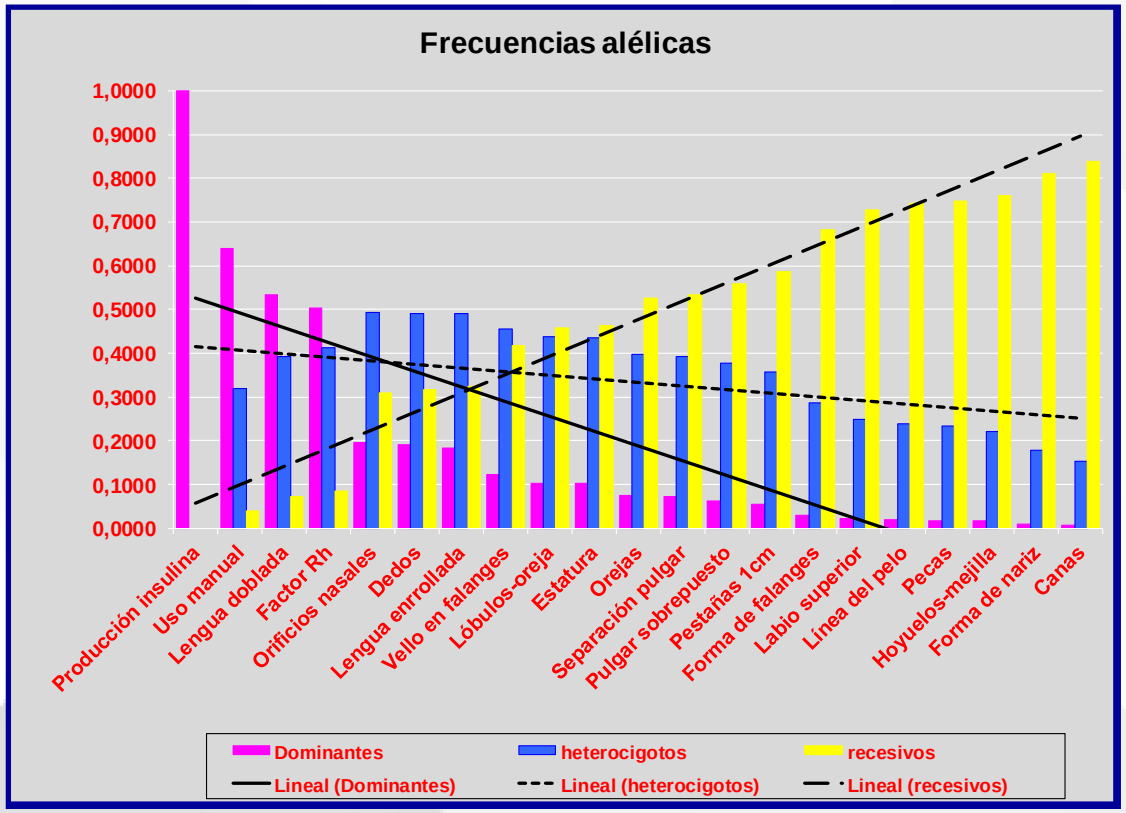












Rev. Facultad de Ciencias Médicas, UCE. 2000; 25(2):23-26

EDUCA - https://www.facebook.com/EducaTele/videos/1383376915184229/

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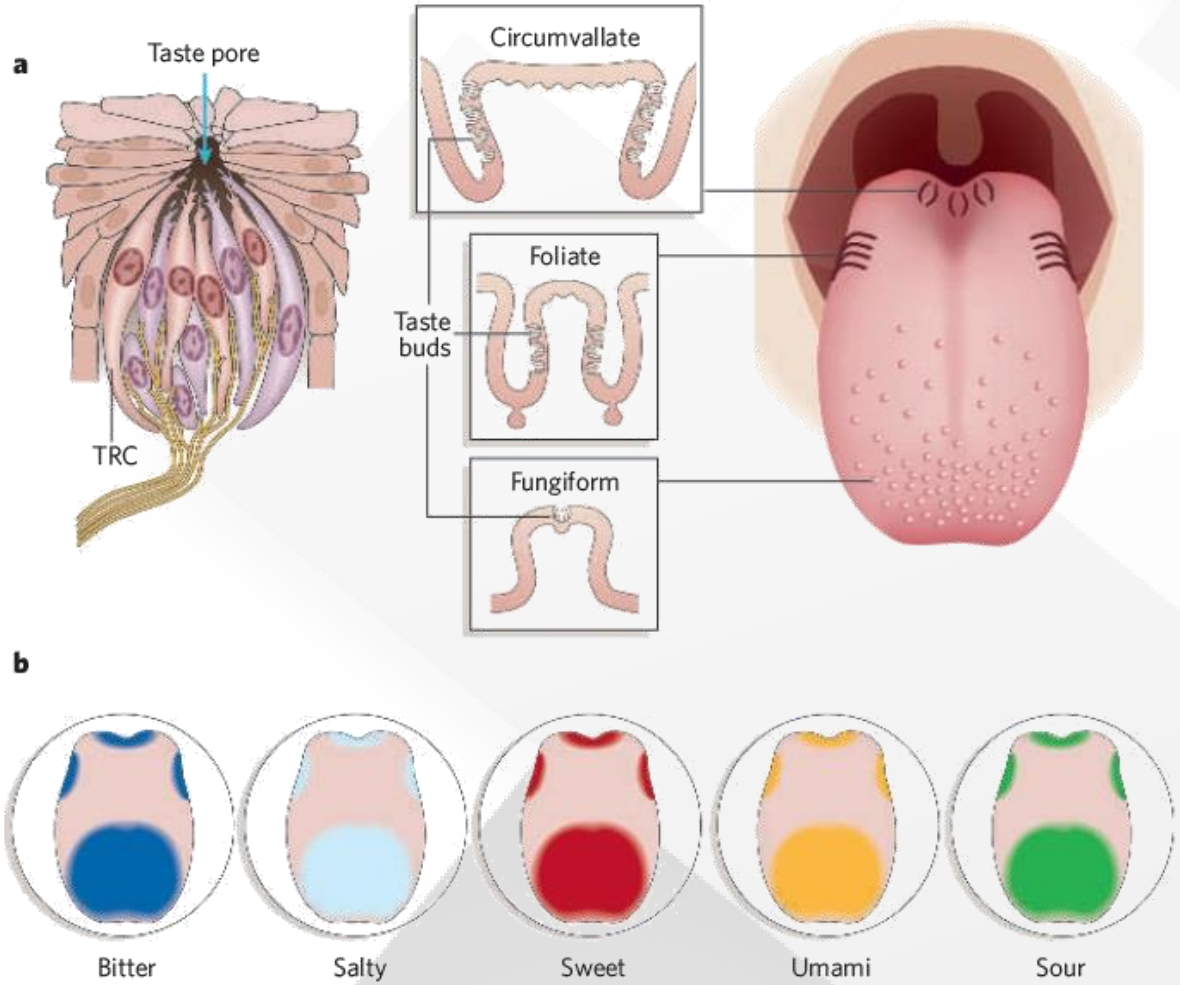
Tipos de sabores



Genes determinantes de la percepción de los sabores ecuatorianos
En: El sabor de mi Ecuador, 22-24 (2013)

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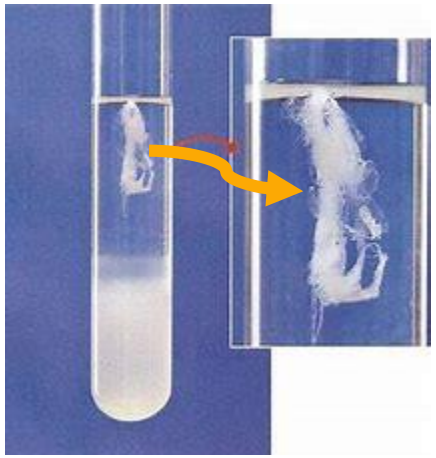

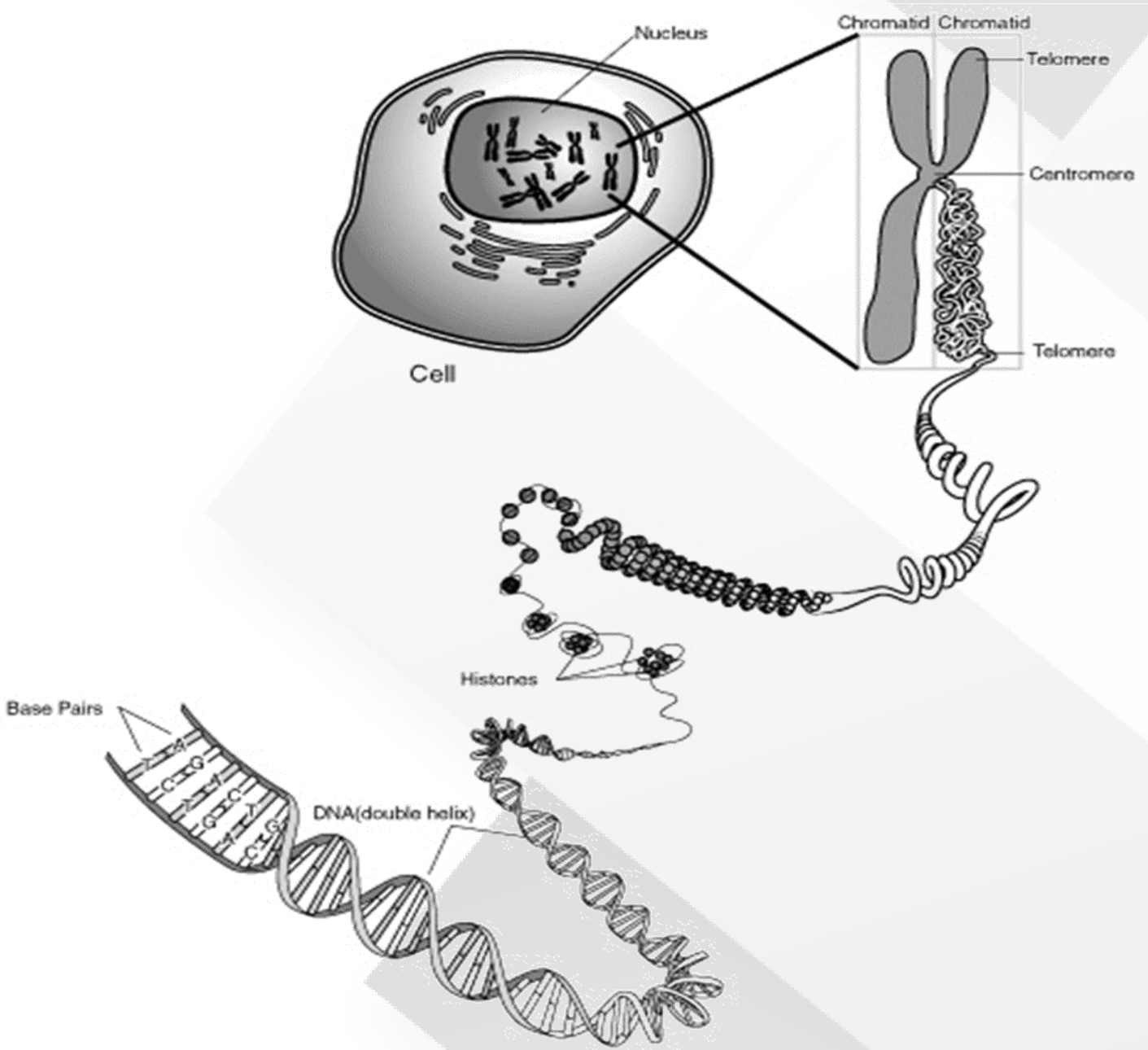

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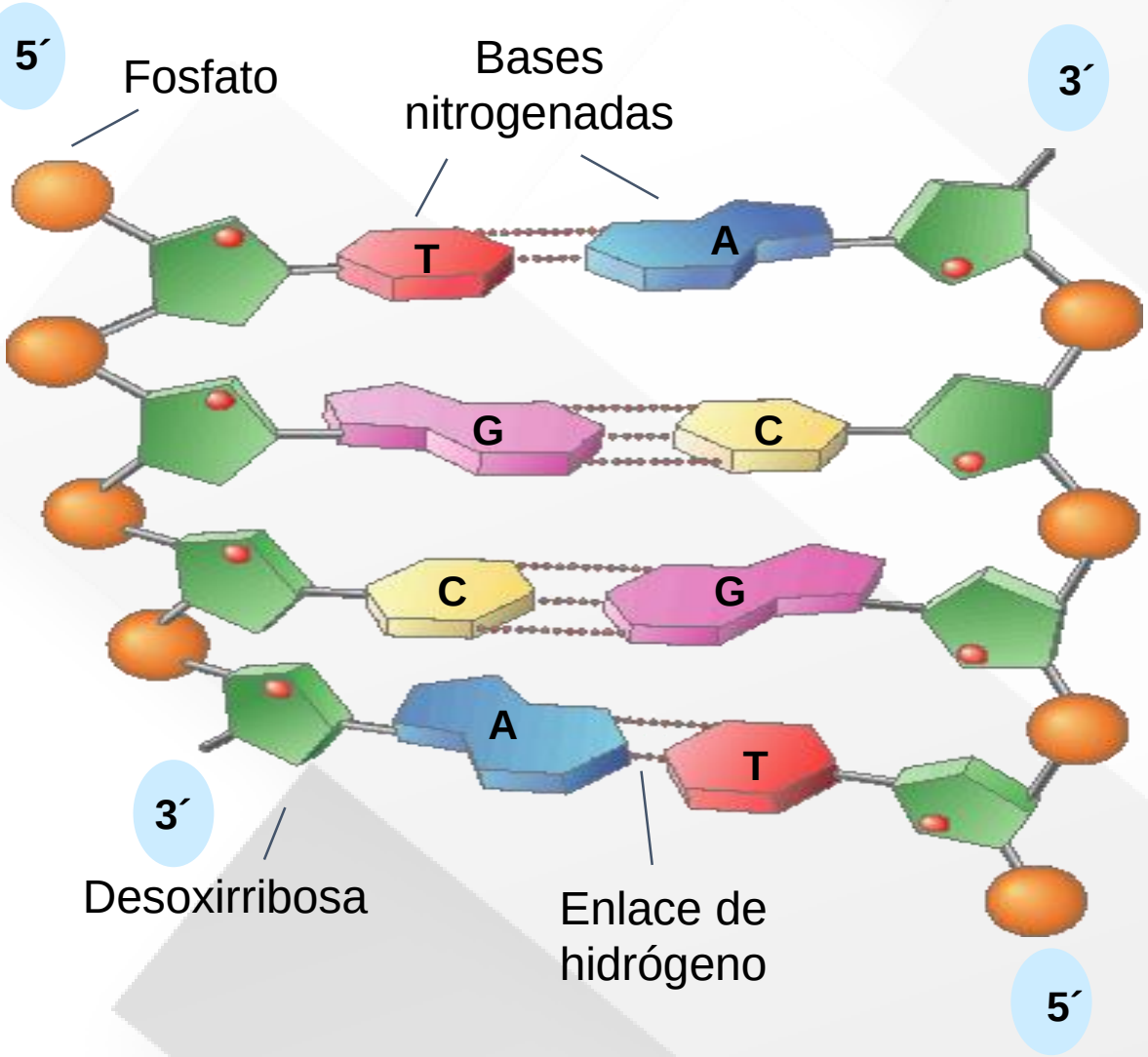
Estructura del ADN

Doble hélice de ADN



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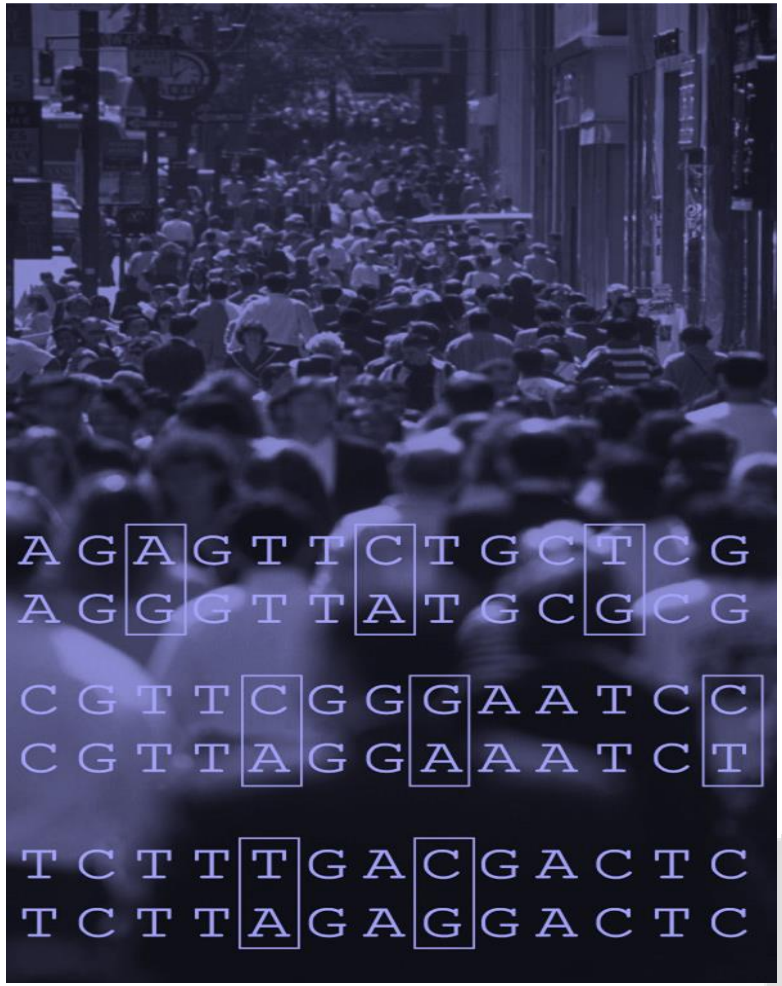
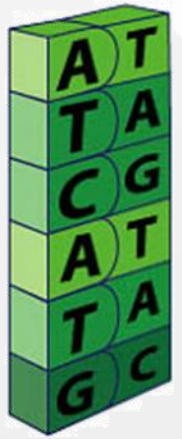
Variabilidad genética





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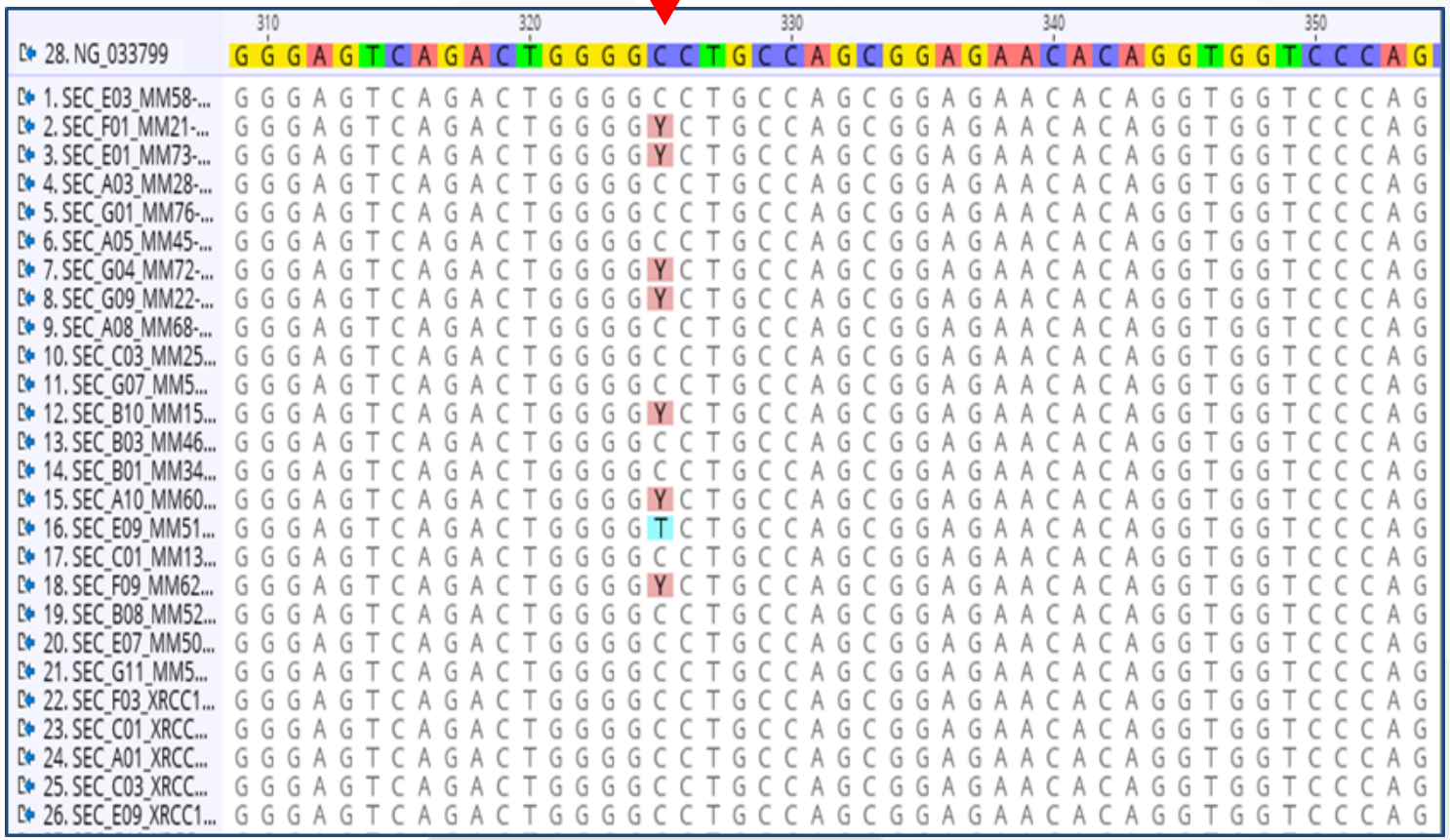
Gen *XRCC1*: mutación nueva

43.551.656



Genética en el Ecuador: 30 años PO-34, 569-570 (2016)

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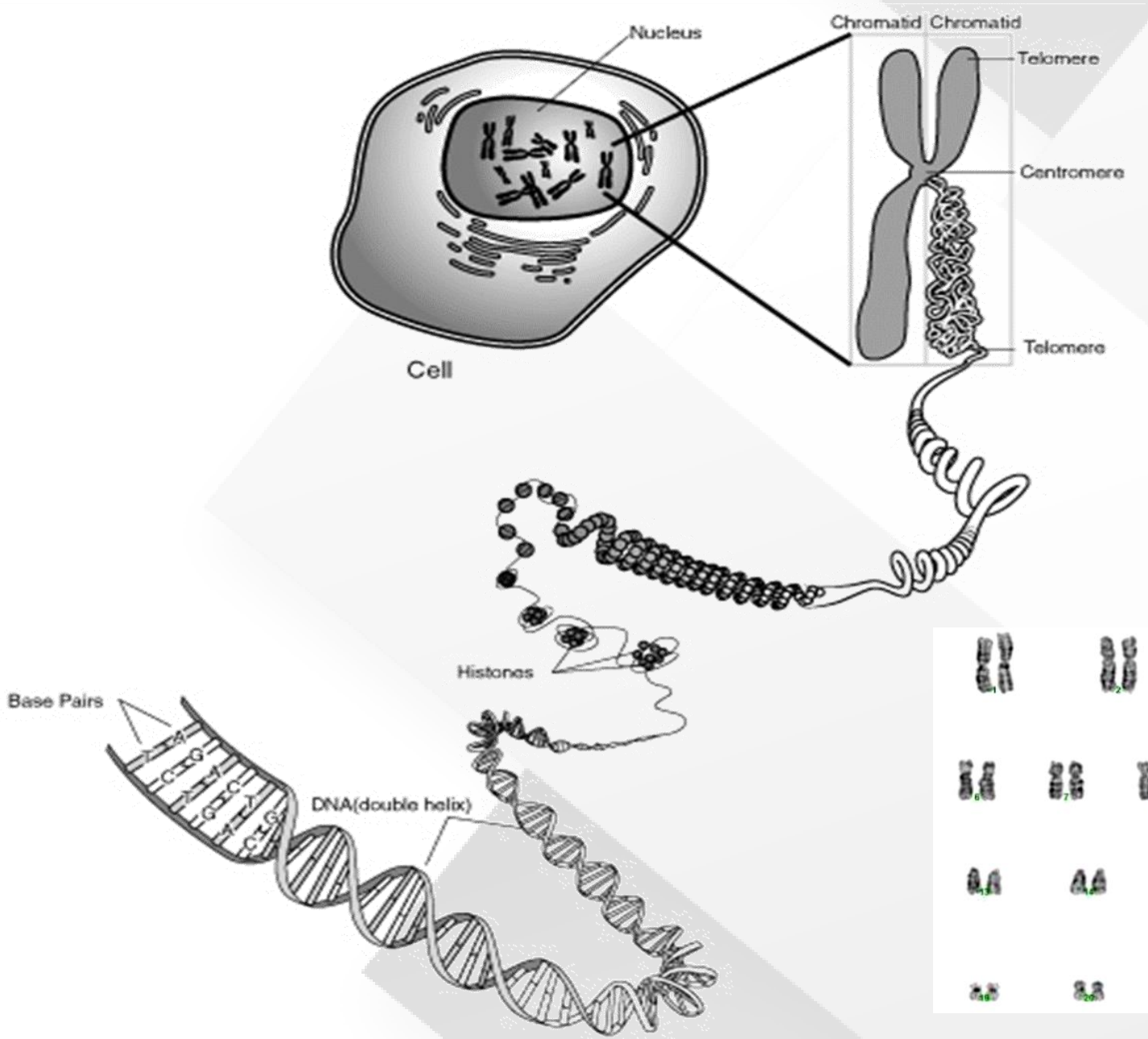

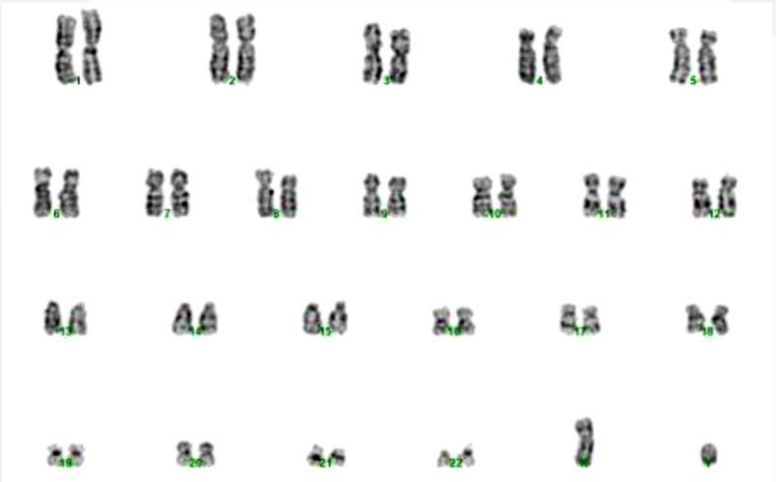

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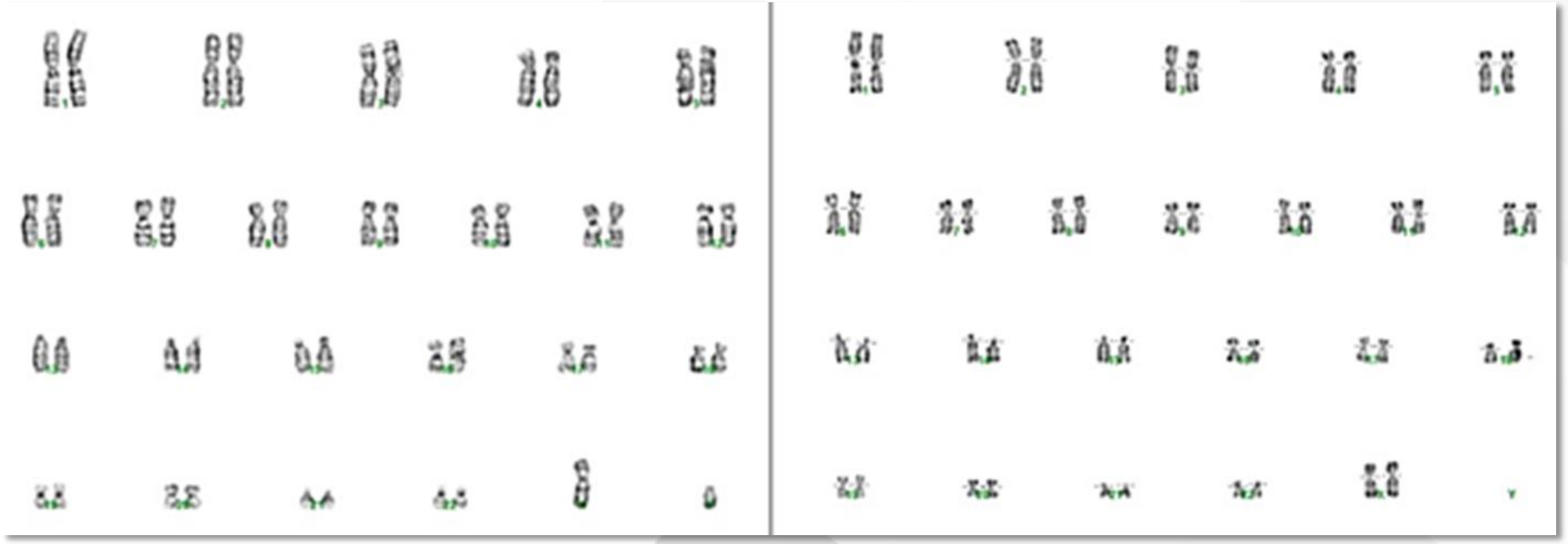
Cromosomas humanos



46,XY

46,XX

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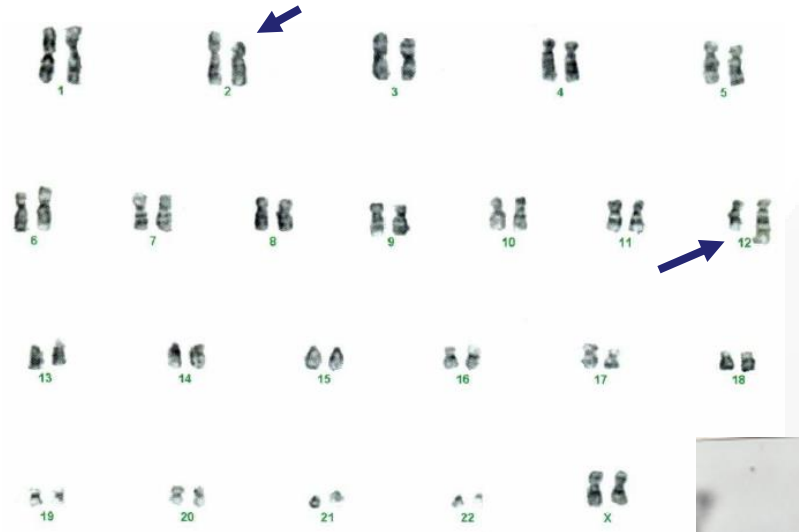
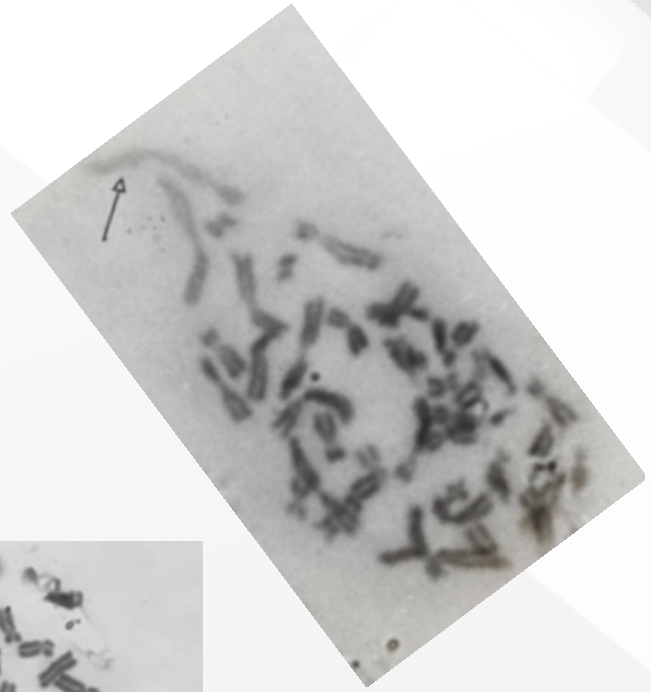
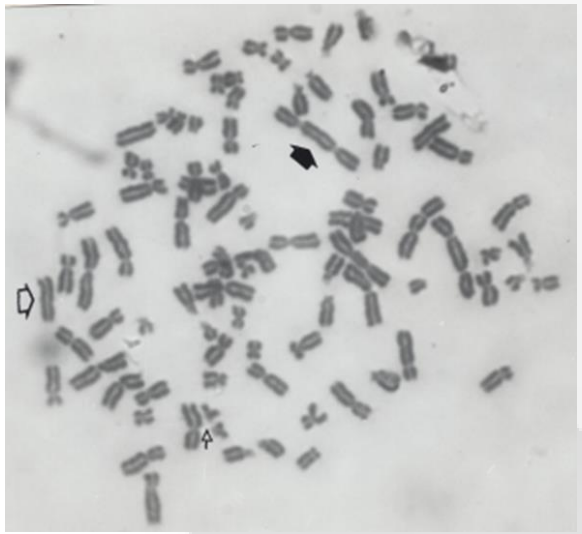
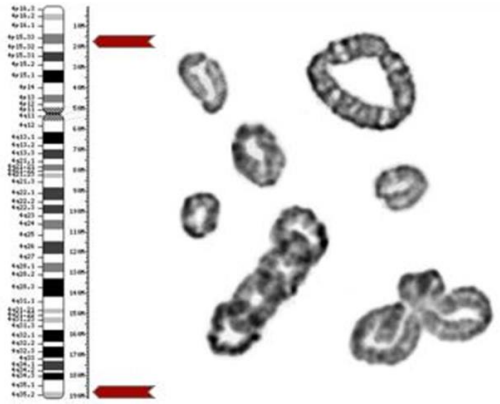
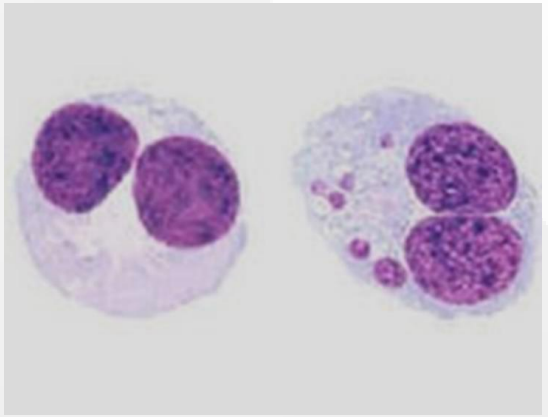
Alteraciones cromosómicas











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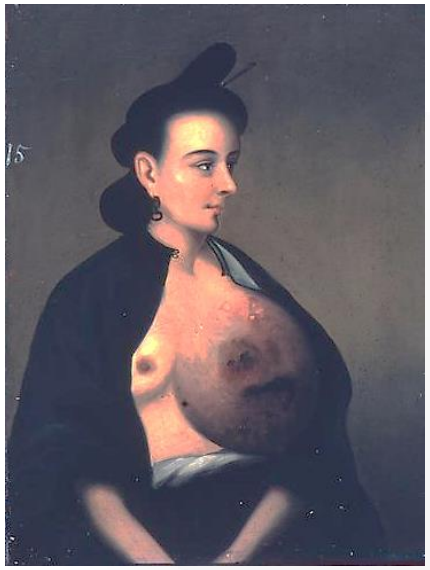
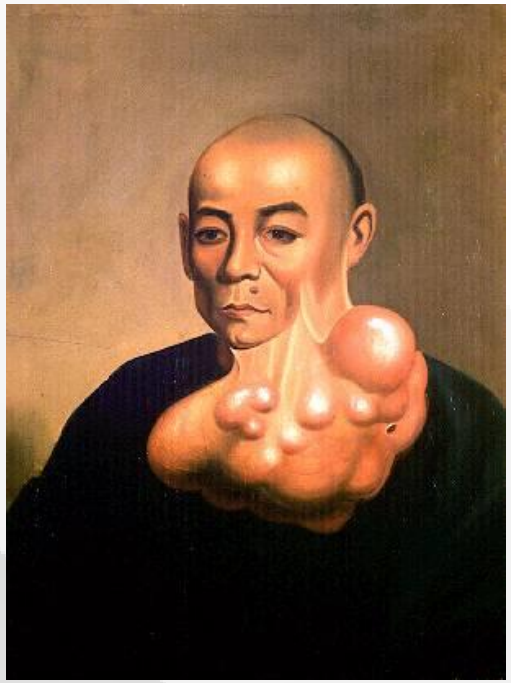
Cáncer en la pintura





Lam Qua, 1801-1860

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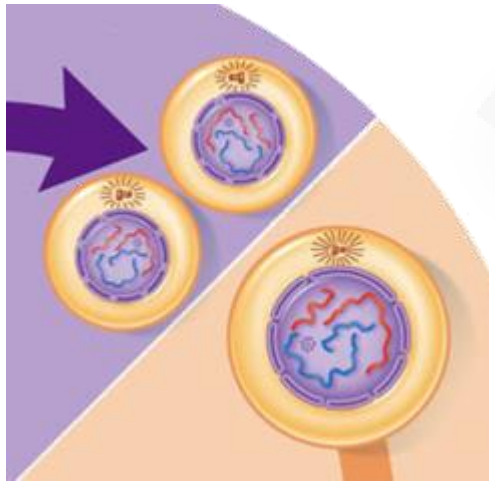
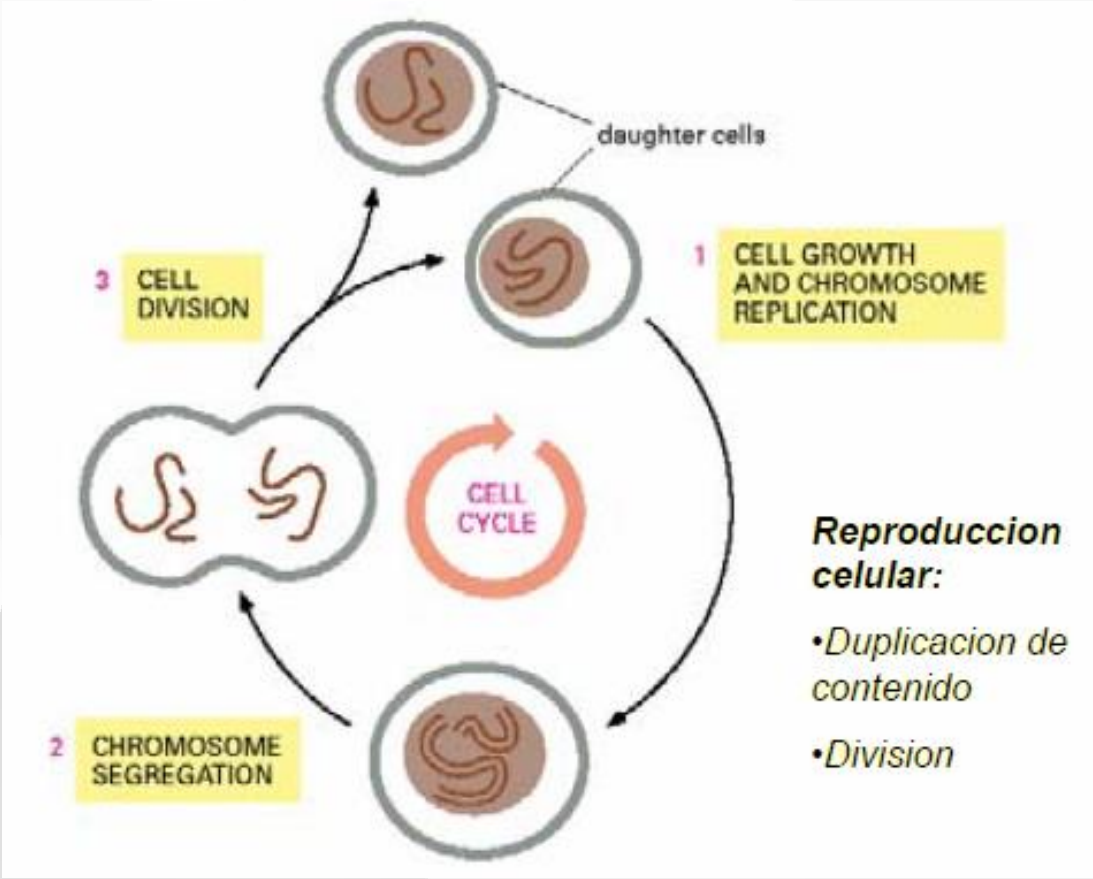
Ciclo celular

Conjunto ordenado de sucesos que conducen al crecimiento de la célula y la división en dos células hijas.





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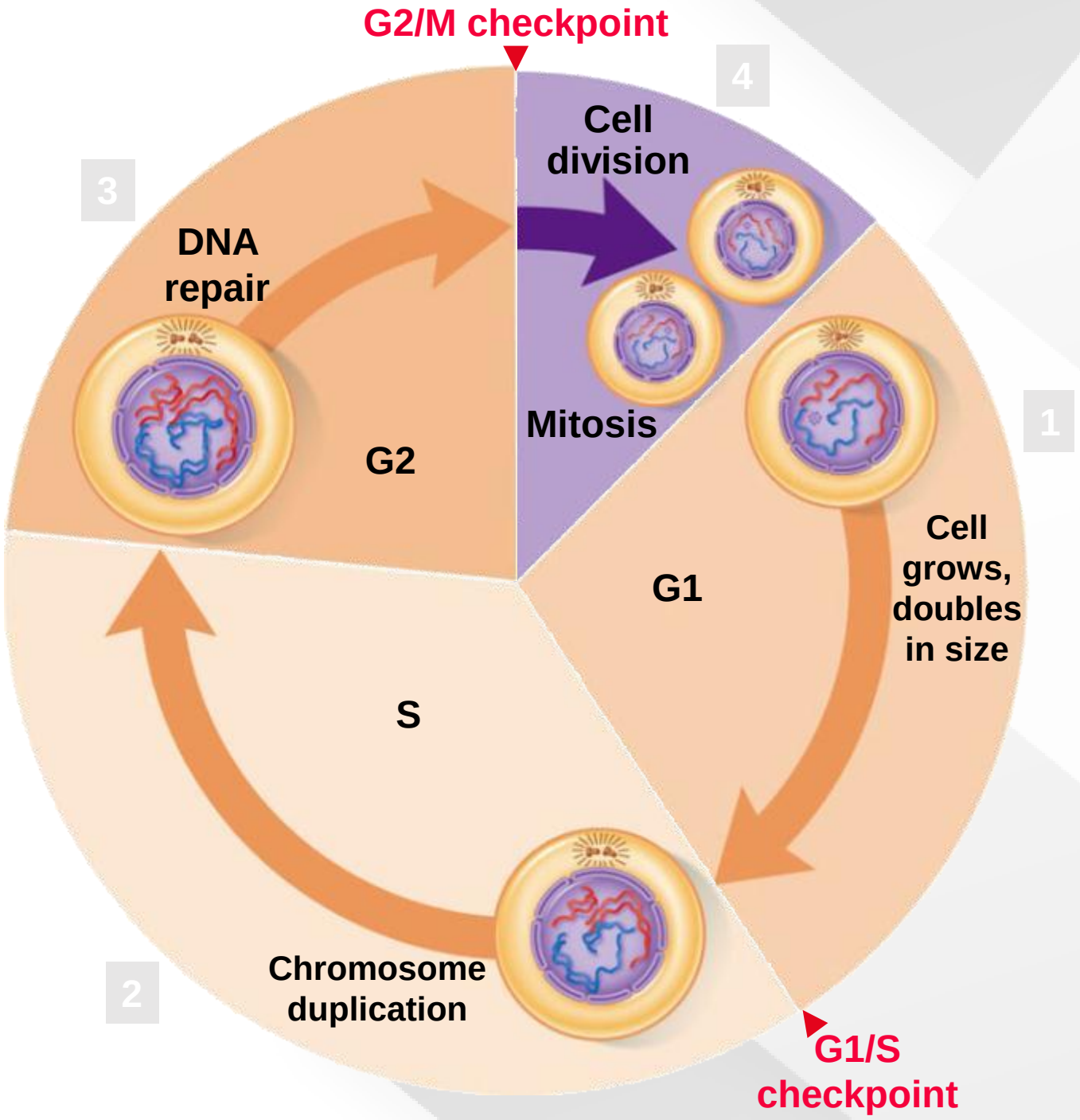

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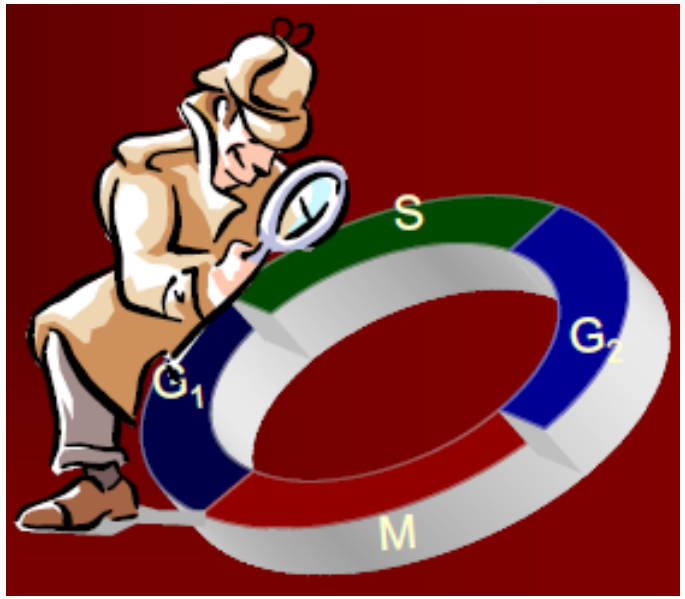
Checkpoint: Puntos de control

Son mecanismos moleculares que verifican que se cumplen las condiciones necesarias para permitir el paso de una fase del ciclo celular a otra.



Vista al este

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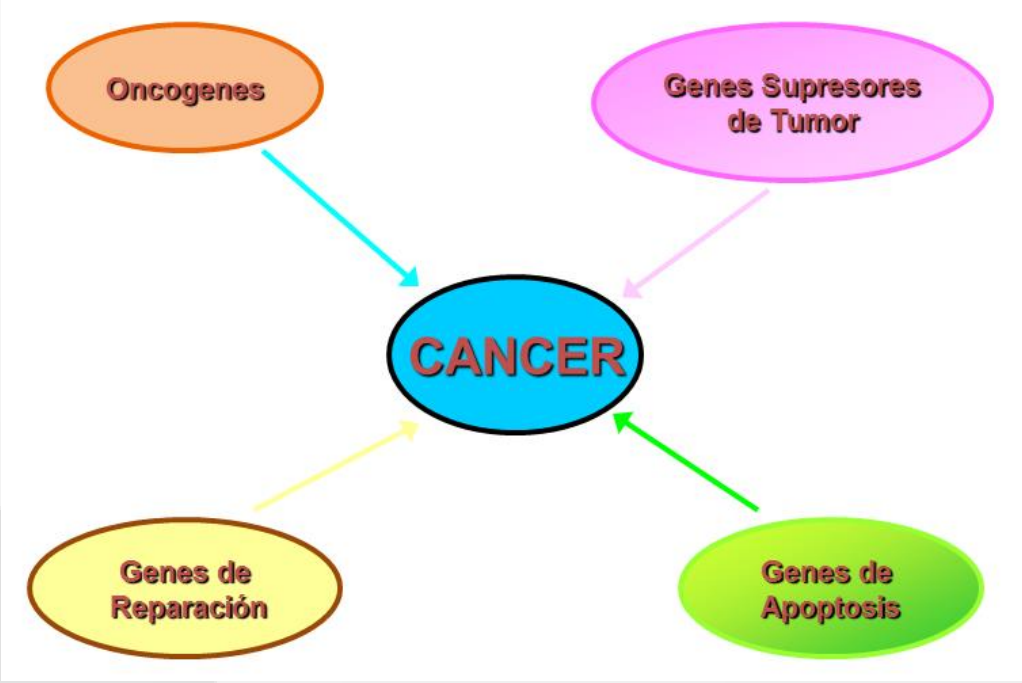
Componentes reguladores

Genes asociados a cáncer controlan estos checkpoints:

- Genes supresores de tumor reducen la tasa de división celular
- Proto-oncogenes aumentan la división celular
- Genes reparación
- Genes de apoptosis



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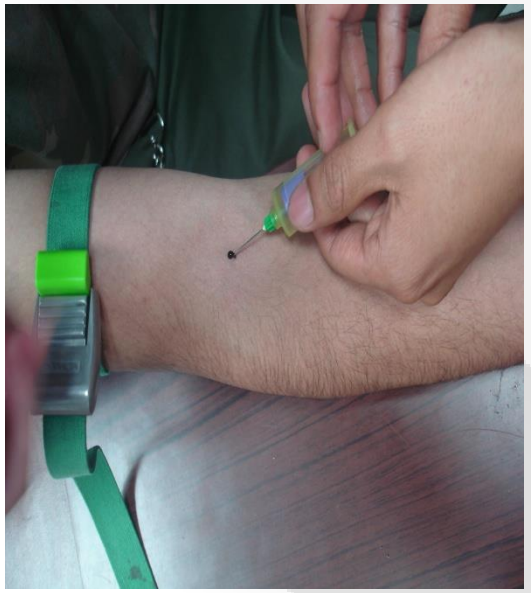
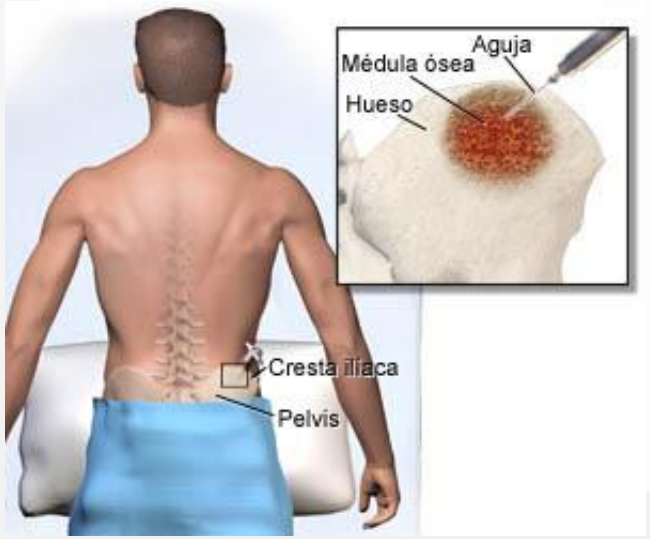
Muestras de estudio

Tumor fresco o parafina

Raspado bucal, saliva o pelo



Sangre periférica



Médula ósea

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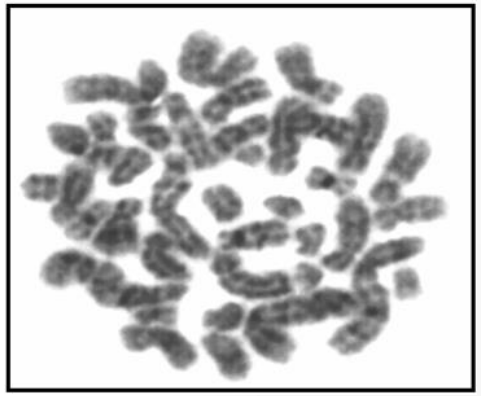
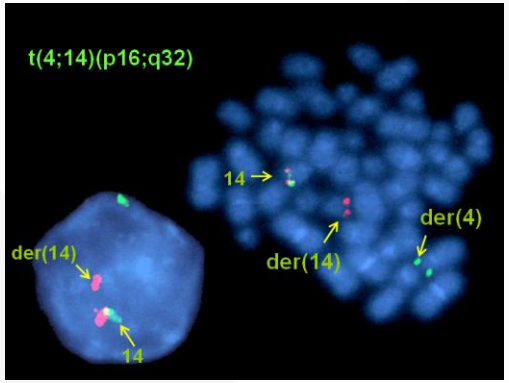
Detección de alteraciones cromosómicas

Citogenética convencional



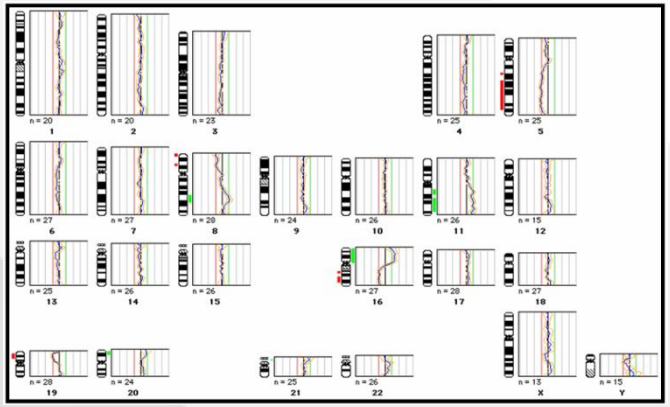
Hibridación *in situ* fluorescente (FISH)



Resolución 20 Mb

Cariotipo espectral (SKY)

Hibridación genómica comparada (CGH)



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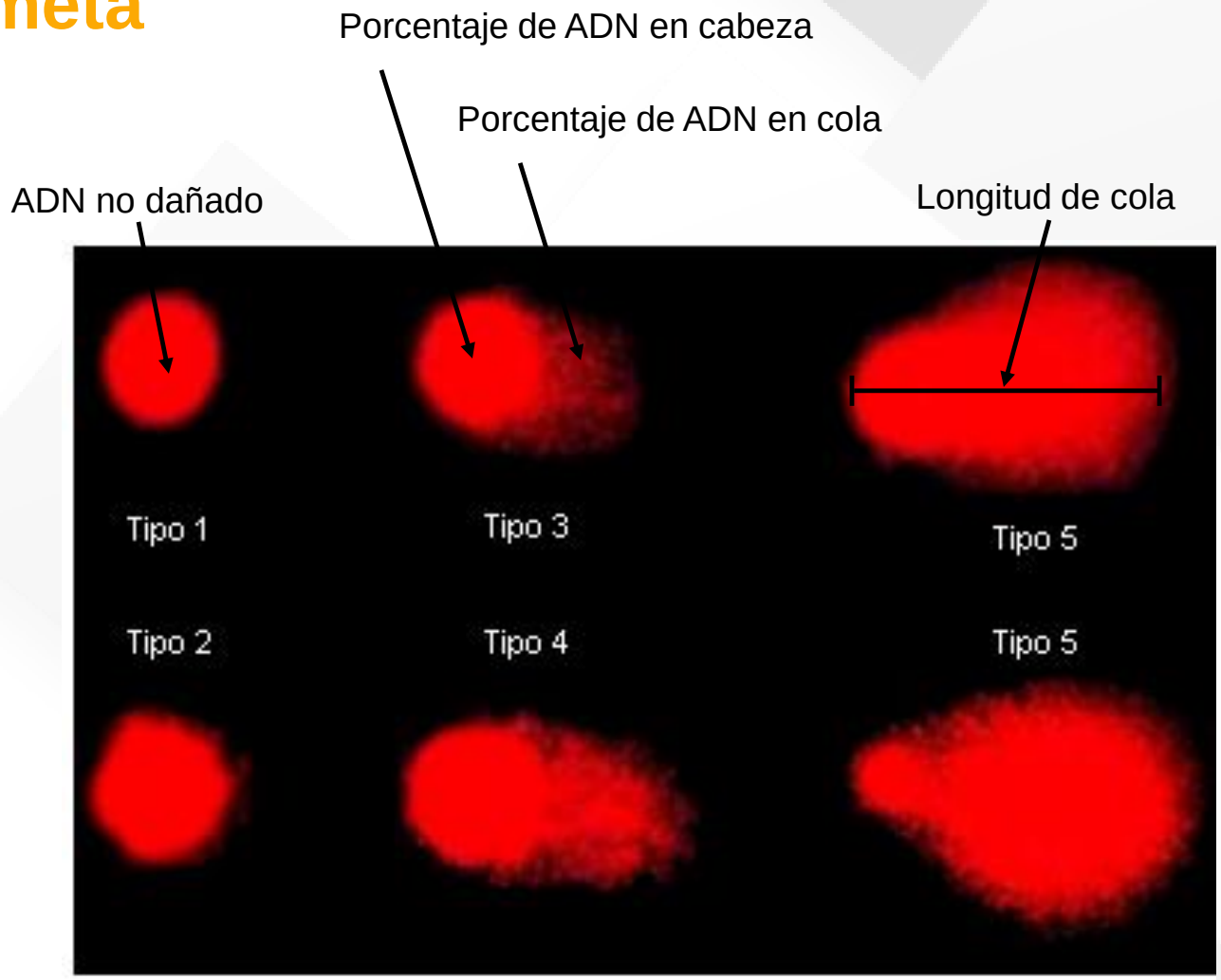
Ensayo Cometa



Momento de cola = longitud de cola / porcentaje de ADN en cola

modificado de Paz y Miño et al., Ann NY Acad Sci. 2008; 1140, 121-8

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Chip/array en la vida diaria

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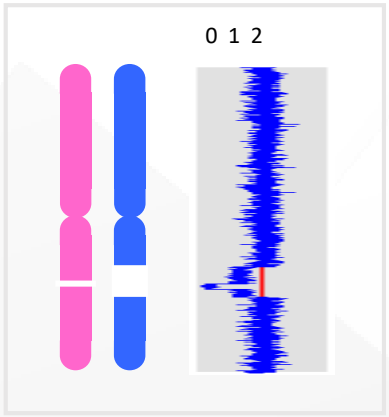
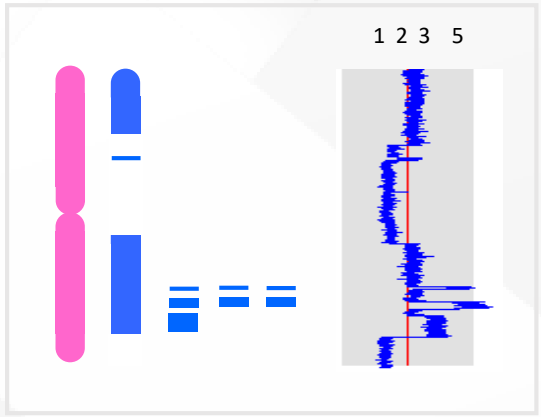
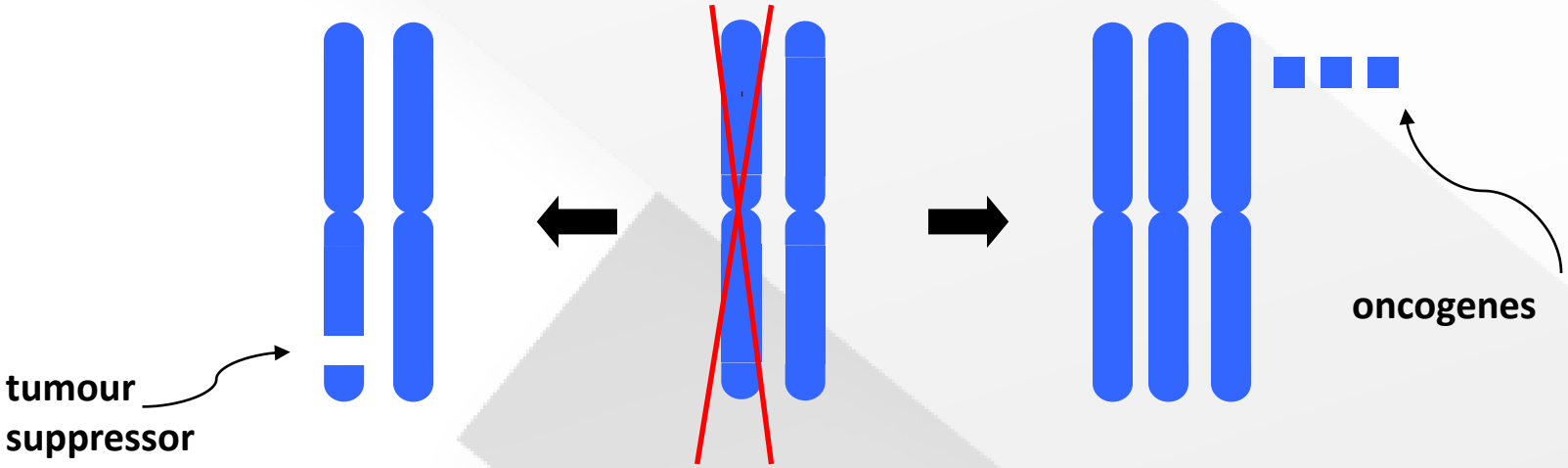
Cambios en el número de copias cromosómicas

500K SNP GeneChip
Mapping arrays





Resolución Submegabase



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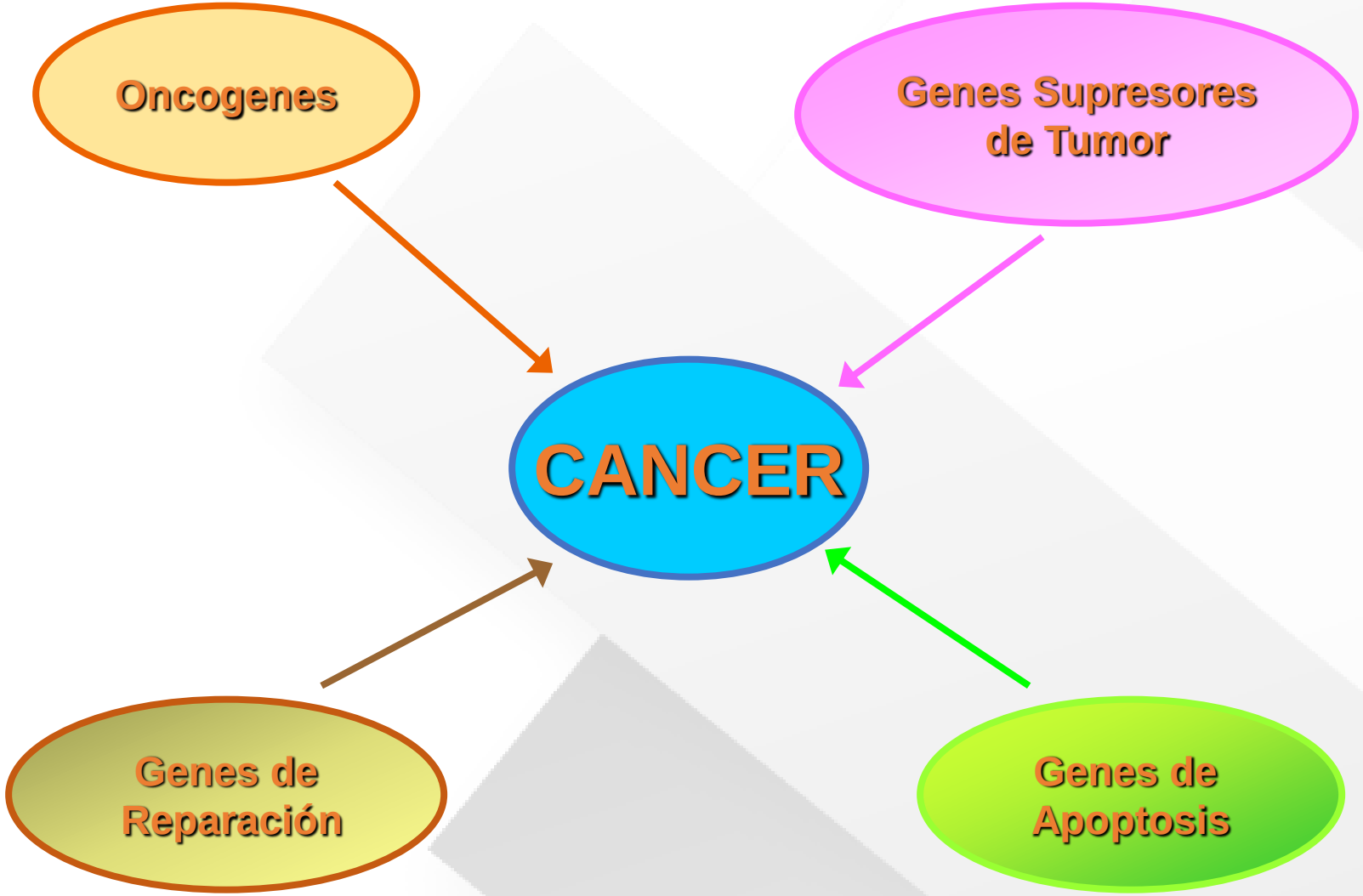
Genes de cáncer: Oncogenes



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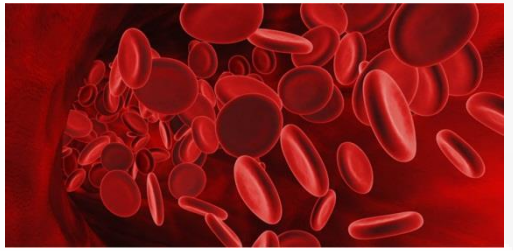
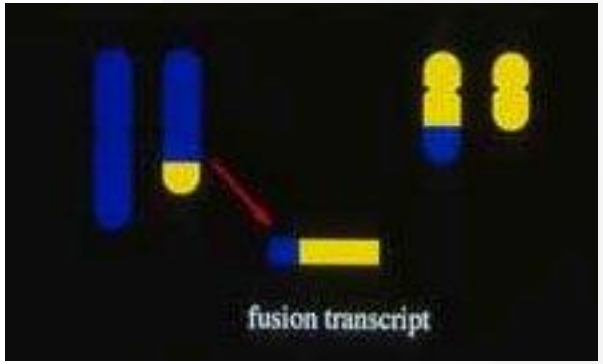
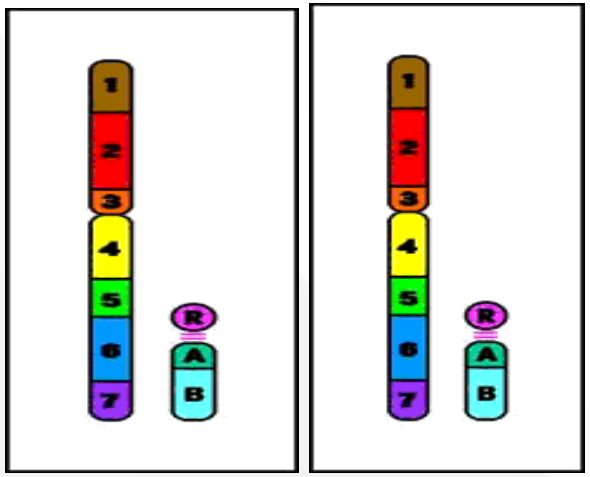
Oncogenes en cáncer

Oncogenes



Rearreglos cromosómicos y moleculares:





Translocaciones cromosómicas & mutaciones:

Protoncogen → **Oncogen**

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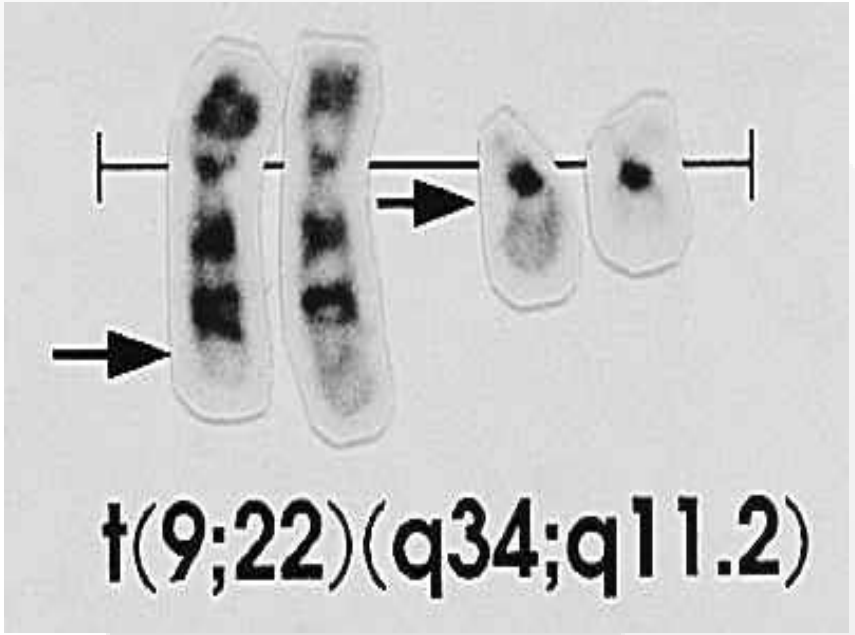
t(9;22)(q34;q11)

Cromosoma Philadelphia (Ph) es marcador para LMC y para LLA



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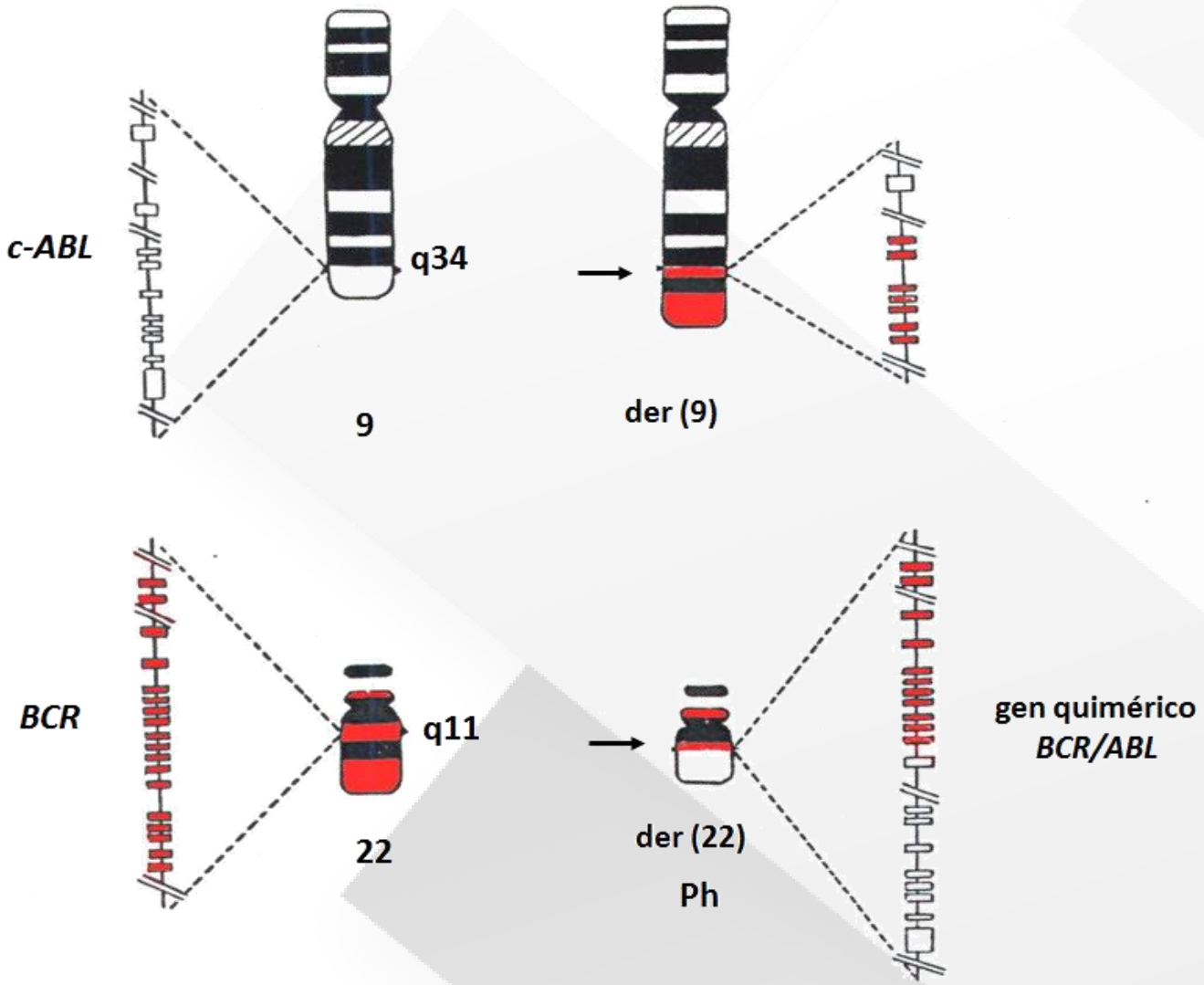
Oncogen: *BCR-ABL*



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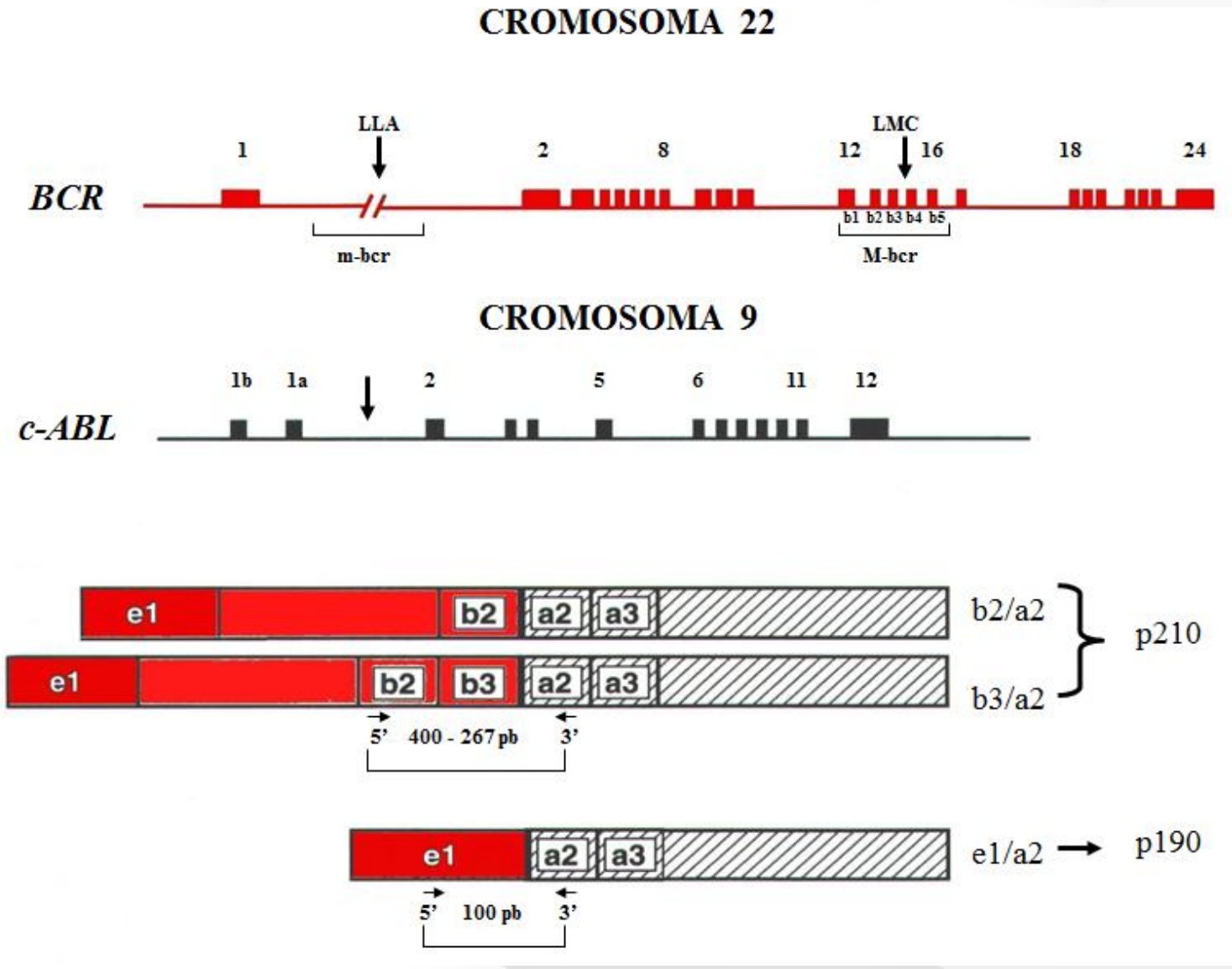
BCR-ABL: gen quimérico



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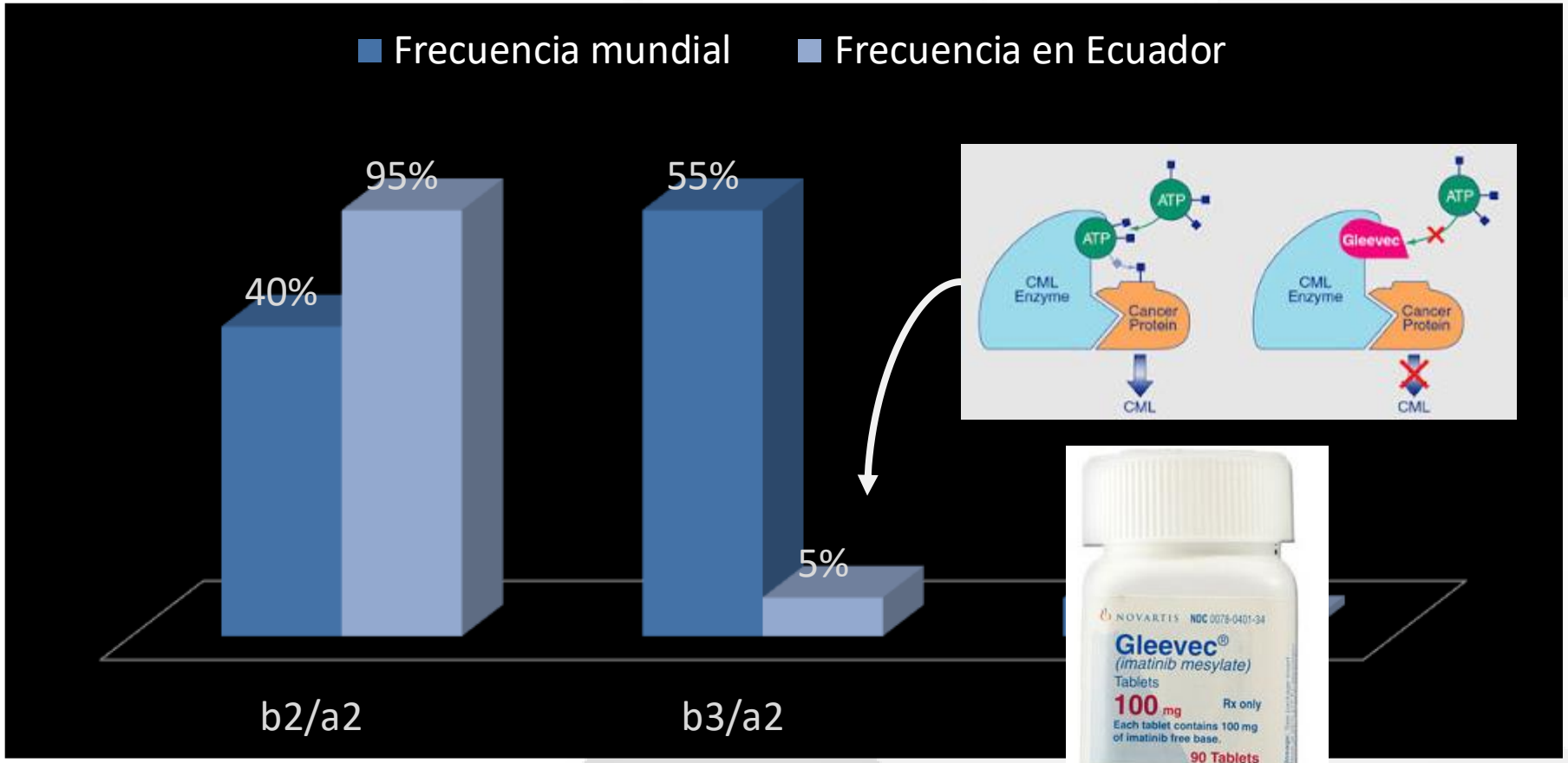
Rearreglos del gen influyen en respuesta a tratamiento



Cancer Genet Cytogenet. 2002; 132, 65-67; Leukemia Lymphoma. 2003; 44, 375-376

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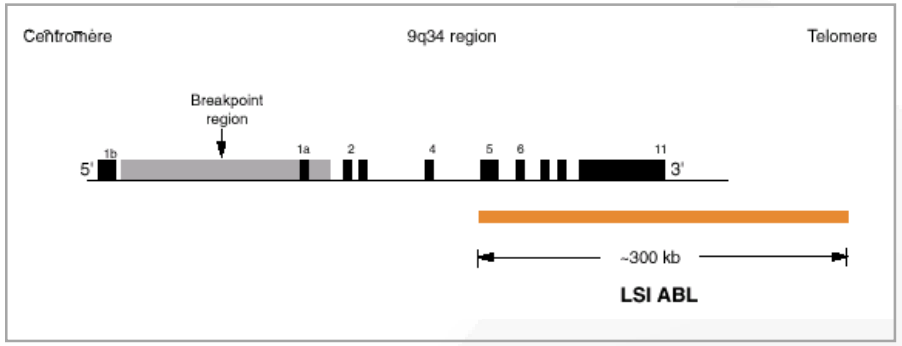
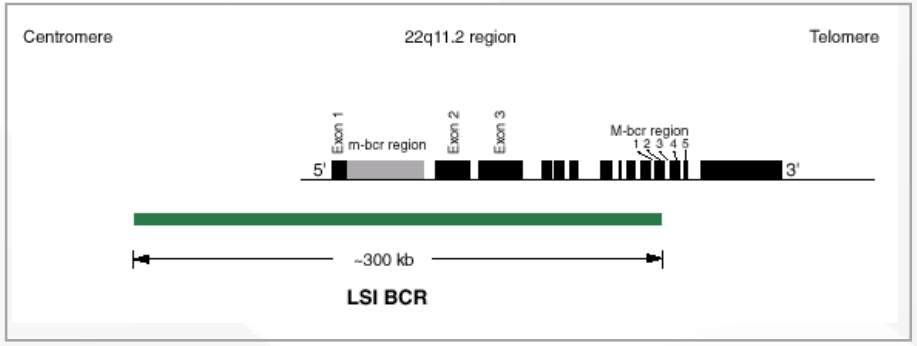
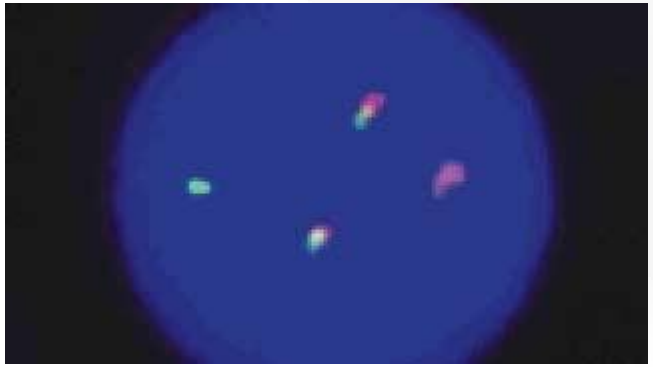
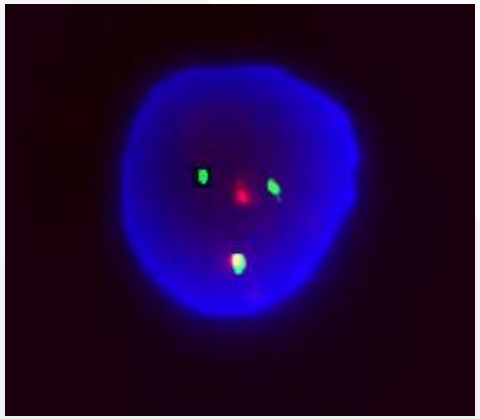
t(9;22) *BCR/ABL*: Deleción de 9q







LSI BCR/ABL Dual Color,
Dual Fusion Translocation Probe



10% del(9q34) ➡ pacientes refractarios a Glivec™

AEHH (2003)

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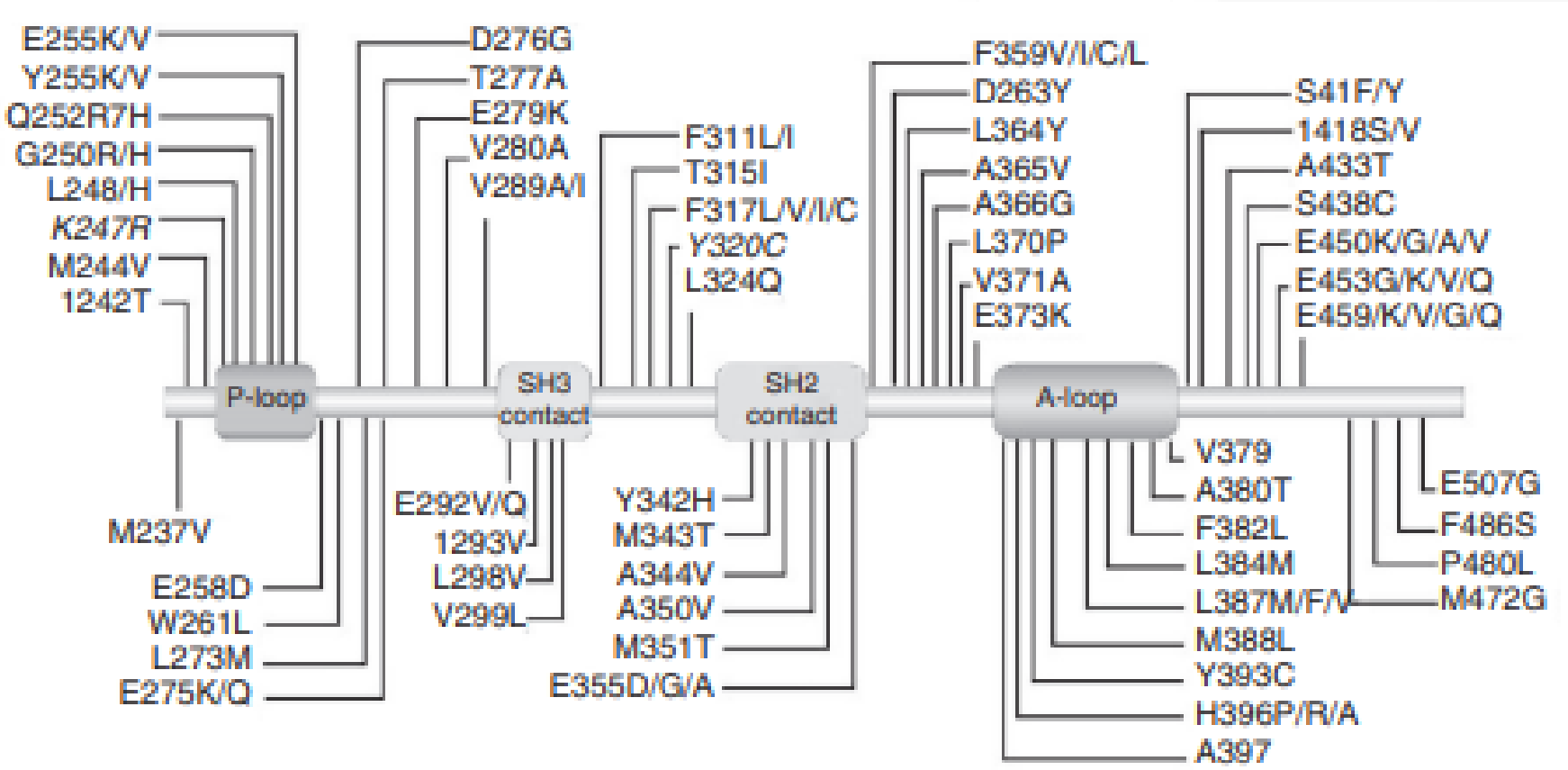
Mutaciones asociadas a resistencia a Imatinib

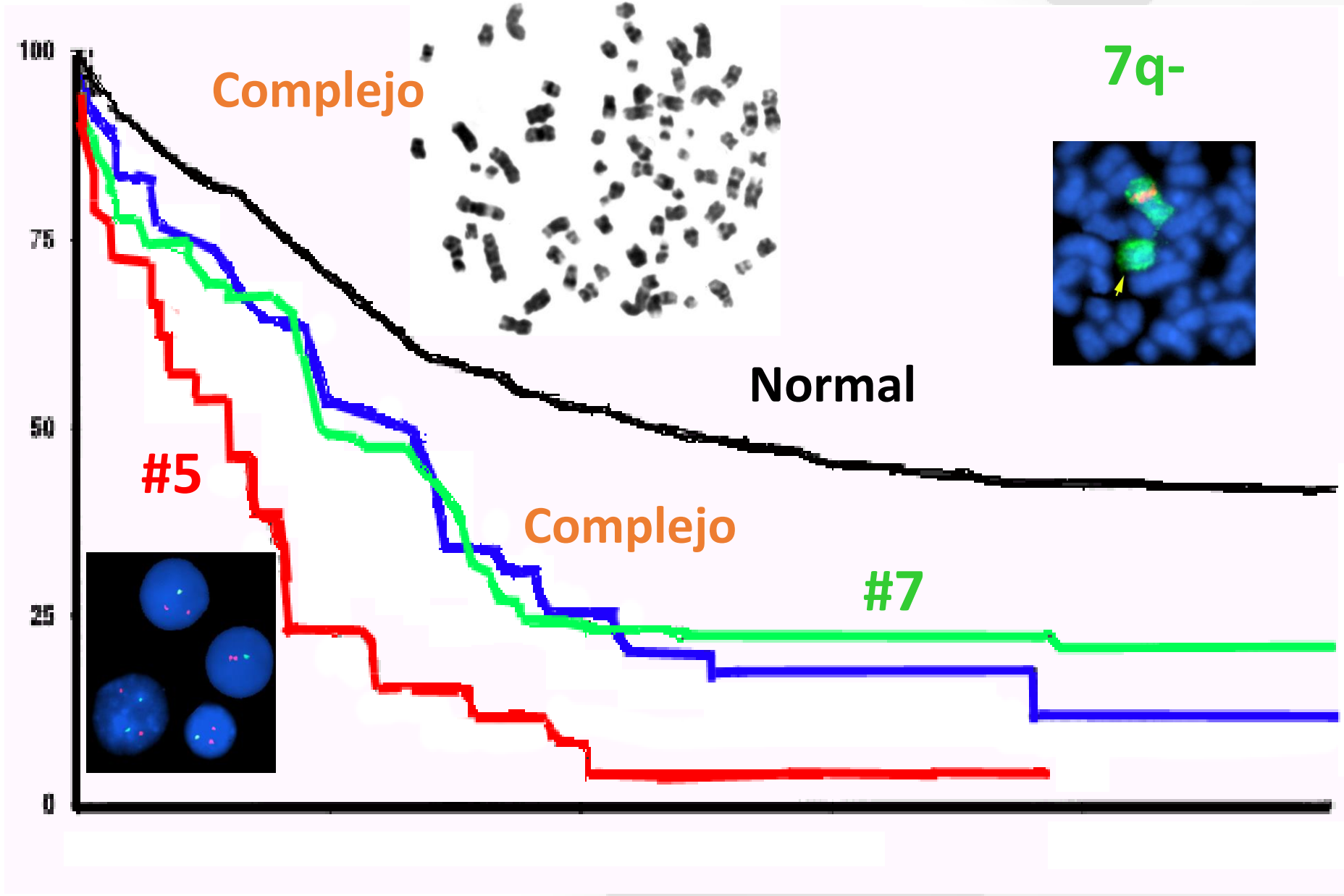


100 mutaciones

Leukemia Res. 2014; 38, 10-20

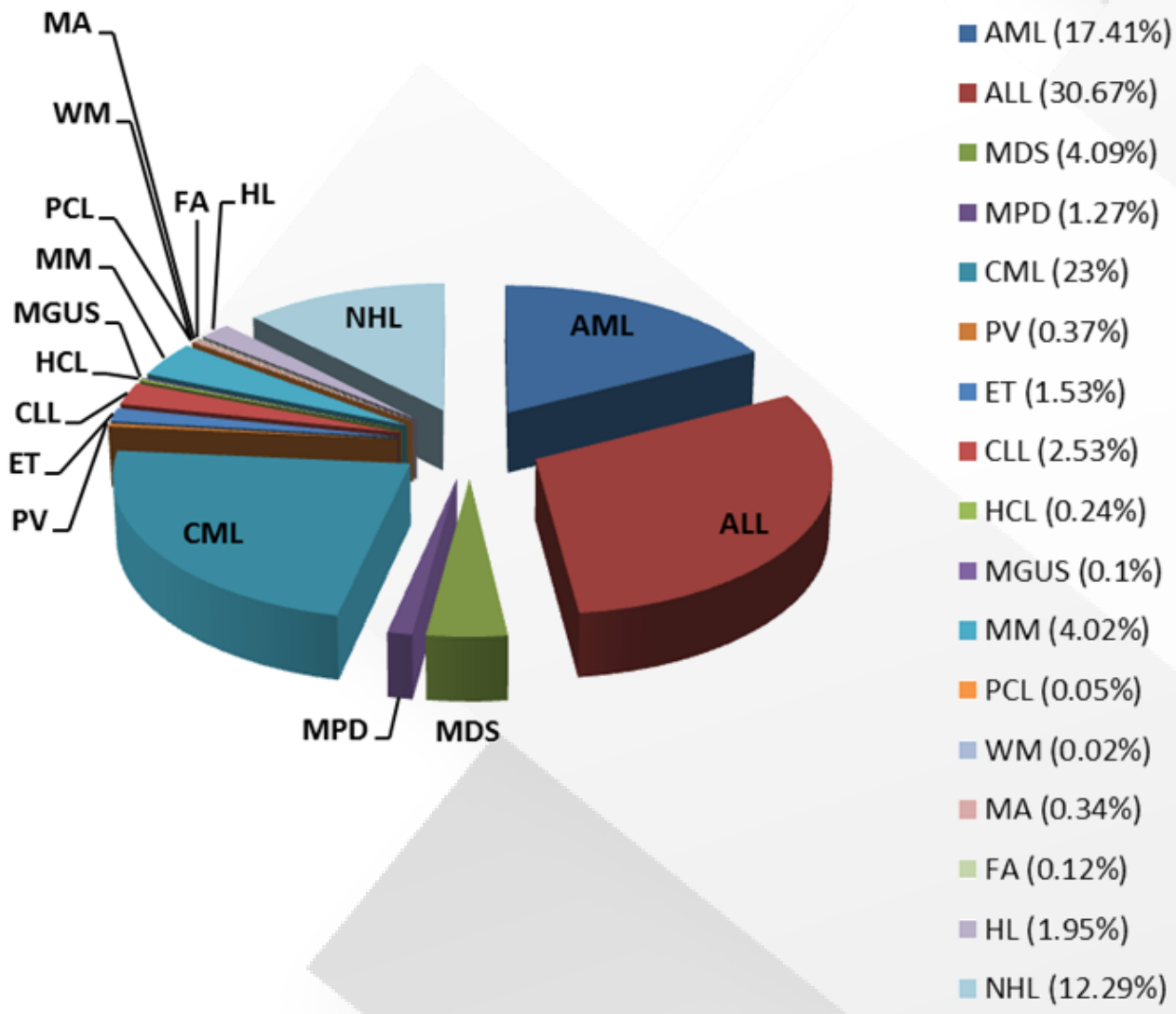
NÚCLEO DE QUITO

Leucemias: Pronóstico



NÚCLEO DE QUITO

Hemopatías en Ecuador 1984-2012



Open J Blood Diseases 3, 108-15 (2013)

NÚCLEO DE QUITO

Citogenética en hemopatías de Ecuador

Hematological diseases[a]	Cases (n)	Normal Karyotype		Altered Karyotype								No methaphases	
				Hyperdiploid		Hypodiploid		Translocation		Complex			
		n	%	n	%	n	%	n	%	n	%	n	%
AML	715	259	36.2	66	9.2	57	8.0	68	9.5	110	15.4	155	21.7
ALL	1260	419	33.3	102	8.1	92	7.3	99	7.9	191	15.2	357	28.3
MDS	168	75	446	15	8.9	9	5.4	4	2.4	20	11.9	45	26.8
MPD	52	26	50.0	8	15.4	3	5.8	3	5.8	8	15.4	4	7.7
CML	945	100	10.6	6	0.6	6	0.6	756	80.0	10	1.1	67	7.1
PV	15	9	60.0	1	6.7	1	6.7	0	0	0	0	4	26.7
ET	63	35	55.6	0	0	1	1.6	1	1.6	4	6.3	22	34.9
CLL	104	46	44.2	7	6.7	5	4.8	2	1.9	15	14.4	29	27.9
HCL	10	5	50.0	1	10.0	0	0	0	0	0	0	4	40.0
MGUS	4	3	75.0	0	0	0	0	0	0	0	0	1	25.0
MM	165	63	38.2	14	8. 5	7	4.2	8	4.8	30	18.2	43	26.1
PCL	2	1	50.0	0	0	0	0	0	0	0	0	1	50.0
WM	1	1	100.0	0	0	0	0	0	0	0	0	0	0
MA	14	5	35.7	0	0	0	0	0	0	2	14.3	7	50.0
FA	5	2	40.0	0	0	0	0	0	0	3	60.0	0	0
HL	80	56	70.0	3	3.8	2	2.5	0	0	9	11.3	10	12.5
NHL	505	300	59.4	30	5.9	27	5.3	14	2.8	66	13.1	68	13.5
Total	4108												

Instituto de Investigaciones Biomédicas

Sociedad de Lucha Contra el Cáncer
Núcleo de Quito

HCAM
IESS HOSPITAL CARLOS ANDRADE MARIN

Open J Blood Diseases 3, 108-15 (2013)

NÚCLEO DE QUITO

FISH & RT-PCR en casos sin metafases

FISH		RT-PCR		
AML				
probe	No. Cases	**fusion gene**	No. Cases	transcripts
t(8,21)	4	*AML1-ETO*	4	
t(15;17)	5	*PML-RARA*	11	4 (bcr2) & 7 (bcr3)
inv(16)	1	*CBFB-MYH11*	7	7 (type F)
(v 11q23)	3			
ALL				
probe	No. Cases	**fusion gene**	No. Cases	transcripts
t(9;22)	9	*BCR-ABL*	18	18 (e1a2)
(v 11q23)	10	*MLL-AF4*	4	4 (e8-e7)
t(1;19)	1	*E2A-PBX1*	1	7 (type F)
t(12;21)	9			
t(8;14)	2			
CML				
probe	No. Cases	**fusion gene**	No. Cases	transcripts
t(9;22)	7	*BCR-ABL*	65	62 (b2-a2) & 3(b3a2)

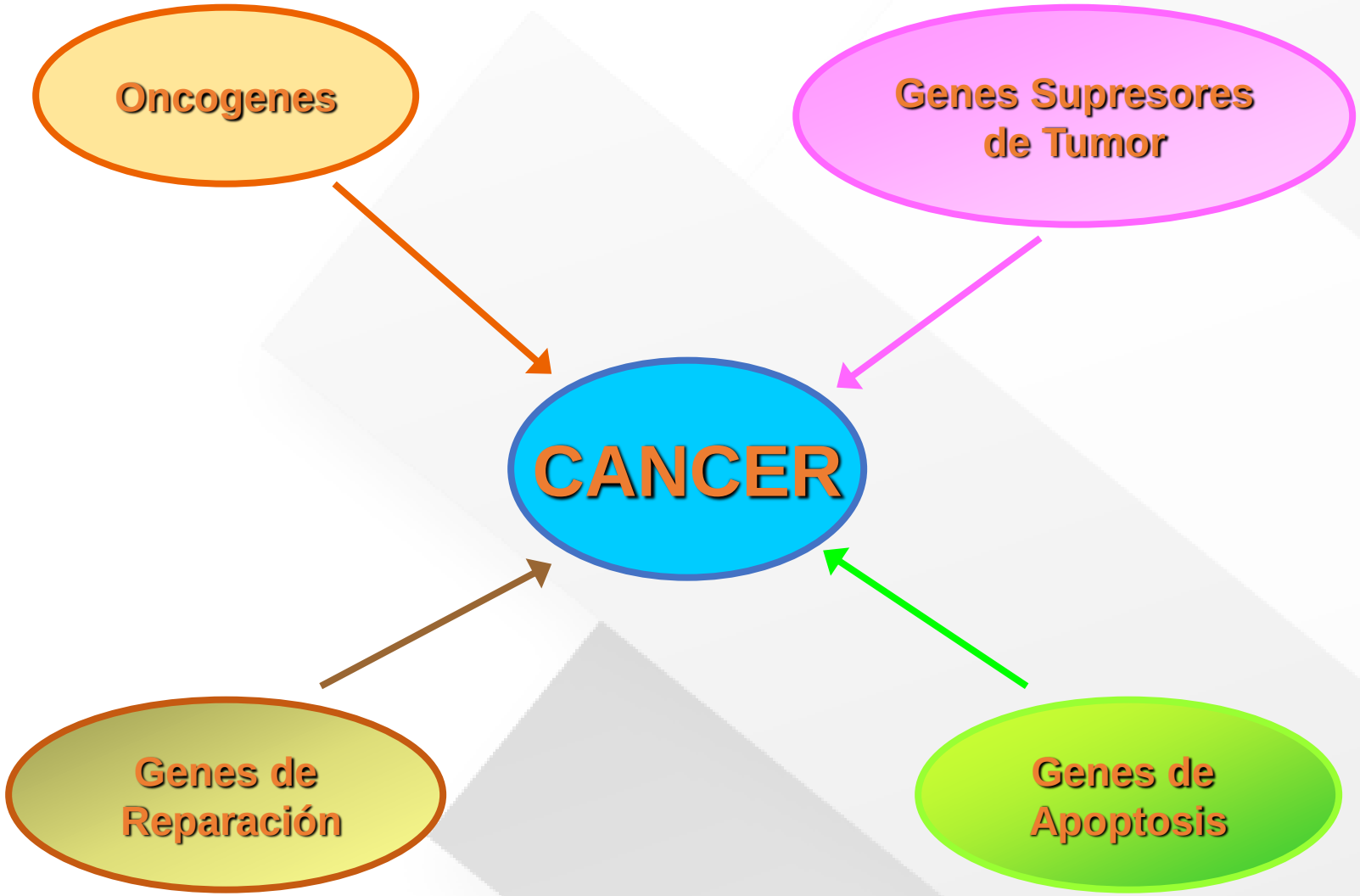
→ 1,8%

→ 4,1%

Open J Blood Diseases 3, 108-15 (2013)

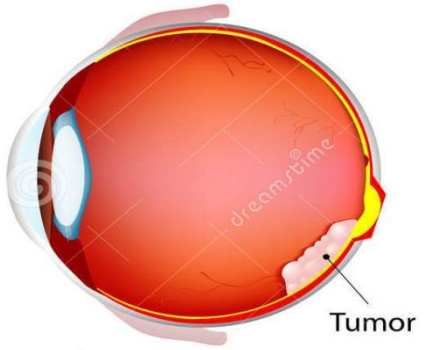
NÚCLEO DE QUITO

Genes de cáncer: Genes supresores de tumor

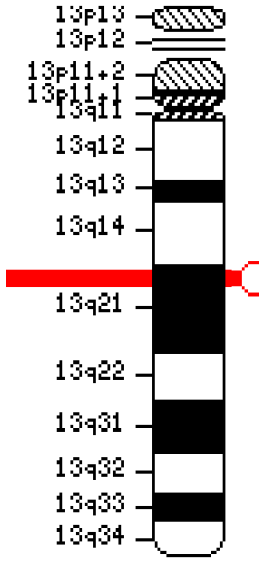


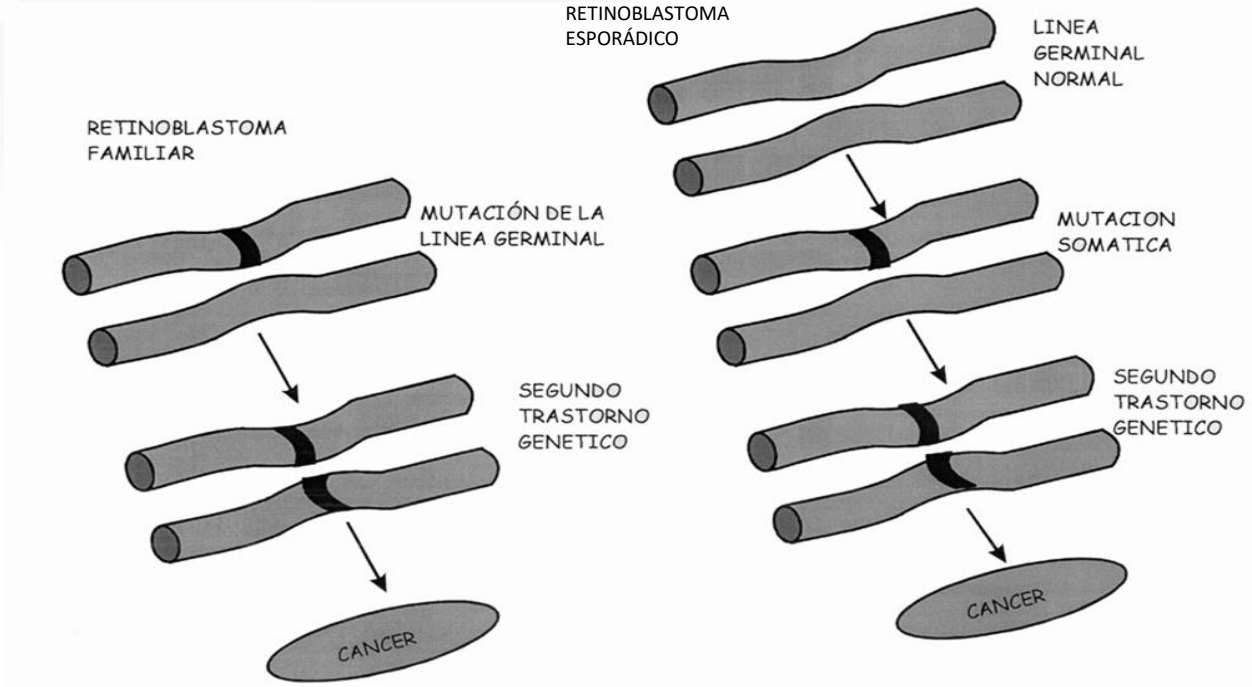
NÚCLEO DE QUITO

Gen supresor de tumor: *RB1*



Genes Supresores de Tumor





Teoría de Knudson: doble mutación

NÚCLEO DE QUITO

Gen *RB1*: Responsable de retinoblastoma

IVS3+45 T/C			
		Ecuador	España
Secuencia 1	AAATGA	0,125	0,64
Secuencia 2	AAACGA	0,875	0,36

IVS2+75 T/C			
		Ecuador	España
Secuencia 1	AAAAATTG	1	0,963
Secuencia 2	AAAAACTG	0	0,037

IVS4+23 G/T			
		Ecuador	España
Secuencia 1	AGGGTT	0,8	0,92
Secuencia 2	AGGTTT	0,2	0,08

IVS11-72 T/G			
		Ecuador	España
Secuencia 1	ATTGAAAA	1	0,91
Secuencia 2	ATGGAAAA	0	0,09

c1770 T/C			
		Ecuador	España
Secuencia 1	TTGTCC	1	0,98
Secuencia 2	TTGCCC	0	0,02

IVS19-77 A/G			
		Ecuador	España
Secuencia 1	AGCAATTT	0,9	0,895
Secuencia 2	AGCGATTT	0,1	0,115

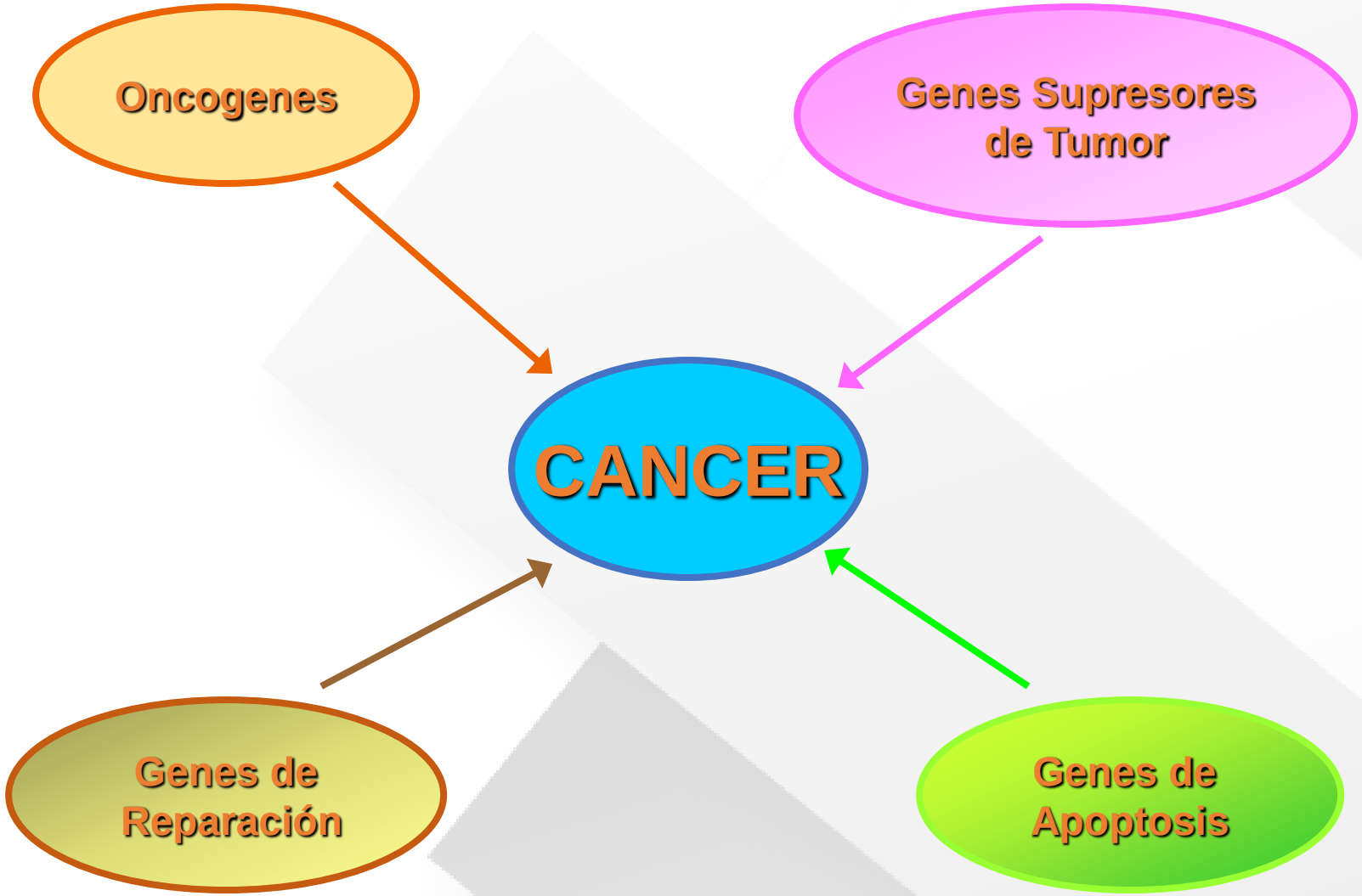
IVS16-57 A/delA			
		Ecuador	España
Secuencia 1	CAAAAAAAT	0,5	0,93
Secuencia 2	CAAAAAAT	0,5	0,07

IVS25-10 T/A			
		Ecuador	España
Secuencia 1	TTTTTTTA	0,86	0,76
Secuencia 2	TTTTTTAA	0,14	0,24

J Human Genetics.2003; 48, 639-641

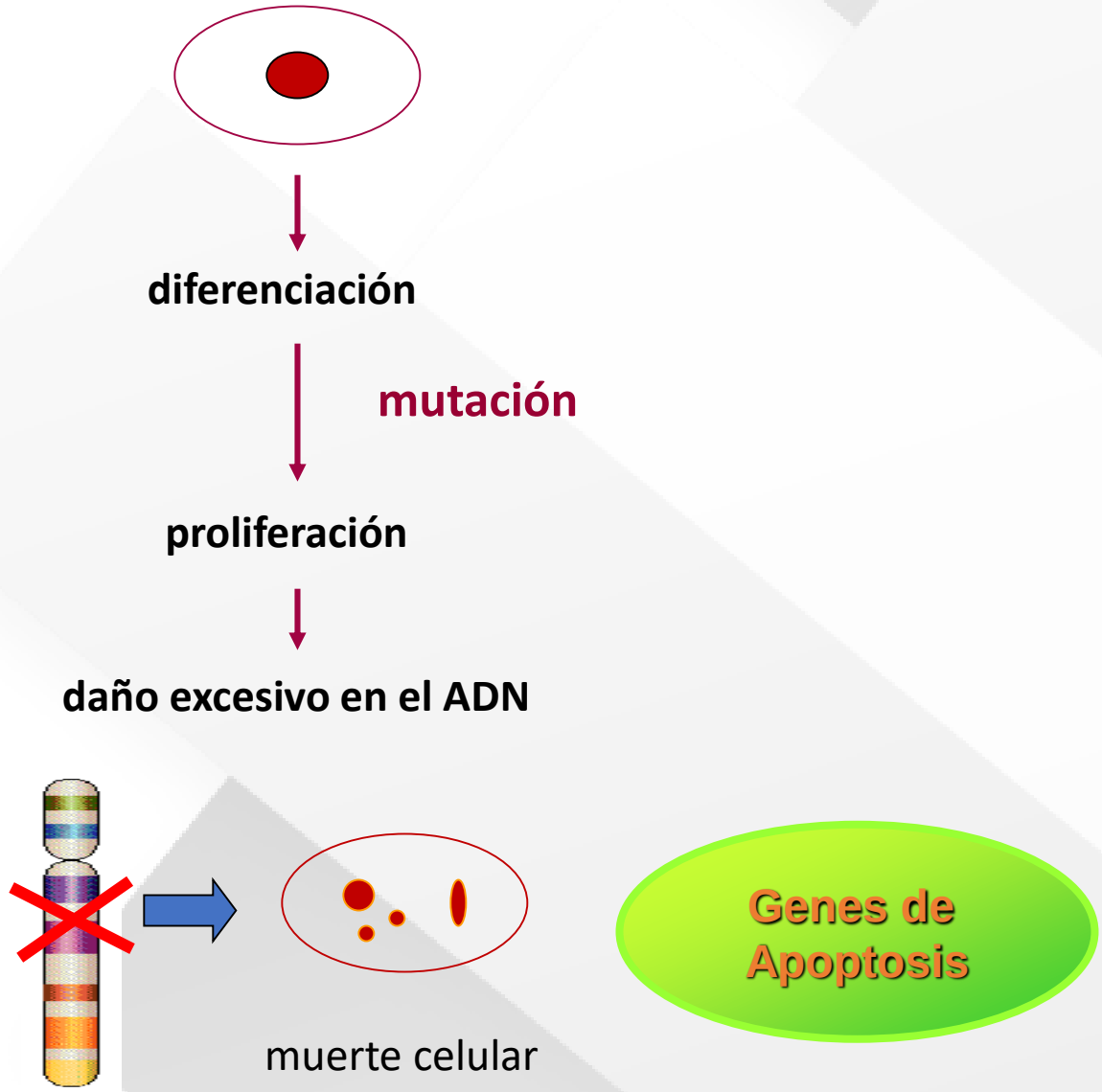
NÚCLEO DE QUITO

Genes de cáncer: Apoptosis



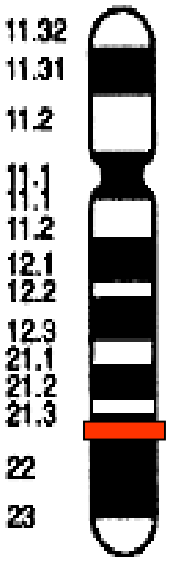
NÚCLEO DE QUITO

Apoptosis: muerte celular programada



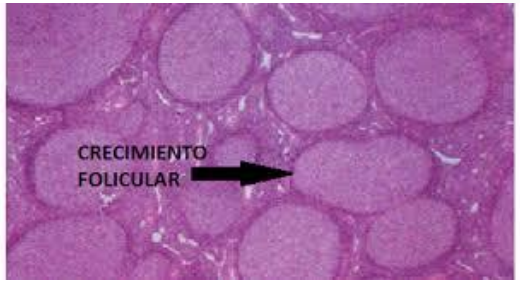
NÚCLEO DE QUITO

Bcl-2 / t(14;18) es rara en Ecuador

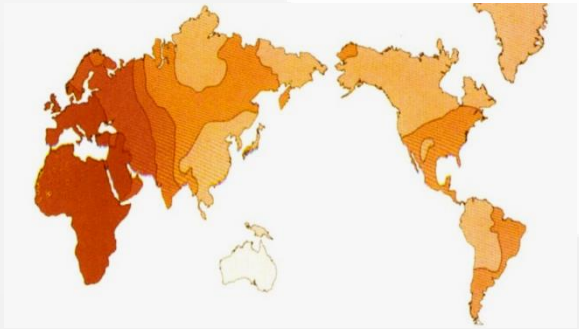


Non-Hodgkin lymphoma subtypes and frequency of MBR and mcr rearrangement of t(14;18)(q32;q21)

Non-Hodgkin lymphoma subtypes	Case no.	Incidence (%)	t(14;18)(q32;q21) rearrangements		
			MBR	mcr	Control
Follicular	5	7.7	—	—	5
Diffuse	60	92.3	—	—	60



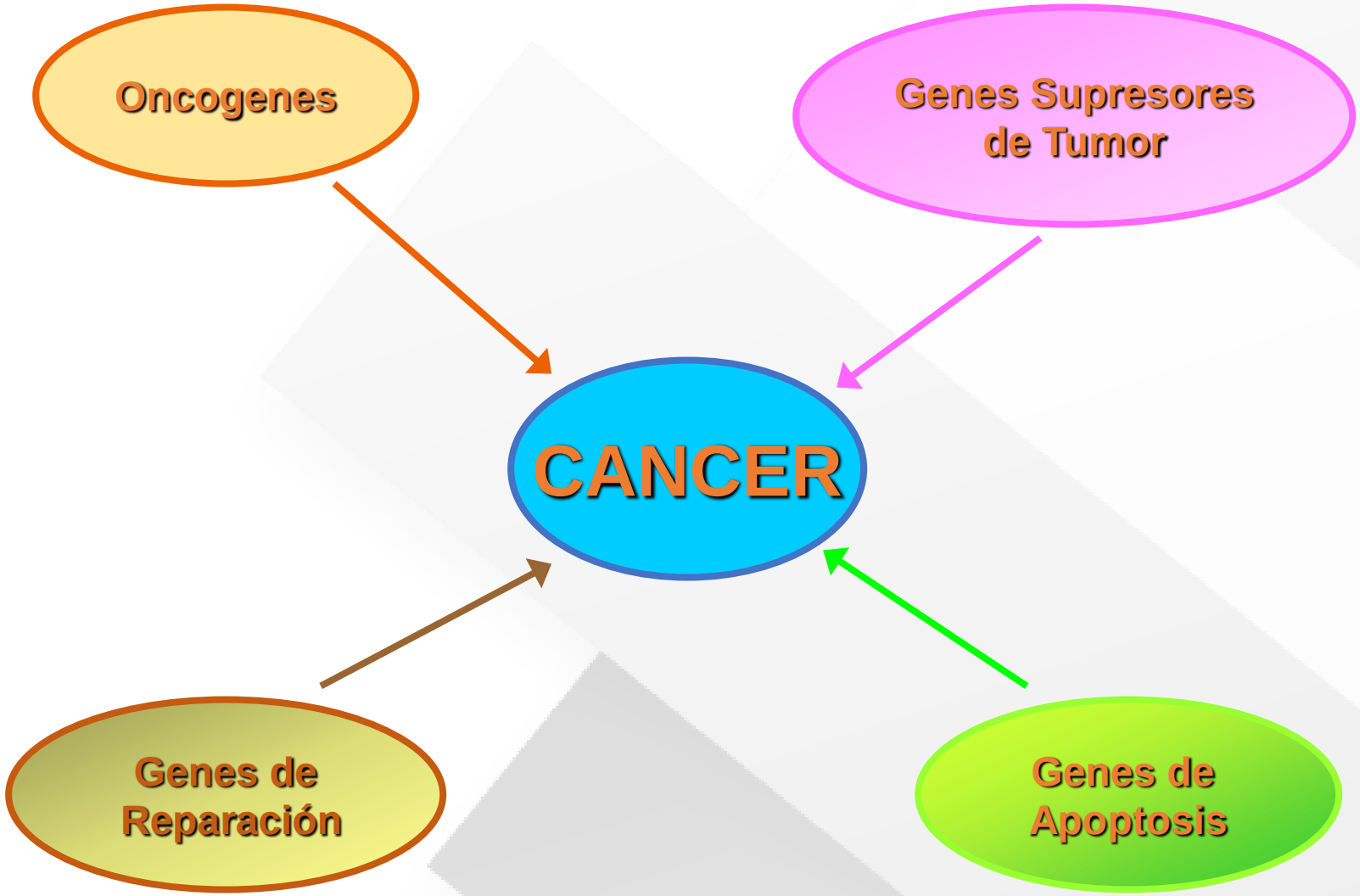
30-40% Norteamérica
20-30% Europa
10% Asia



Cancer Genet Cytogenet. 2002; 137, 72-74

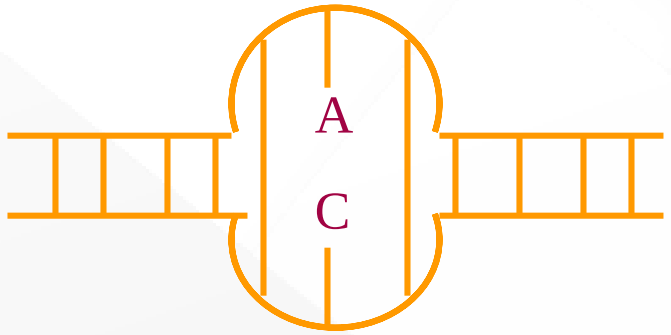
NÚCLEO DE QUITO

Genes de cáncer: Reparación

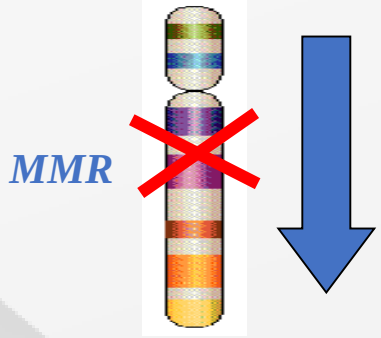


NÚCLEO DE QUITO

Reparación del ADN



mal emparejamiento



Genes de Reparación

ADN reparado

NÚCLEO DE QUITO

Gen de reparación: MSH2

2p21

Población	No. individuos analizados	No. cromosomas analizados	No. cromosomas polimorfismo	Frecuencia de C → T
Normal	40	80	4	0,05
Linfomas	22	44	5	0,11 p<0,01
Leucemias	10	20	1	0,05
FQ	7	14	3	0,21
DMD	2	4	1	0,25

Cancer Genet Cytogenet 133, 29-33 (2002); Leukemia Lymphoma 44, 505-508 (2003)

NÚCLEO DE QUITO

Genes de reparación en hemopatías

RAD54

Table 1 - Distribution of the 2290 C/T polymorphism in leukemia (CML, ALL) and control populations.

Group	Genotype	Individual (%)	Genotypic frequency	Allele frequency
Leukemia ($n = 137$)	C/C	112 (82)	0.82	0.9
	C/T	23 (17)	0.17	
	T/T	2 (1)	0.01	0.1
CML ($n = 60$)	C/C	45 (75)	0.75	0.86
	C/T	13 (22)	0.22	
	T/T	2 (3)	0.3	0.14
ALL ($n = 61$)	C/C	55 (90)	0.90	0.95
	C/T	6 (10)	0.10	
	T/T	0 (0)	0	0.05
Control ($n = 102$)	C/C	87 (85)	0.85	0.925
	C/T	15 (15)	0.15	
	T/T	0 (0)	0	0.075

hMSH2

Table 1
Distribution of the allele found (gIVS12-6T>C)

	Number of individuals				Polymorphism frequency	% of individuals with the polymorphism
	Analyzed	T/T	C/T	C/C		
Normal	50	46	3	1	0.05	7.5
NHL	22	17	5	0	0.114*	22.73*

Abbreviation: NHL, non-Hodgkin lymphoma.
*$P<0.01$ when compared with normal group.

TABLE I Distribution of the allele [gIVS12-6T > C]

Group	Number of individuals				Polymorphism Frequency
	Sample size	T/T	T/C	C/C	
Control	50	46	3	1	0.05
Lymphoma	87	70	17	0	0.09**
Leukemia	90	81	8	1	0.05
MDS	4	4	0	0	0.00

**Significant differences when compared to the control group ($p < 0.01$).

Genet Mol Biol. 33(4), 646-9 (2010); Leukemia & Lymphoma 44, 375-6 (2003); Cancer Genet Cytogenet 133, 29-33 (2002)

NÚCLEO DE QUITO

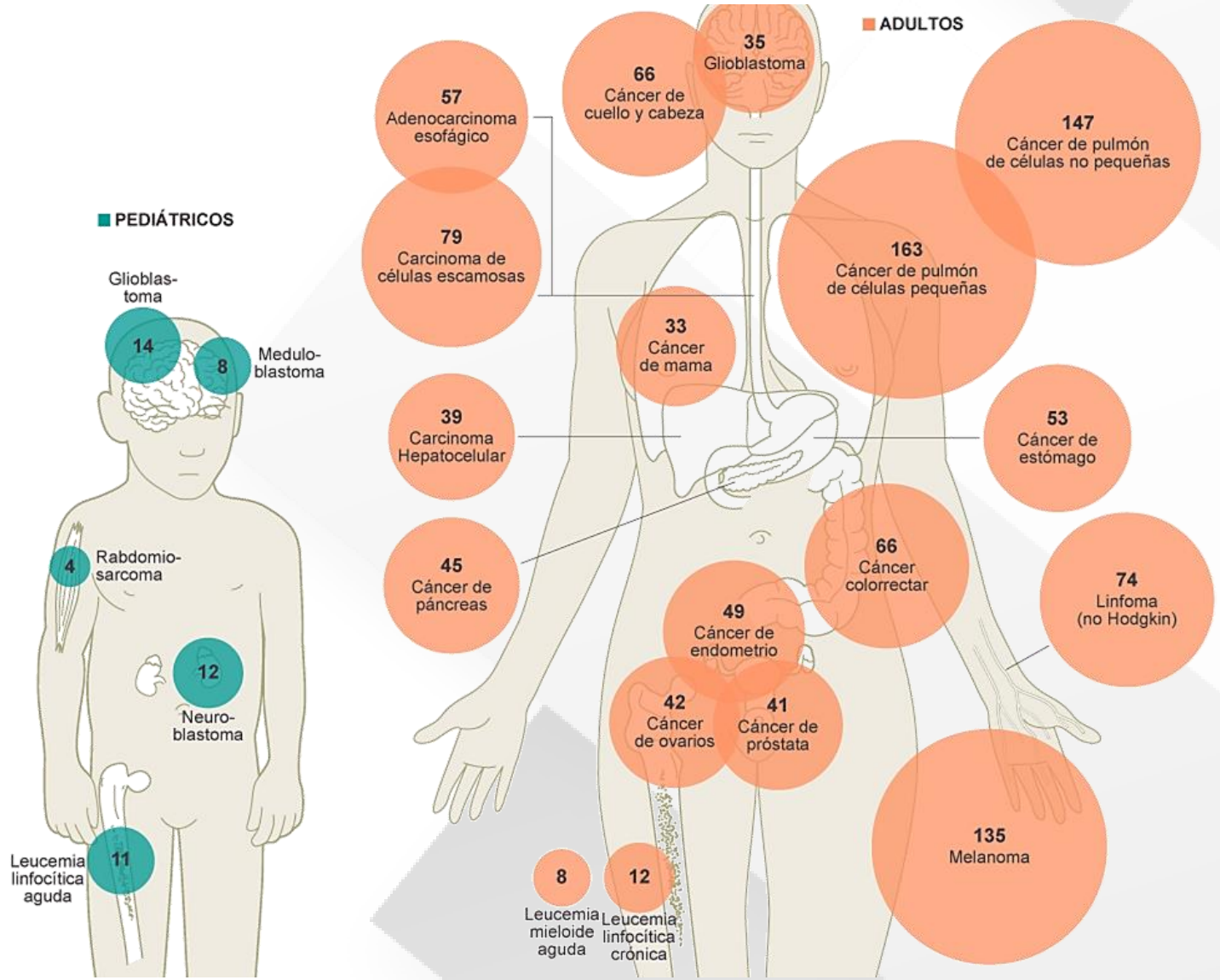
Genes de reparación en retinoblastoma

SNP	GENOTIPO	Casos (n=80), n %	Controles (n=80), n %	OR[a]	95% IC[b]	P
rs13181 ERCC2	A/A	48 (60,0)	60 (765)	1,0[R]	-	-
	A/C	31 (38,75,0)	19 (23,8)	2,03	1,02 - 4,04	0,040[S]
	C/C	1 (1,25)	1 (1,3)	1,25	0,07 – 20,5	0,69
	A/C + C/C	32 (40,0)	20 (25,0)	2	1.01 – 3,92	0,042[S]
rs2228001 XPC	A/A	21 (26,25)	30 (37,5)	1,0[R]		
	A/C	45 (56,25)	43 (53,8)	1,49	0,74 - 3,00	0,25
	C/C	14 (17,5)	7 (8,8)	2,86	0,99 - 8,28	0,052
	A/C + C/C	59 (73,75)	50 (62,5)	1,69	0,86 - 3,30	0,126
rs17655 XPG	G/G	23 (28,75)	14 (17,5)	1,0[R]		
	G/C	56 (70,0)	65 (81,3)	0,52	0,24 - 1,11	0,09
	C/C	1 (1,25)	1 (1,1)	0,61	0,03 - 10,5	0,62
	G/C + C/C	57 (71,25)	66 (82,5)	0,52	0,25 - 1,12	0,09
rs25487 XRCC1	G/G	9 (11,25)	43 (53,8)	1,0[R]		
	A/G	70 (87,6)	27 (33,8)	12,4	5,3 - 28,82	< 0,001[S]
	A/A	1 (1,25)	10 (12,5)	0,47	0,05 - 4,2	0,44
	A/G + A/A	71 (88,75)	37 (46,25)	9,1	4,03 – 20,8	< 0,001[S]
rs861539 XRCC3	C/C	65 (85,0)	68 (85,0)	1,0[R]		
	C/T	14 (13,8)	11 (13,8)	1,33	0,56 - 3,14	0,51
	T/T	1 (1,3)	1 (1,3)	1,04	0,06 - 17,0	0,740
	C/T + T/T	15 (18,75)	12 (15,0)	1,31	0,57 - 3,00	0,53

Genética en el Ecuador: 30 años CO-34, 505-506 (2016)

NÚCLEO DE QUITO

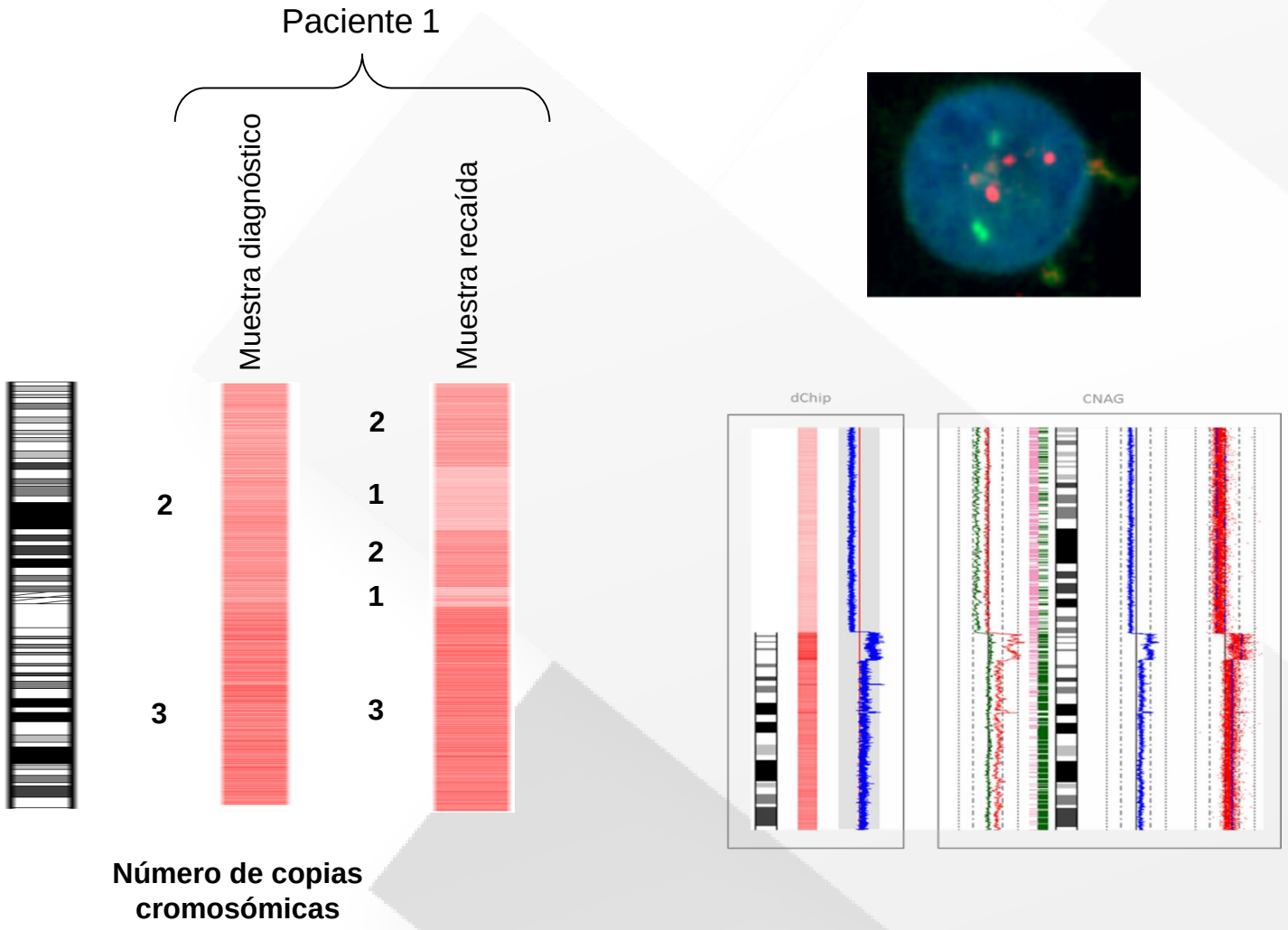
Genes del cáncer



Tomado de Science, 2013

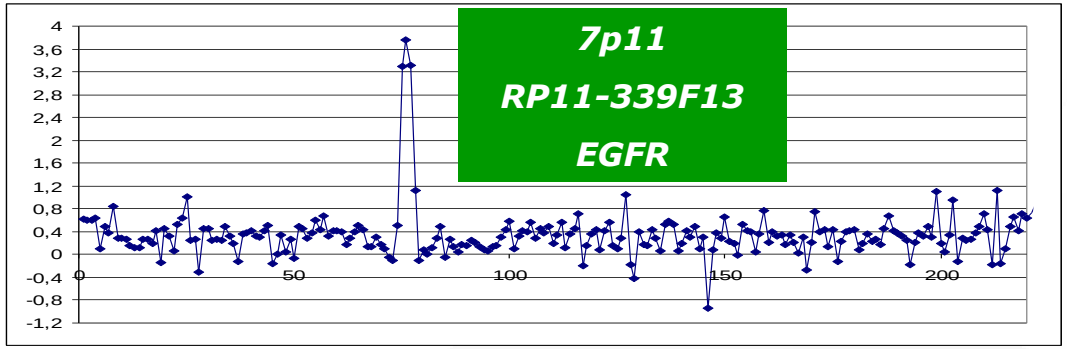
NÚCLEO DE QUITO

Seguimiento de pacientes con Mieloma

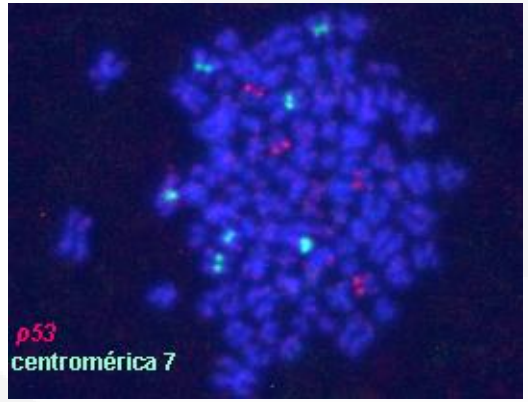


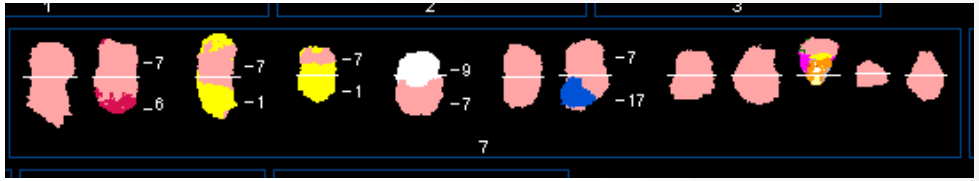
NÚCLEO DE QUITO

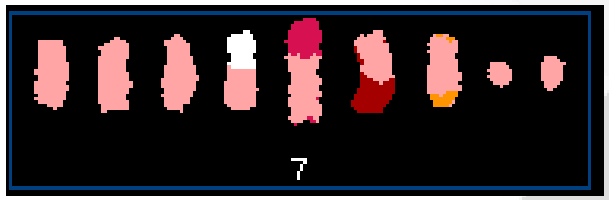
Daño de 7p11: Receptor de factor de crecimiento



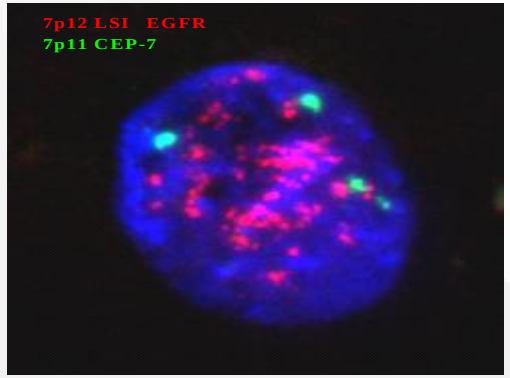
CGH array



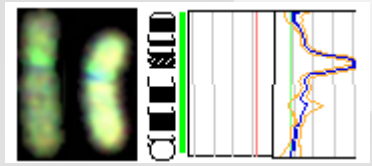




SKY



FISH



CGH

NÚCLEO DE QUITO

MM: Evolución de la enfermedad

45 años
Dolor lumbar
3% CP

46,XX/166,XX

RB1: N
P53: del (36%)
IgH: t (40%)
t(4;14)

1q21: N
6q21: N

14/05/2019

4 ciclos

46,XX

RB1: N
P53: N
IgH: N

1q21: G
6q21: G
9q34: N
11q21: G
15q22: N
19q13: N

05/09/2019

8, 6, 3 ciclos

46,XX

RB1: N
P53: N
IgH: t (9%)
t(4;14)
t(11;14)
t(14;20)

1q21: N
6q21: N
9q34: N
11q21: N
15q22: N
19q13: N

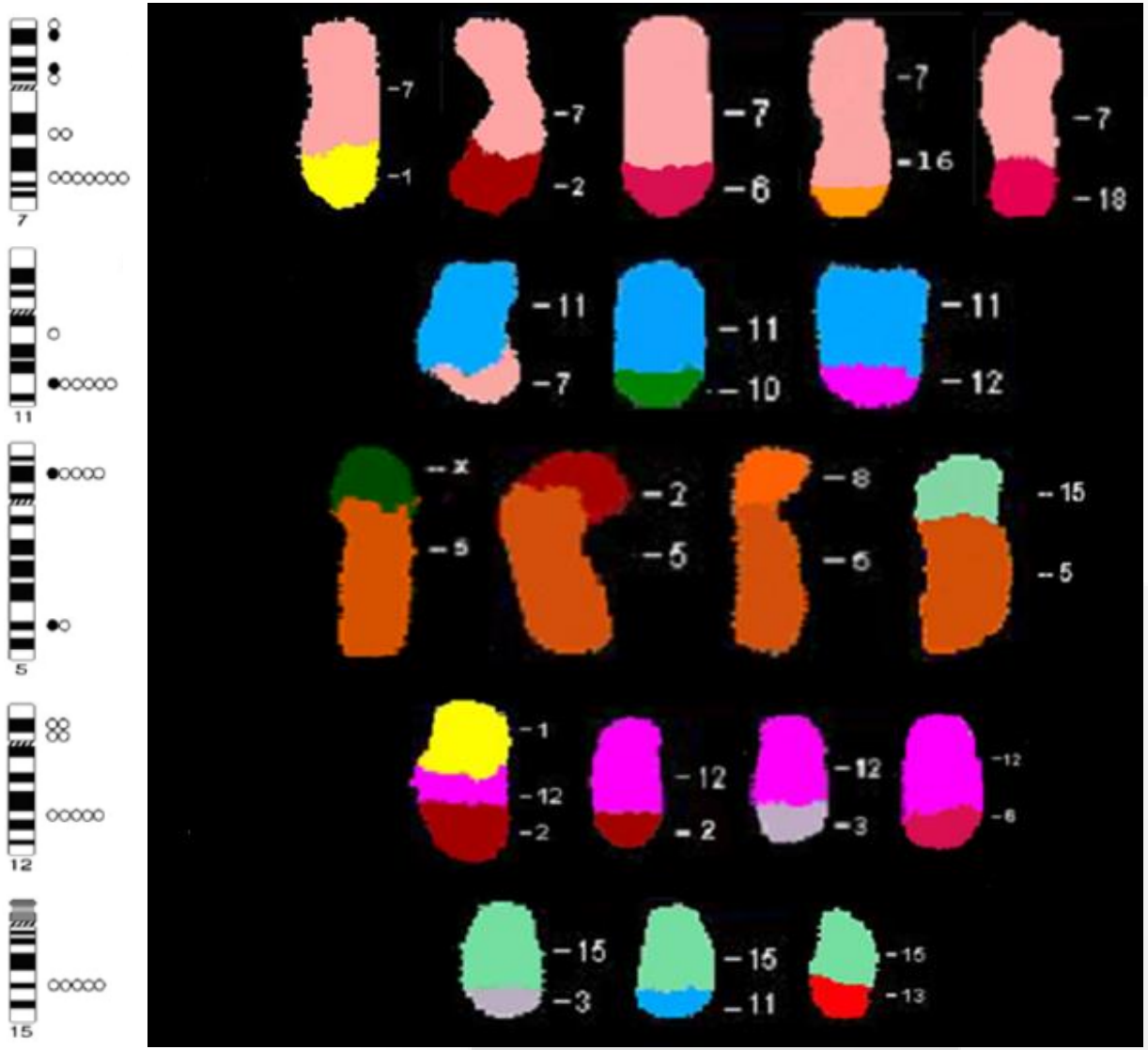
16/01/2020

pronóstico
recaída
trasplante

Rotura de vértebra

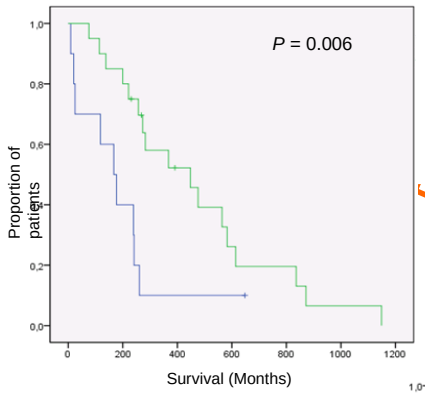
NÚCLEO DE QUITO

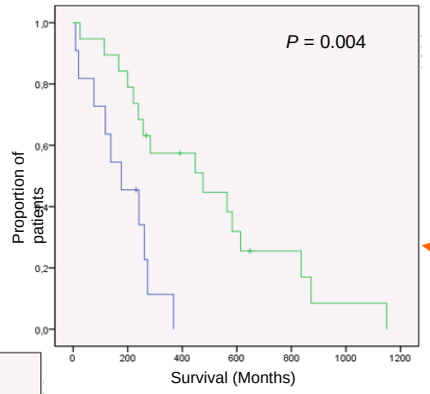
Glioblastoma: Puntos de rotura frecuentes por SKY

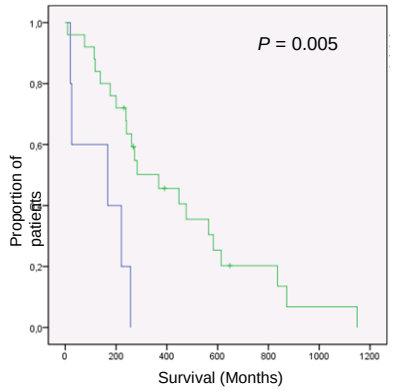


NÚCLEO DE QUITO

Efecto de los 406 genes en supervivencia







Fold change >2 (GBM vs NORMAL)
AKR7A2, C1orf144, C1QA, C1QB, CAPZB, CLIC4, DDOST, EIF1AX, ENO1, FUSIP1, HMGN2, ID3, NECAP2, NPM1, PDPN, PGD, RER1, RPL11, RPL12, RPL18A , RUNX3, SH3BGRL3, TNFRSF1B, VAMP3
ACOT7, CAMK2N1, CAMTA1, CDC42, CHD5, CLSTN1, DVL1, EXTL1, FBXO2, GABRD, KCNAB2, KIF1B, LUZP1, NBL1, PINK1, PRDM2, PRKCZ, RAP1GAP, RERE, RP1-21O18.1, STMN1, UBE4B, VPS13D
C1orf106, CHI3L1, DTL, DYRK3, IKBKE, KIF14, MAPKAPK2, PTPRC, RNPEP, TMEM189-UBE2V1
CAMK1G, DSTYK, KIF21B, NFASC, PLXNA2, PPFIA4, TIMM17A, TMCC2
EIF2AK2, PRKD3, RPLP0, SFRS7
FAM98A
ARF4, WNT5A
CACNA2D3, ERC2, FEZF2, MAGI1
DAG1, GNAI2, GPX1, HYAL2, IFRD2, MAP4, NT5DC2, RHOA, SMARCC1, STAB1, TKT, ZNF167
BSN, CAMKV, CELSR3, DOCK3, IP6K1, LZTFL1, NCKIPSD, NISCH, P4HTM, SEMA3B
ACTL6A, BCHE, FNDC3B, FXR1, GMPS, KPNA4, MFSD1, NMD3, PLOD2, PLSCR1, RAP2B, RARRES1, SELT, SERP1, SGEF, SMC4, SOX2, WWTR1
KCNAB1, PLCH1, SERPINI1
FAM114A1, LAP3, MED28, NCAPG, **PROM1**, RBM47
LDB2, QDPR, SLIT2
MSN
AKTIP, CDH10, CDH18
ANKHD1, CD14, CD74, CDC25C, CSF1R, CSNK1A1, DCTN4, DPYSL3, EGR1, G3BP1, GALNT10, GM2A, H2AFY, KIF20A, KIF4A, PCDHGA 1-12, PCDHGB 1-7, PCDHGC 3-4, SAR1B, SPARC, TGFBI, TXNDC15
CAMK2A, CYFIP2, FABP6, KLHL3, LARP1, LRRTM2, PCDHA 1-13, PCDHC 1-2, PCYOX1, **PPP2R2B**, RURA, SKP1, UBE2D2
ARPC1B, CDK6, GAL3ST4, GNB2, MCM7, POLR2J, SERPINE1, SLC25A13, SRI, SRRT, SYPL1, TFPI2, ZNHIT1
ACTL6B, ASNS, DYNC1I1, GRM3, PCLO, PFTK1, PRKAR2B, RUNDC3B, SRPK2, TAC1
CALU, EEF1G, UBE2H
DERL1, GPR172A, MYC, RPL8, SLA, TMED10
EFR3A, ENPP2, LY6H, PTK2

Genes con efecto en supervivencia

NÚCLEO DE QUITO

Gen *XRCC1*: mutación nueva

GeneView via analysis of contig annotation: XRCC1 *X-ray repair cross complementing 1*

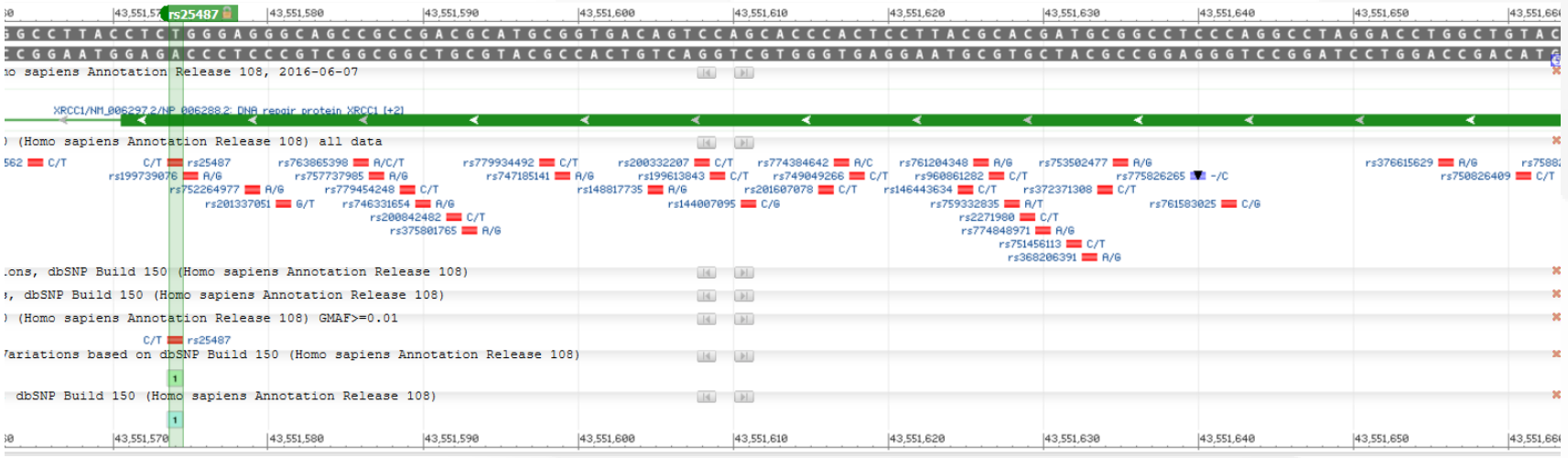
View more variation on this gene (click to hide).

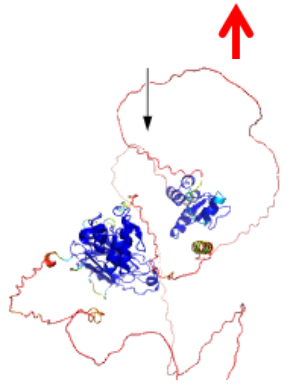
Clinical Source: ○ in gene region ◉ cSNP ○ has frequency ○ double hit [Go]

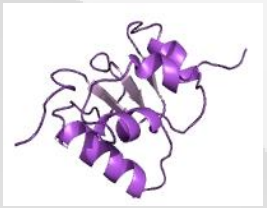
Primary Assembly Mapping

Assembly	SNP to Chr	Chr	Chr position	Contig
GRCh38.p7	Rev	19	43551574	NT_011109.17

a 82pb ➡ 43.551.656 C>T





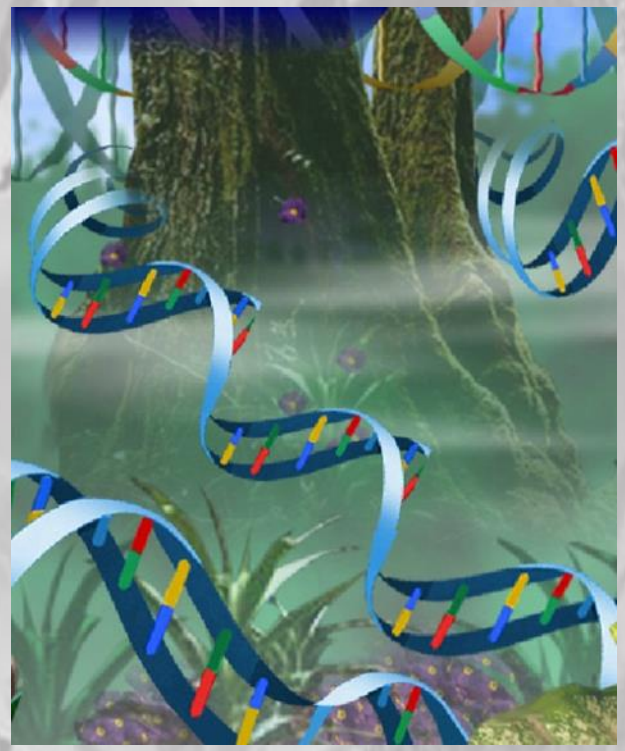


Allele	
Variation Class:	SNV: single nucleotide variation
RefSNP Alleles:	A/G (REV)
Allele Origin:	
Ancestral Allele:	G
Clinical Significance:	With drug-response allele [ClinVar]
MAF/MinorAlleleCount:	T=0.2604/1304 (1000 Genomes) T=0.2908/3782 (GO-ESP) T=0.2639/7685 (TOPMED)

Genética en el Ecuador: 30 años PO-34, 569-570 (2016)

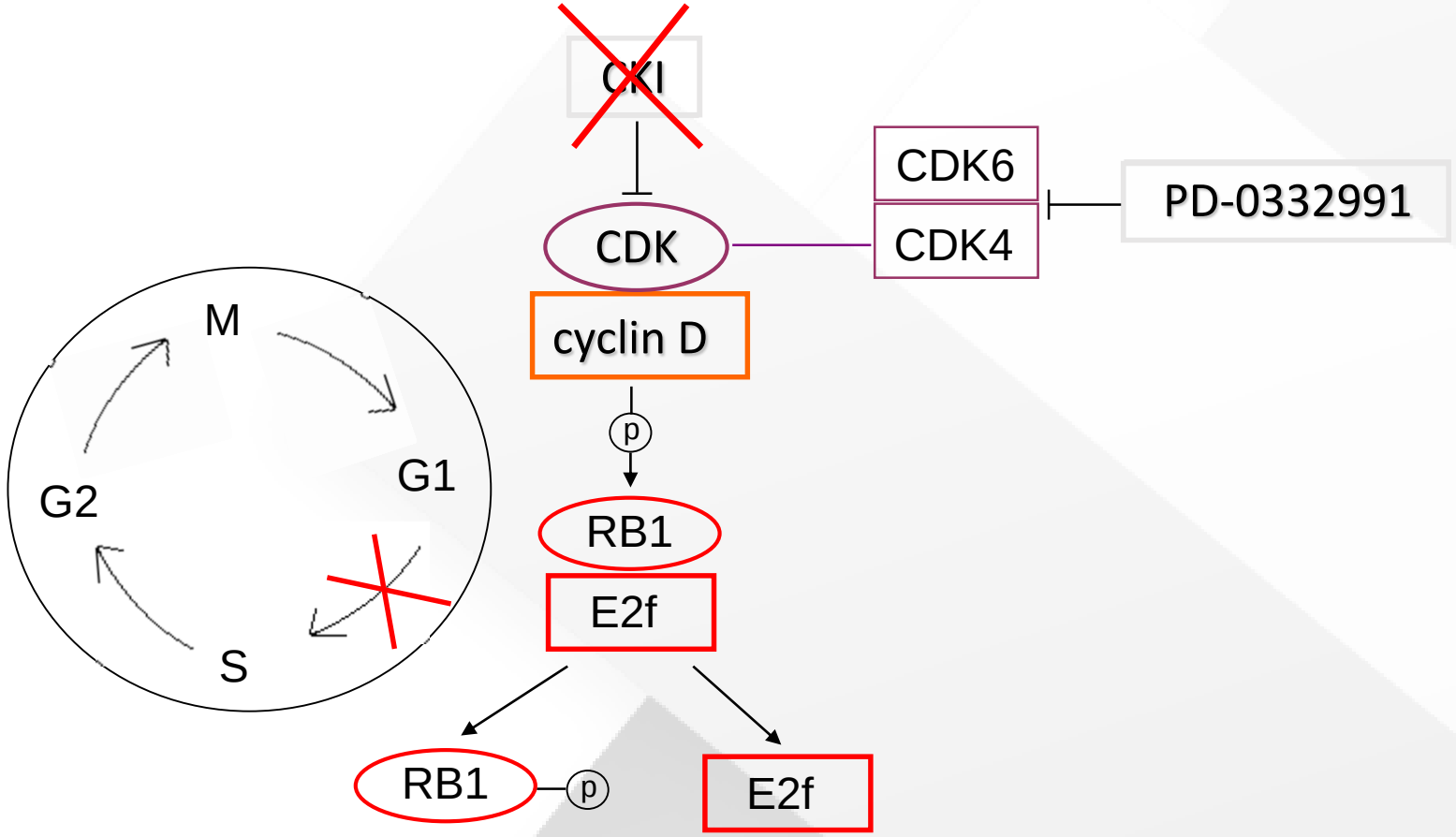
NÚCLEO DE QUITO

ADN: base del cáncer



NÚCLEO DE QUITO

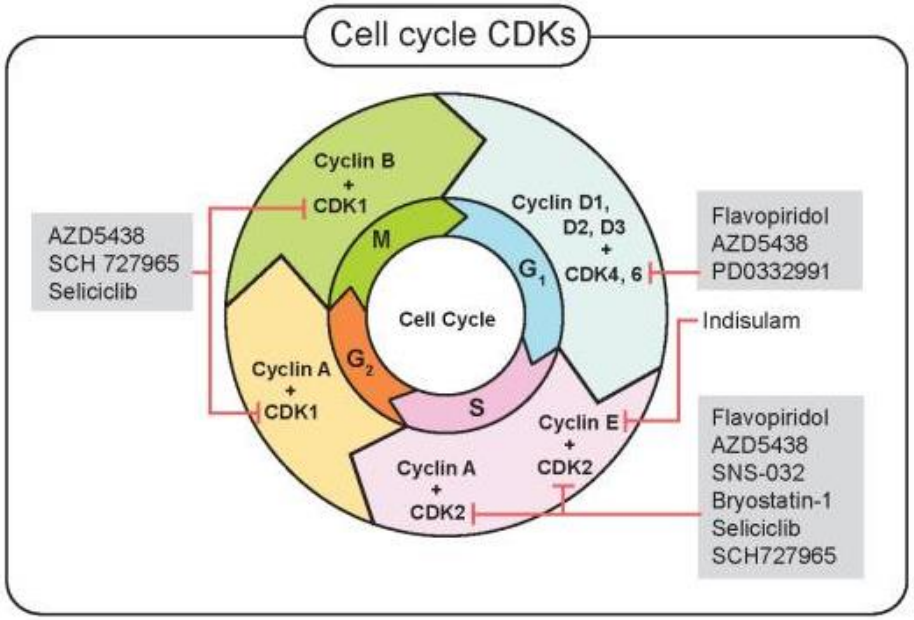
PD-0332991 es un inhibidor de *CDK4* y *CDK6*

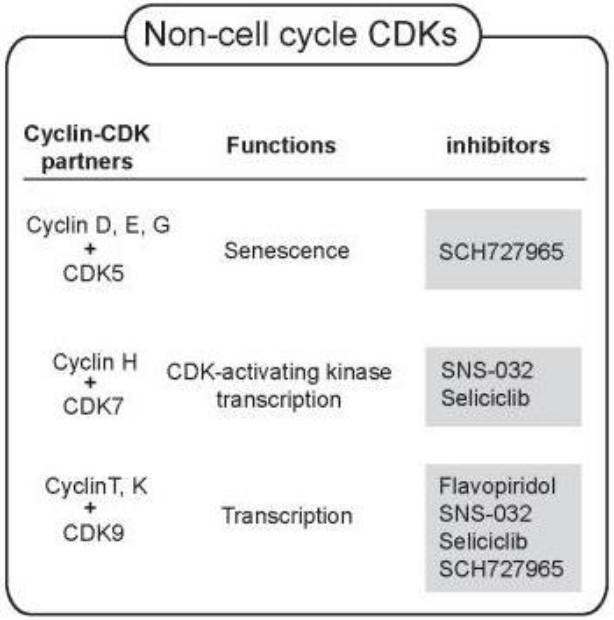


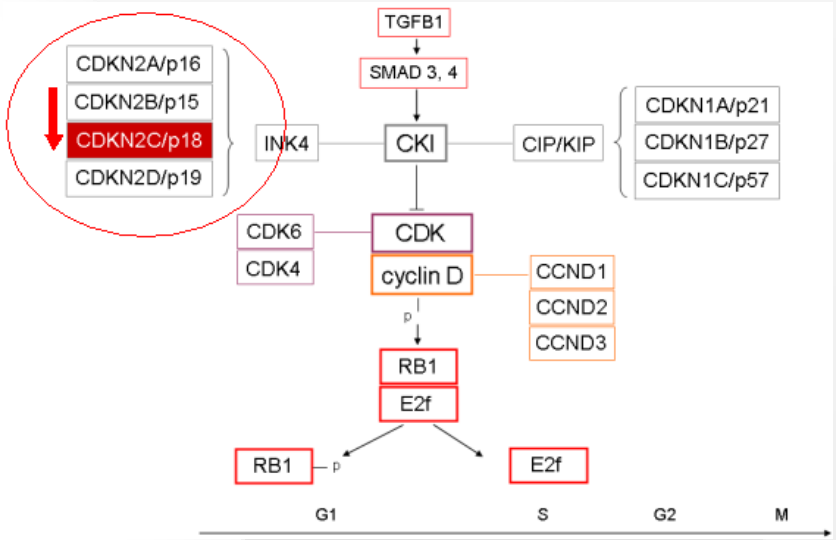
ClinicalTrials.gov: NCT00555906

NÚCLEO DE QUITO

Inhibidores de CDKs







Curr Oncol 16(2), 36–43 (2009)

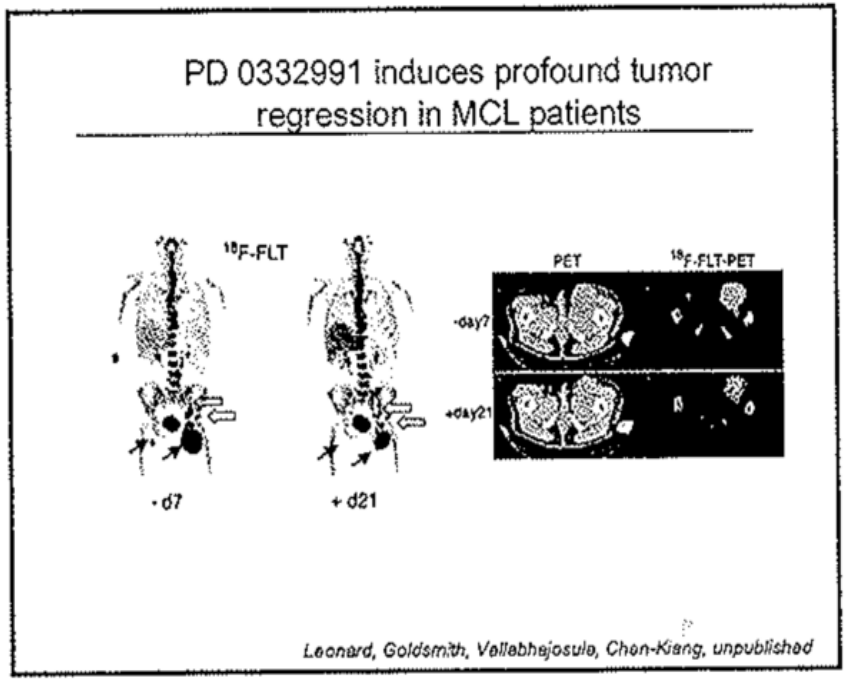
NÚCLEO DE QUITO

www.aacrjournals.org Clin Cancer Res 2008;14(19), 2008

Human Cancer Biology

Deletions of *CDKN2C* in Multiple Myeloma: Biological and Clinical Implications

Paola E. Leone,[1] Brian A. Walker,[1] Matthew W. Jenner,[1] Laura Chiecchio,[2] GianPaolo Dagrada,[2] Rebecca K.M. Protheroe,[2] David C. Johnson,[1] Nicholas J. Dickens,[1] Jose Luis Brito,[1] Monica Else,[1] David Gonzalez,[1] Fiona M. Ross,[2] Selina Chen-Kiang,[3] Faith E. Davies,[1] and Gareth J. Morgan[1]



Fuente: Emerging Approaches in Apoptotic and Cell Cycle Control of Hematopoietic Malignancies, ASH 2008

NÚCLEO DE QUITO

Ensayo clínico usando PD-0332991 en Mieloma

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Home Search Study Topics Glossary
Search

Full Text View | Tabular View | No Study Results Posted | Related Studies

An Investigational Drug, PD 0332991, Is Being Studied In Combination With Velcade And Dexamethasone In Patients With Multiple Myeloma. Patients Must Have Received Prior Treatment For Multiple Myeloma.

palbociclib

This study is currently recruiting participants.
Verified by Pfizer, May 2010

First Received: November 8, 2007 Last Updated: May 20, 2010 History of Changes

Sponsor:	Pfizer
Information provided by:	Pfizer
ClinicalTrials.gov Identifier:	NCT00555906

Purpose

This is a Phase 1/2 study evaluating the safety and anti-tumor activity of PD 0332991 in combination with Velcade and dexamethasone in patients who have received at least one previous treatment for multiple myeloma.

Condition	Intervention	Phase
Multiple Myeloma	Drug: Bortezomib Drug: Dexamethasone Drug: PD 0332991	Phase I Phase II

Further study details as provided by Pfizer:

Estimated Enrollment: 62
Study Start Date: January 2008
Estimated Study Completion Date: February 2013
Estimated Primary Completion Date: February 2012 (Final data collection date for primary outcome measure)

Arms	Assigned Interventions
1: Experimental	Drug: Bortezomib Escalating doses of bortezomib will be administered intravenously on Days 8, 11, 15 and 18 of a 28-day cycle (Schedule A) or of a 21-day cycle (Schedule B). The planned doses to be evaluated are 0.7, 1 and 1.3 mg/m2 in combination with PD 0332991 and dexamethasone. Drug: Dexamethasone 20 mg, orally on Days 8, 11, 15 and 18 of a 28 day cycle (Schedule A) or of a 21-day cycle (Schedule B) in combination with PD 0332991 and bortezomib. Drug: PD 0332991 Escalating doses of PD 0332991 will be administered orally on Days 1-21 of a 28-day cycle for Schedule A and on Days 1-12 of a 21-day cycle for Schedule B. The planned doses to be evaluated are 50, 75, 100 mg and 125 mg once daily in combination with bortezomib and dexamethasone.

Fuente: modificado de http://clinicaltrials.gov/ct2/show/NCT00555906

NÚCLEO DE QUITO

Reprogramación células madre pluripotentes

fibroblastos de MM

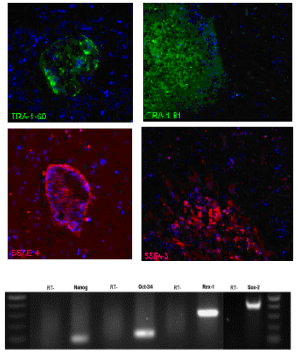
células iPS

células HSC

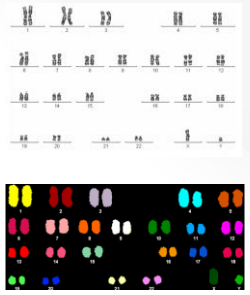
estudios estabilidad genética

Estudios de viabilidad y funcionalidad en modelos animales

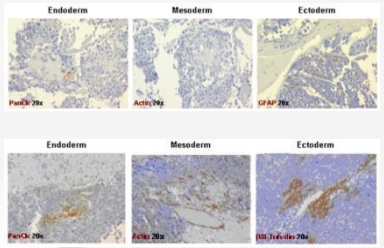
Utilización de las células HSC en terapia celular de pacientes MM



marcadores de pluripotencia



estudios estabilidad genética

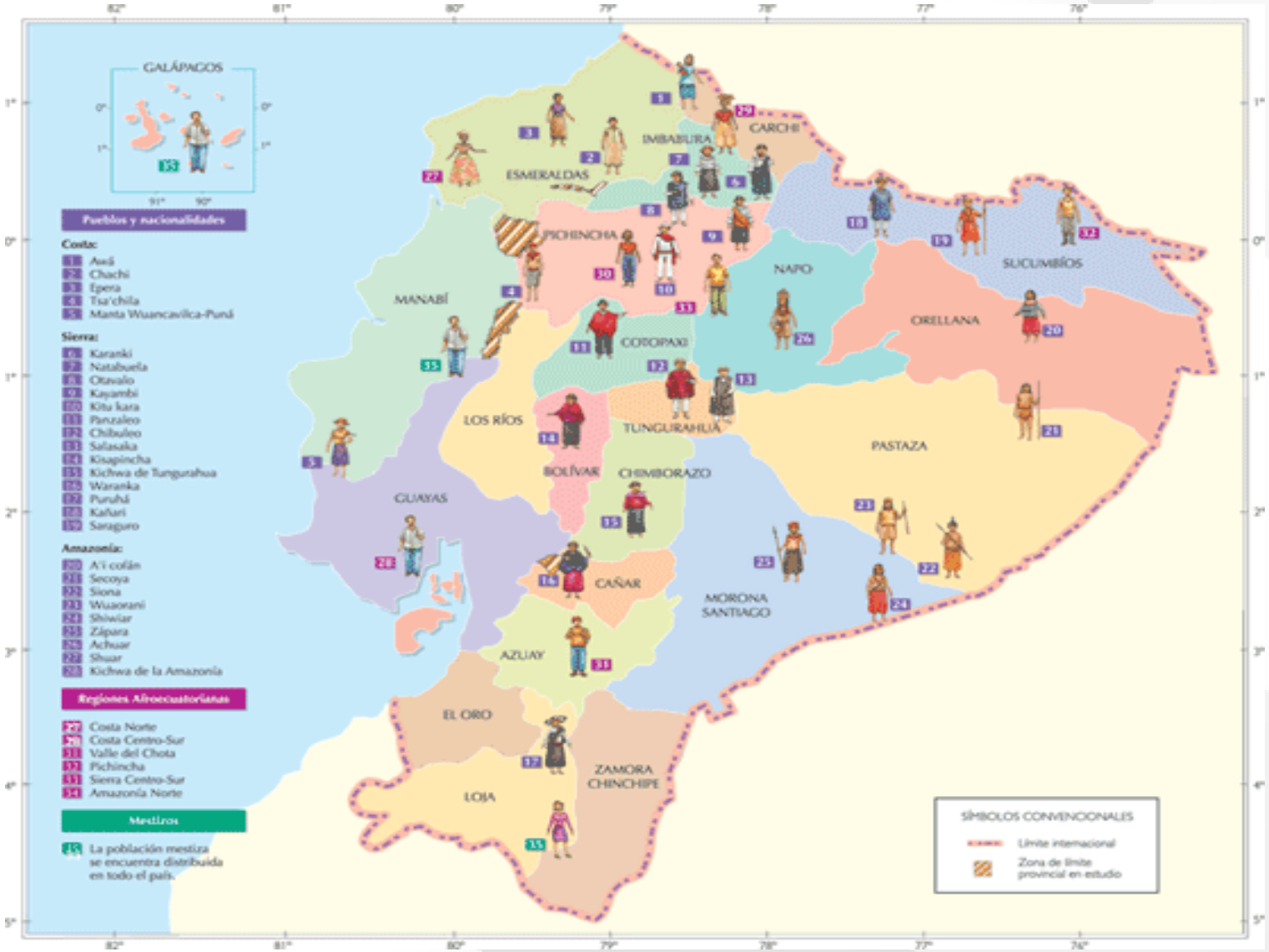


diferenciación *in vivo*

Proyecto de Investigación en Salud – ISCIII. PI11/00125: Generación de células madre pluripotentes humanas a partir de fibroblastos de pacientes con mieloma múltiple

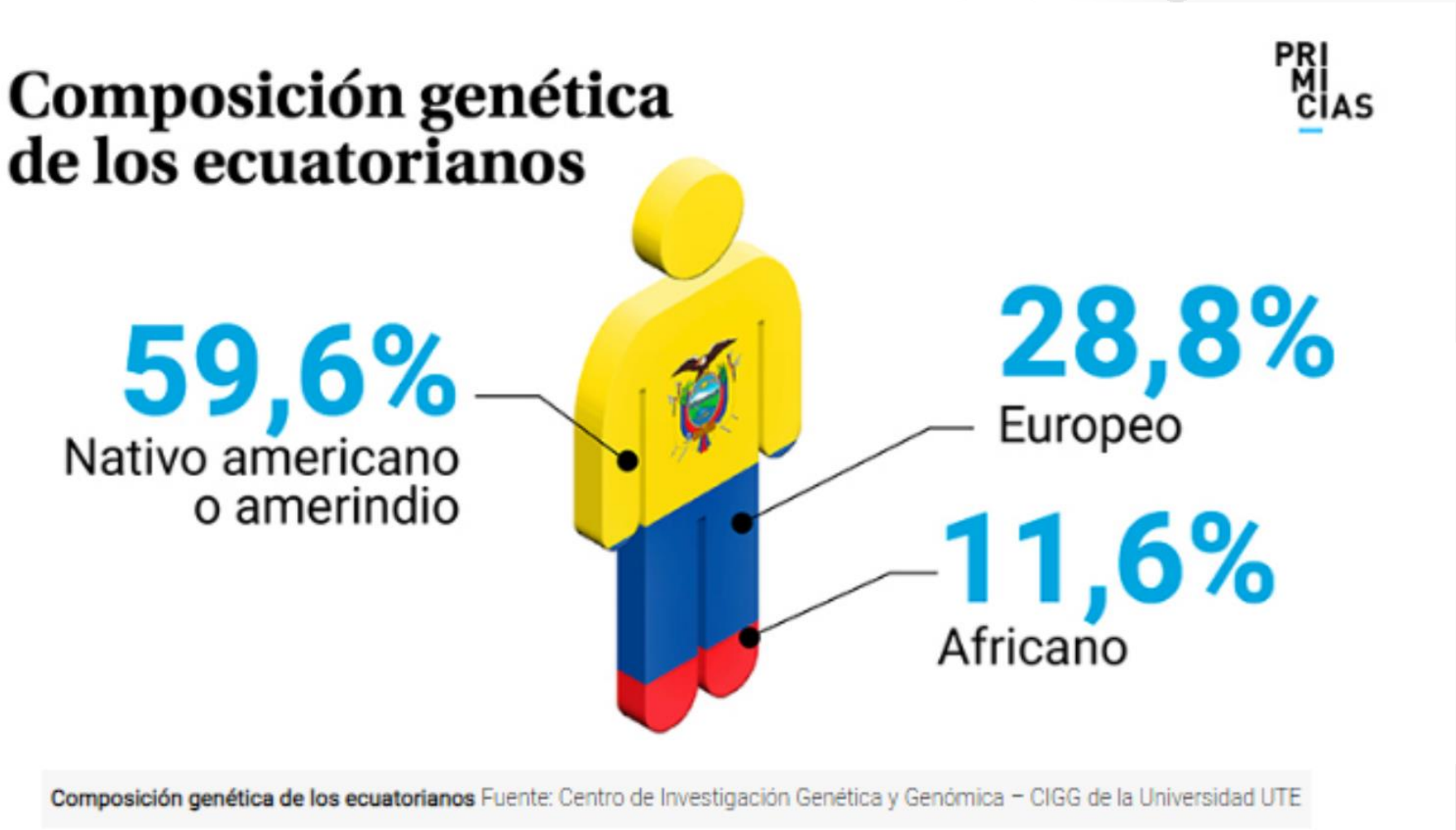
NÚCLEO DE QUITO

Grupos étnicos del Ecuador



NÚCLEO DE QUITO

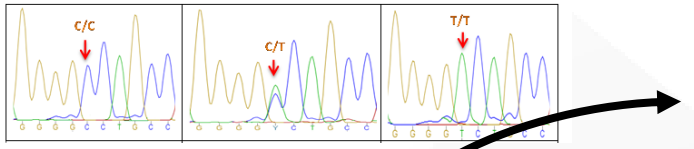
Población ecuatoriana: Trihíbrida

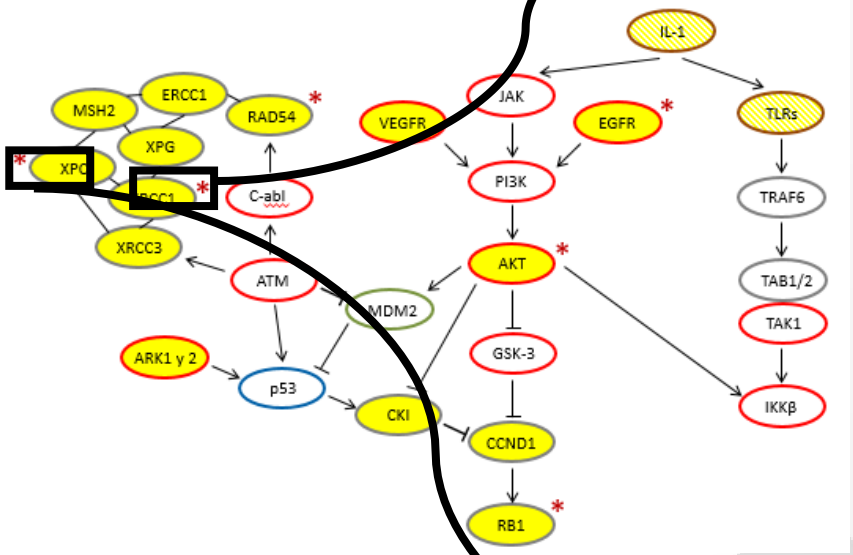


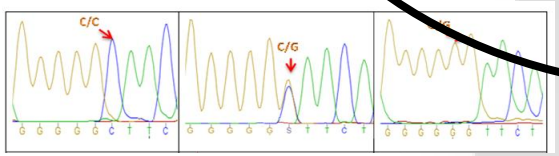
Scientific Reports. 2019; 9(1), 9247

NÚCLEO DE QUITO

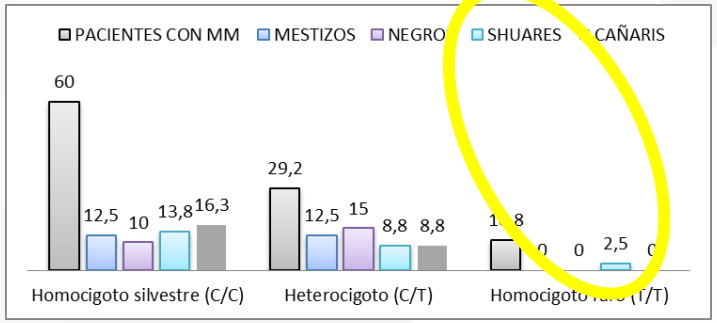
Mieloma múltiple: afectados

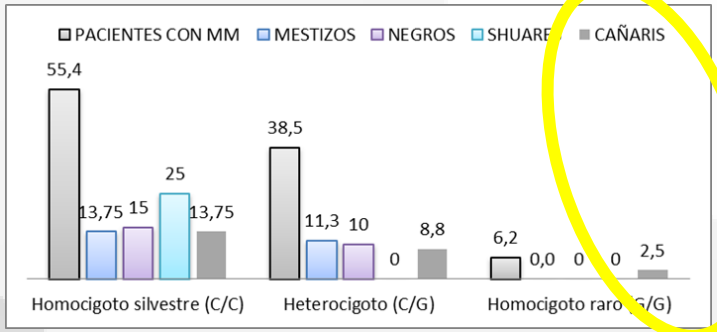






mutación	proteína	tipo	gen
43.551.656 C>T	Q426Stop	Nonsense	exon 10

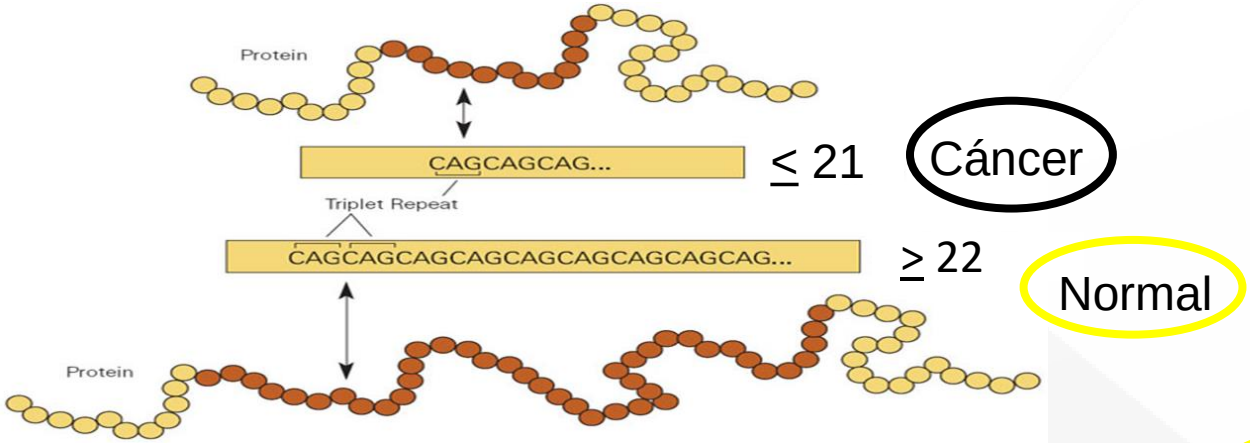




mutación	proteína	tipo	gen
14.146.053 C>G	W904S	Missense	exon 15

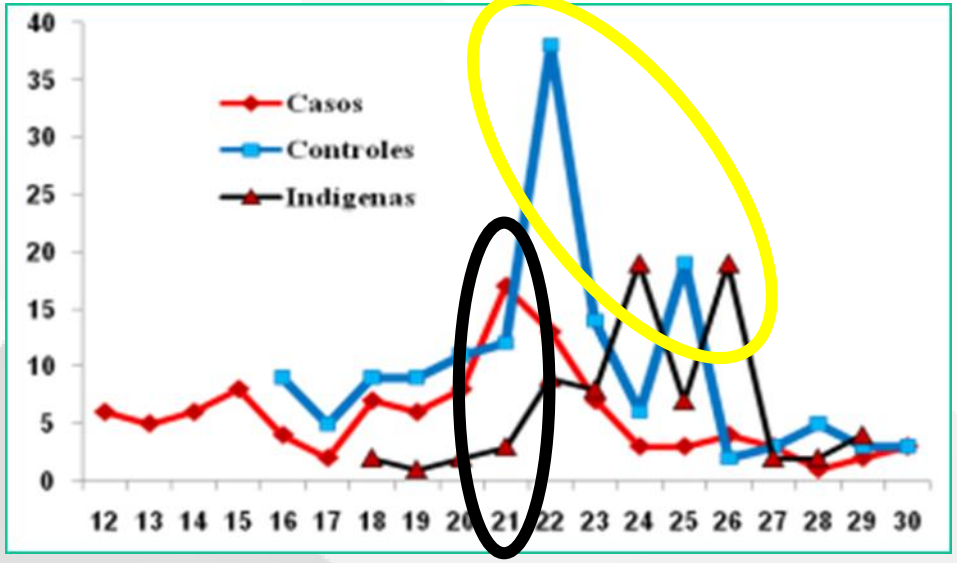
NÚCLEO DE QUITO

Cáncer Próstata menos frecuente en nativoamericanos



≤ 21 Cáncer

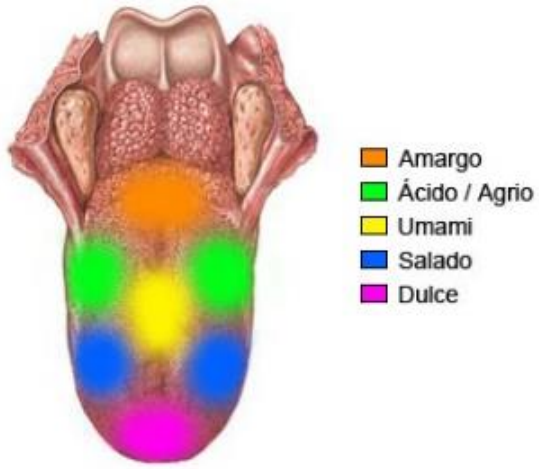
≥ 22 Normal

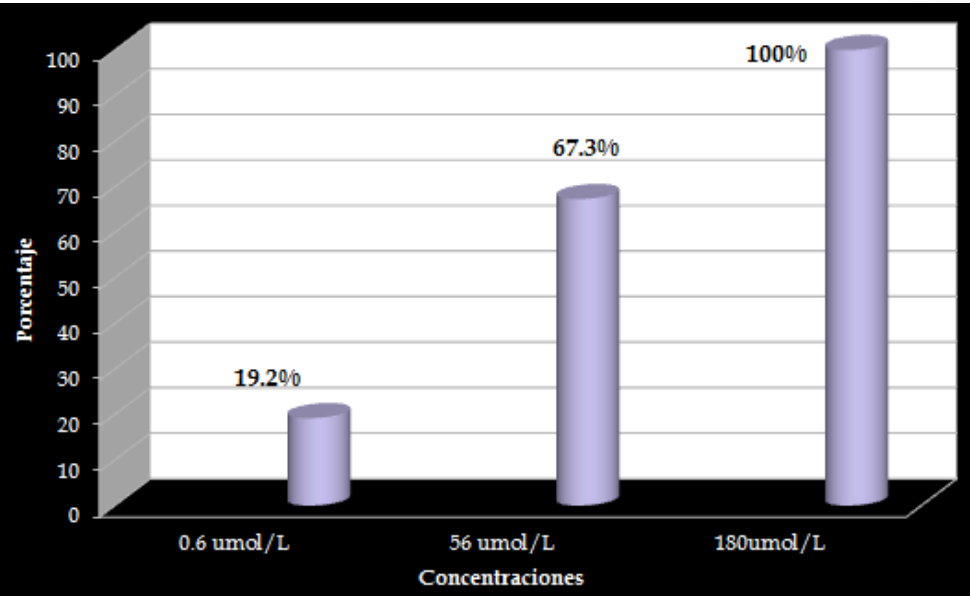


BioMed Res Int. 2017; 2017, 3507671

NÚCLEO DE QUITO

Percepción del sabor amargo





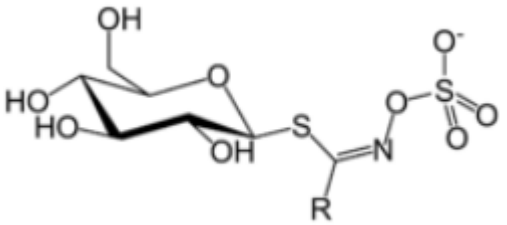
	Dosis (totales)		
	0,001%	0,08%	0,25%
# Individuos	10/52	35/52	52/52
Porcentaje	19,2%	67,3%	100%

Concentración umbral: inferior a 0,6 umol/L – 0,001% (Wittig de Penna, 2001)

Forensic Sci Int. 2019; 59-61; Forensic Sci Int. 2017; e171-172

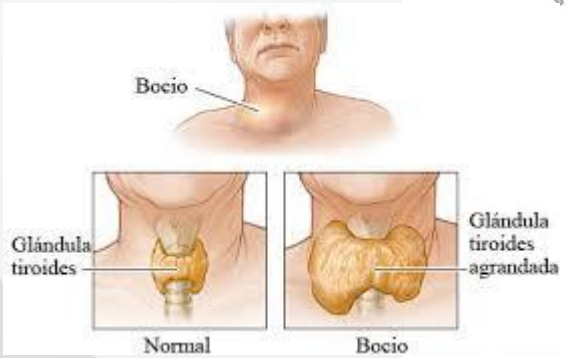
NÚCLEO DE QUITO

Falta de percepción de sabor amargo asociado a cáncer de Tiroides y Colon



<u>Zonas abundante Yodo</u>
glucosinolato no inhibe la función de tiroides
Ventaja: no detectar el sabor

<u>Zonas bajo Yodo</u>
glucosinolato podría ser dañino salud
Ventaja: poseer variante sensible

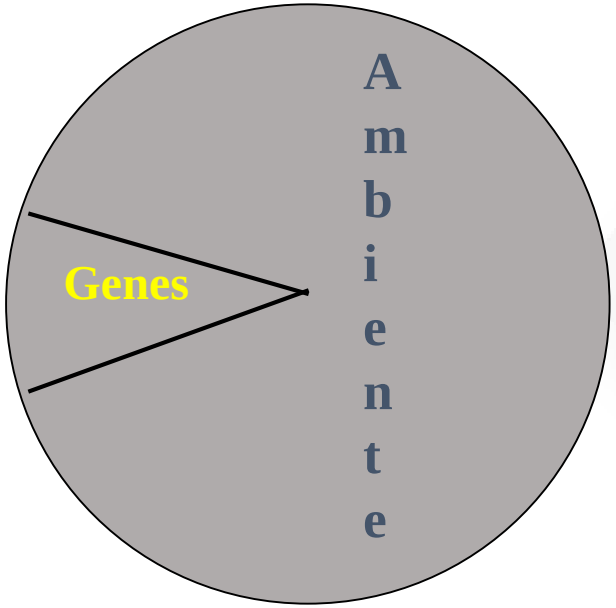


Forensic Sci Int. 2019;59-61; Forensic Sci Int. 2017;e171-172

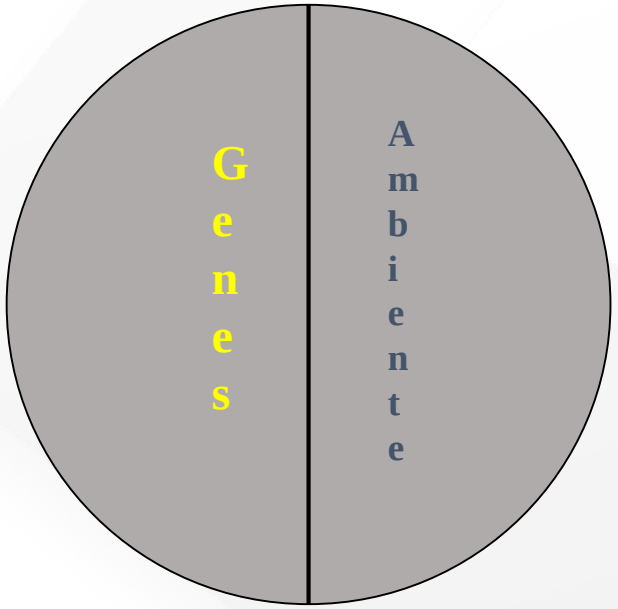
NÚCLEO DE QUITO

Relación Genes y ambiente

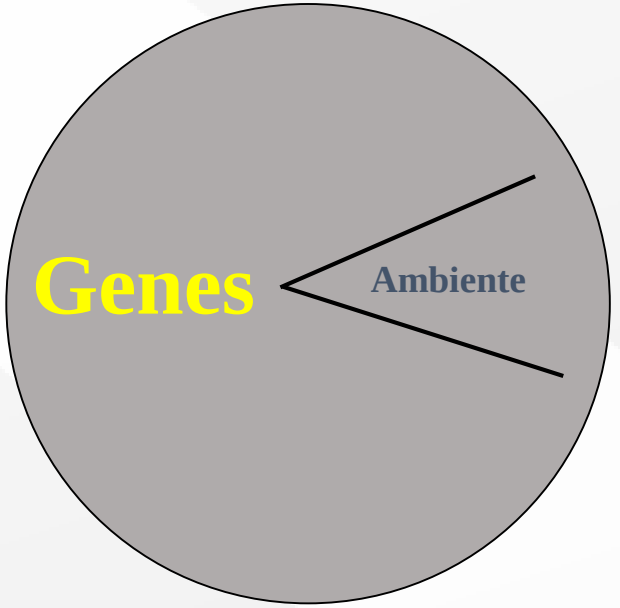
FENOTIPO = GENOTIPO + AMBIENTE



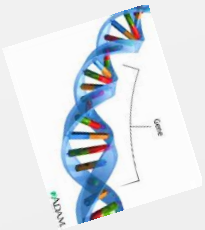
Multifactorial



Multifactorial/Poligénico



Monogénico



NÚCLEO DE QUITO

CONTROL DE LA FASE G_2

¿Se ha producido daño en el DNA?

Maquinaria de replicación del DNA

¿Se ha replicado todo el DNA?

Entorno → ¿Es el entorno favorable?

Crecimiento celular → ¿Tiene la célula el tamaño adecuado?

CONTROL DE LA METAFASE

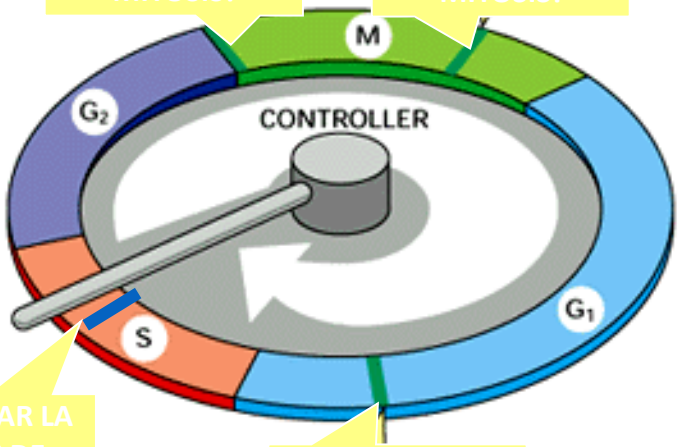
Maquinaria de la mitosis

¿Están todos los cromosomas alineados en el huso?

CONTROL DE LA FASE S

¡CONTINUAR LA SÍNTESIS DE DNA!

¿Se ha producido daño en el DNA?



¿Se ha producido daño en el DNA?

CONTROL DE LA FASE G_1

¡ENTRAR EN CICLO

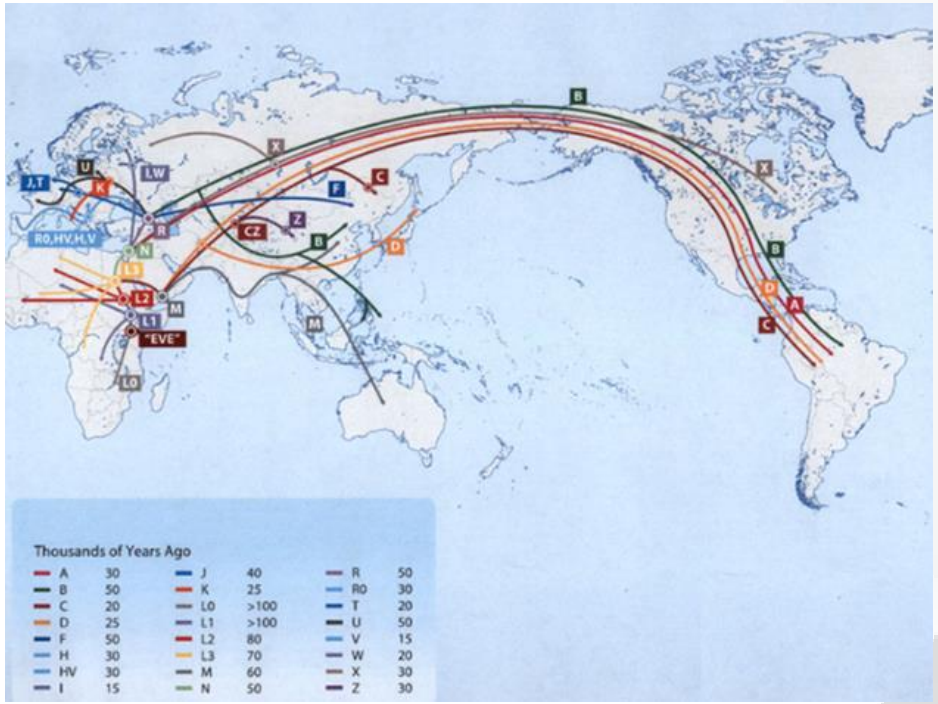
¿Tiene la célula el tamaño adecuado? ← Crecimiento celular

¿Se ha producido daño en el DNA?

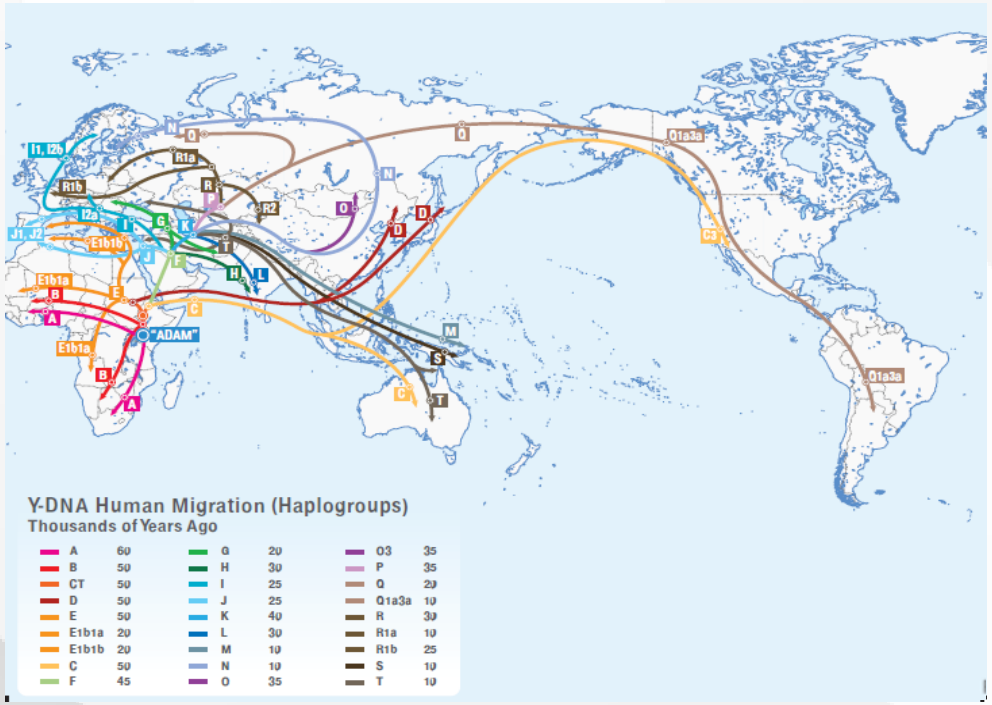
¿Es el entorno favorable? ← Entorno

NÚCLEO DE QUITO

Origen de la población americana



ADN mitocondrial

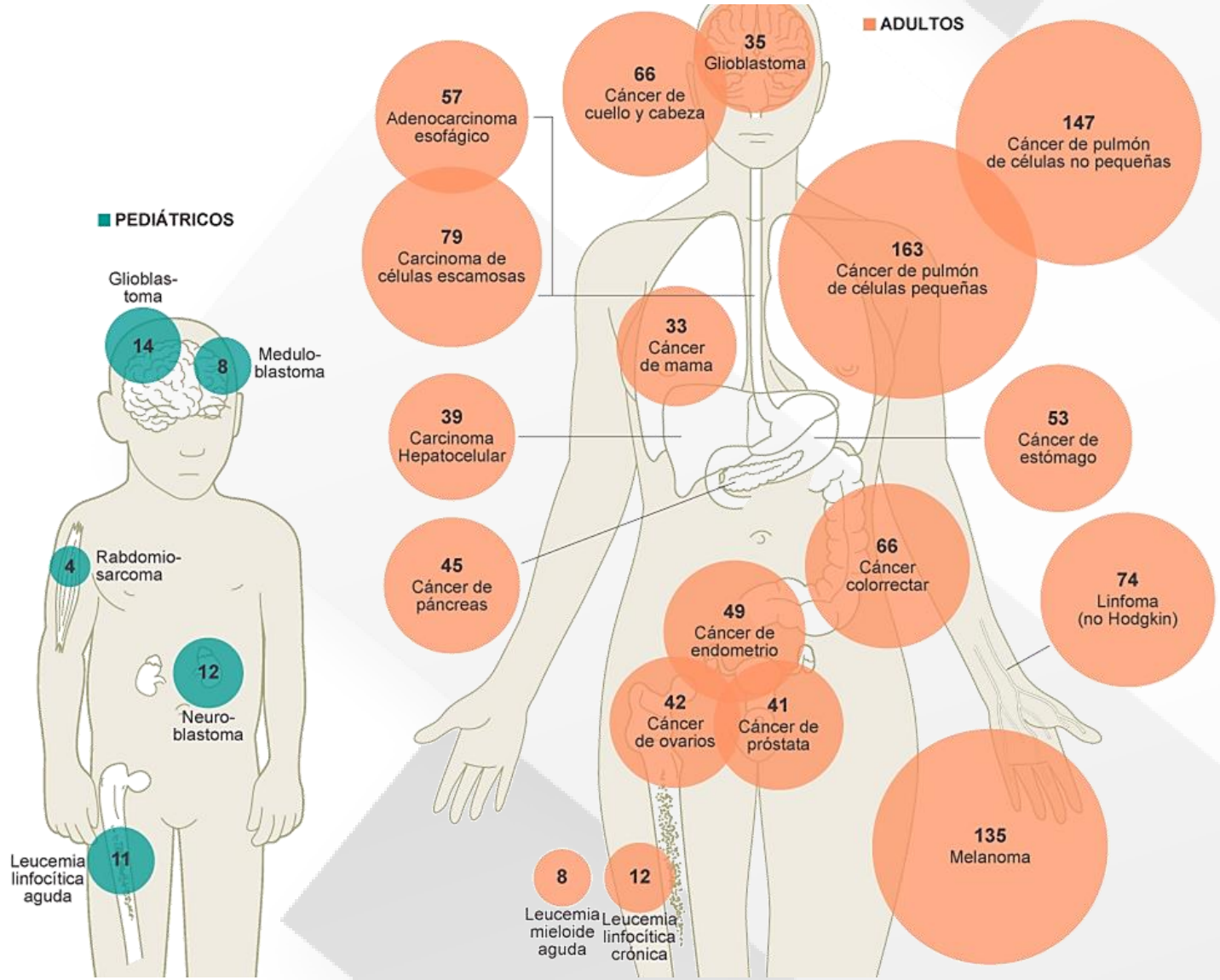


ADN cromosoma Y

Family Tree DNA

NÚCLEO DE QUITO

Genes del cáncer



Tomado de Science, 2013

NÚCLEO DE QUITO

Población ecuatoriana trihíbrida

- Incidencia de enfermedades
- Pronóstico de enfermedades
- Diferente frecuencia de mutaciones
- Mutaciones nuevas
- Diferente respuesta a tratamientos

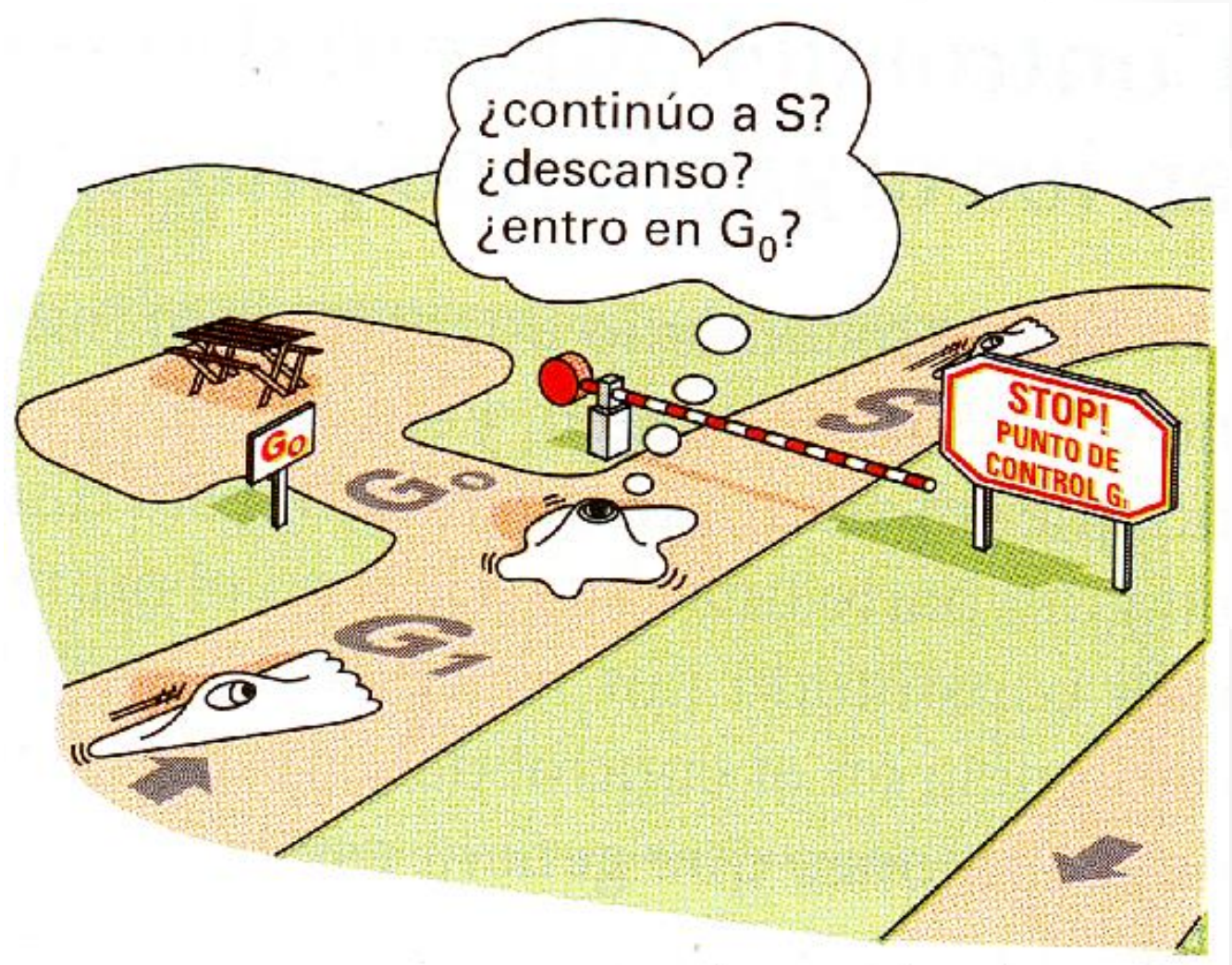
NÚCLEO DE QUITO

Conclusiones

- El **control** del **ciclo celular** es importante en biología celular y genética.
- Tiene importantes implicaciones prácticas en la **lucha contra el cáncer**, al estar producido por **alteraciones** en la **capacidad** de la célula **de regular** su propia **división**.
- El descubrimiento de genes que codifican **inhibidores** del **ciclo celular**, puso en marcha la **síntesis** de **nuevos** tipos de **fármacos anticancerígenos** que **bloquean** el **crecimiento celular descontrolado** imitando los efectos de estos inhibidores.

NÚCLEO DE QUITO

… y ahora?



Agradecimientos

NÚCLEO DE QUITO

1990-1993

Cultivos
Citogenética convencional

1993-1997
2000, 2001

Southern blot
PCR-SSCP
Secuenciación
Cultivos

1997

Cultivos
Citogenética convencional

PCR
Secuenciación

RT-PCR

1998

Cromatografía
Espectrofotometría de masas

1997-2003

Citogenética convencional
RT-PCR
PCR-SSCP
Secuenciación
Cometa

2003-2005

Citogenética convencional
FISH
CGH
CGH array

2005-2008

Cultivos
Array mapeo
Array expresión
Secuenciación

2008-2012

Cultivos
Citogenética convencional
FISH
Array mapeo
Array expresión

2012-2016

Citogenética
Convencional
Cometa
FISH
Cometa-FISH
Análisis de arrays y secuenciación

2016-2021

Citogenética
Convencional
Cometa
FISH
Cometa-FISH
Análisis de arrays
Secuenciación y NGS

2021 a la fecha

Citogenética convencional
FISH
Array mapeo
Array expresión

paola.leone@solcaquito.org.ec