



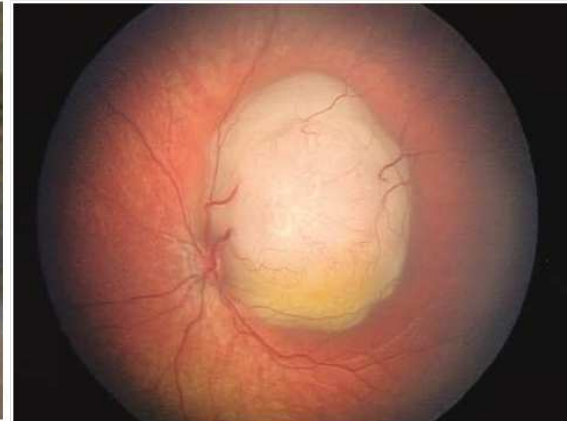
Retinoblastoma

in Maria Antonietta Mencarelli schema
Genetica Medica, AOUS

03/11/09

Tumore embrionale maligno,
endooculare, che origina dalle cellule
della retina

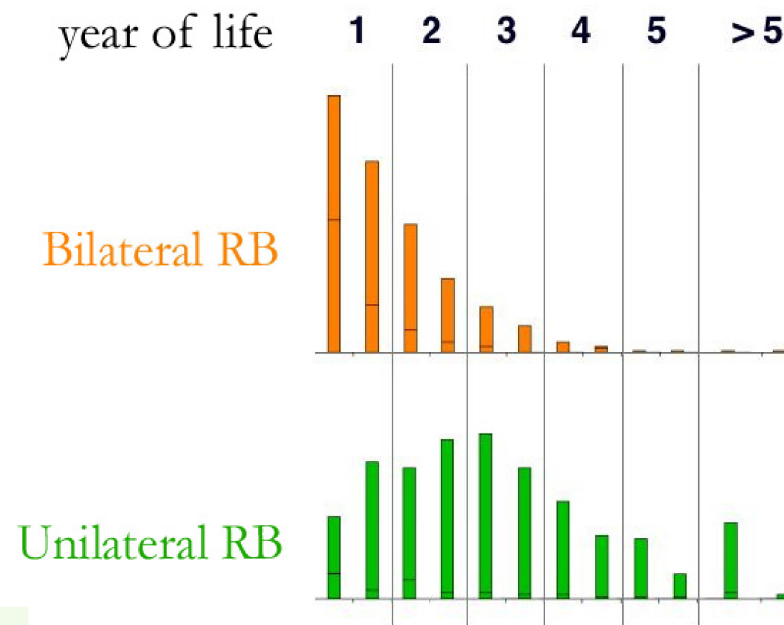
Incidenza: 1:15.000 - 1:20.000



03/11/09

- ❑ Ereditario bilaterale, multifocale 40%
- ❑ Sporadico unilaterale, unifocale 60%

Age at diagnosis



4% delle neoplasie del bambino

~1% di tutti i tumori

03/11/09

Arch Ophthalmol -- Pieter Pauw's Tumor Oculorum: Reappraisal of the Presumed First Description - Windows Internet Explorer

http://archophth.ama-assn.org/cgi/content/full/121/6/881/FIGESA20016F1

petrus pawius

Arch Ophthalmol -- Pieter Pauw's Tumor Oculorum


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38 PETRI PAWIJ

libras fanici effundebat. Præter magnum hunc abscissum plus quam 30 locis hinc inde exigua habebat apostemata vero ac cocto pure albo referta. Tum & variis locis scirrhosus erat pulmo.

OBSERVATIO XXIII.
Tumor oculorum.

ANno 1597. die 7. April. Præsentibus Chirurgis M. Johanne Simonis & Alberto, puerulo trienni aperui caput. Hic aliquot mensibus ingenti laborat tumore ex oculo sinistro, adeo quidem ut integer bulbis ocularis cum musculis omnibus foras protuberaret, in tantamque accevisset molem ut duos pugnos protuberantia æqvaret. Huic duabus ante mortem septimanis alius tumor ortus fuerat, prope musculum temporalem finistrum, quem ablata cute vidimus peculiari (eadem crassa fatis) membra-

OBSER. ANATOM. 39

membrana obductum intra cutem, craniumque hæreere. Cranium exiguum habebat foraminulum, per quod materiam eiecerat natura. Ablato cranio vidimus oculacis tumoris materiam intra cranium & duram matrem collectam universam integro planè & illafo cerebro. Aperto utroque tumore. vidimus eos substantia cerebro planè simili repletos, permixto sanguine concreto, haud aliter ac si molæ substantiam vidisset.

OBSERVATIO XXIV.
Anatome Hydropicæ.

ANno 1597. die 28. Aug. Præsentibus D. Joh. Arfenio & M. Cornelio Chirurgo abdomen femine aperui Hydropicæ, quæ credebatur gravida. Huic magna aquæ flavæ ac foetidæ effluxit copia. Jecur corruptum. Hujus utero exterius circa fundum adnata cernebatur ex-

C 4 cretiscen-

Figure 1. Excerpts from *Observationes Anatomicae Selectiores* by Pieter Pauw, professor of anatomy and botany in Leiden, the Netherlands, from 1589 to 1617, published posthumously by Bartholin.² A detail from a gravure by Andreas Stog shows Pauw performing a public dissection in his anatomical theater. His 23rd observation, "Tumor of the Eyes," describes a 3-year-old boy who died of an orbital and intracranial neoplasm.

Internet | Modalità protetta: attivata 100%

1597 Petrus Pawius

Observationes Anatomicae Selectiores

03/11/09

Internet Explorer window showing the article page 820. The URL is <http://www.pubmedcentral.nih.gov/pagerender.fcgi?artid=389051&pageindex=1>. The article title is "Mutation and Cancer: Statistical Study of Retinoblastoma".

From *Nat. Acad. Sci. USA*
Vol. 68, No. 4, pp. 820-823, April 1971

Mutation and Cancer: Statistical Study of Retinoblastoma

ALFRED G. KNUDSON, JR.
Graduate School of Biomedical Sciences and M. D. Anderson Hospital and Tumor Institute,
The University of Texas at Houston, Houston, Texas 77025
Communicated by James V. Neel, February 8, 1971

ABSTRACT Based upon observations on 48 cases of retinoblastoma and published reports, the hypothesis is developed that retinoblastoma is a cancer caused by two mutational events. In the dominantly inherited form, one mutation is inherited in the germinal cells and the second occurs in somatic cells. In the nonhereditary form, both mutations occur in somatic cells.

The second mutation produces an average of three retinoblastomas per individual inheriting the first mutation. Using Poisson statistics, one can calculate that this number (three) can explain the occasional gene carrier who gets no tumor, those who develop only unilateral tumors, and those who develop bilateral tumors, as well as explaining instances of multiple tumors in one eye.

This value for the mean number of tumors occurring in genetic carriers may be used to estimate the mutation rate for each mutation. The germinal and somatic rates are approximately equal. The germinal mutation may arise in some instances from a delayed mutation.

The origin of cancer by a process that involves more than one discreet stage is supported by experimental, clinical, and epidemiological observations. These stages are, in turn, attributed by many investigators to somatic mutations. (Abbey, 1957)

should be counted as hereditary because the proportion of affected offspring closely approximates the 50% expected with dominant inheritance (5). On the other hand, of the 70-75% of all cases that are unilateral, only 15-20% are thought to be hereditary (3, 5); thus, 10-15% of all cases are unilateral and hereditary. The percentage of all retinoblastoma cases with the hereditary form is, therefore, in the range 35-45; among these, 25-40% are unilateral and 60-75% are bilateral. In contrast, 55-65% of all retinoblastoma cases are of the nonhereditary form and all are unilateral. These distributions are summarized in Table 2.

Some patients that inherit the gene for retinoblastoma are never affected, although they transmit the trait to offspring who may become affected. The size of this group is difficult to estimate. Previous estimates range generally from 1-20%. Some authors have probably overcorrected for ascertainment bias. The estimate by Falls and Neel (2) of a range 1.5-10% represents an attempt to avoid this bias.

If the above estimates are correct, then carriers of the germinal mutation are distributed as follows:

Internet Explorer window showing the article page 823. The URL is <http://www.pubmedcentral.nih.gov/pagerender.fcgi?artid=389051&pageindex=4>. The article title is "Mutation and Cancer: Statistical Study of Retinoblastoma".

Proc. Nat. Acad. Sci. USA 68 (1971)

Mutation and Retinoblastoma 823

direct evidence that a single independent "event" of any kind is involved. If a second, single event is involved, the distribution of bilateral cases with time should be an exponential function, i.e., the fraction of the total cases that develops in a given period of time should be constant, as expressed in the relationship $dS/dt = -kS$, and in $S = -kt$, where S is the fraction of survivors not yet diagnosed at time t , and dS is the change in this fraction in the interval dt . As shown in Fig. 1, this is indeed the case. By contrast, the fractional decrease in unilateral cases per unit time does not show this relationship (Fig. 1). Although 15-20% of the unilateral cases should be of the hereditary type and so contaminate the data, the observations more nearly fit the anticipated two-mutation expression, $\ln S = -kt^2$, derived by Birch (8). That a difference in mean age at diagnosis exists between unilateral and bilateral cases has been noted previously. The respective mean ages at diagnosis for bilateral and unilateral cases have been reported in other series as 15 and 24 months (9) and 15 and 29 months (10), and in the present series are 15 and 32 months.

The exponential decline in new hereditary cases with time reflects the occurrence of a second event at a constant rate in a declining population of embryonal cells. For the nonhereditary cases, this declining population of cells must experience two independently occurring events. New cases of both types occur only in childhood because the embryonal cells vanish.

The data presented here and in the literature are consistent with the hypothesis that at least one cancer, retinoblastoma, can be caused by two mutations, each of which occurs at a rate of the order of 2×10^{-6} per year. One of these mutations may be inherited as a result of a previous germinal mutation that occurs at about the same rate. Those patients that inherit one mutation develop tumors earlier than do those who develop the nonhereditary form of the disease; in a majority of cases those who inherit a mutation develop more than one tumor. On the other hand, the probability that an individual

Fig. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -kt$, the two-hit curve from $\log S = -kt^2$.

03/11/09

Retinoblastoma -- GeneReviews -- NCBI Bookshelf - Windows Internet Explorer

http://www.ncbi.nlm.nih.gov/bookshelf/br.fcgi?book=gene&part=retinoblastoma&rendertype=figure&id=retinoblastoma.F1

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NCBI » Bookshelf » GeneReviews » Retinoblastoma

Non-hereditary Retinoblastoma

First & Second Mutation

RB RB → rb rb

Hereditary Retinoblastoma

First Mutation

rb RB

Germline

Constitutional

RB rb

Second Mutation

Retinoblastoma

rb rb

Figure 1. Schematic of the molecular genetic mechanisms that result in non-hereditary and hereditary retinoblastoma (RB). The development of retinoblastoma is initiated if both alleles of the RBI gene are mutated (rb rb).

In non-hereditary retinoblastoma, both mutations (first and second mutation) occur in somatic cells (somatic mutations).

Fine Internet | Modalità protetta: attivata 100%

TWO HIT HYPOTHESIS

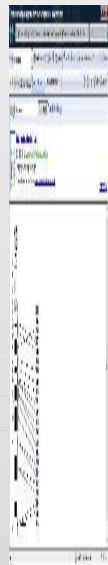
03/11/09



Volume 295:1120-1123
Number 20

November 11, 1976

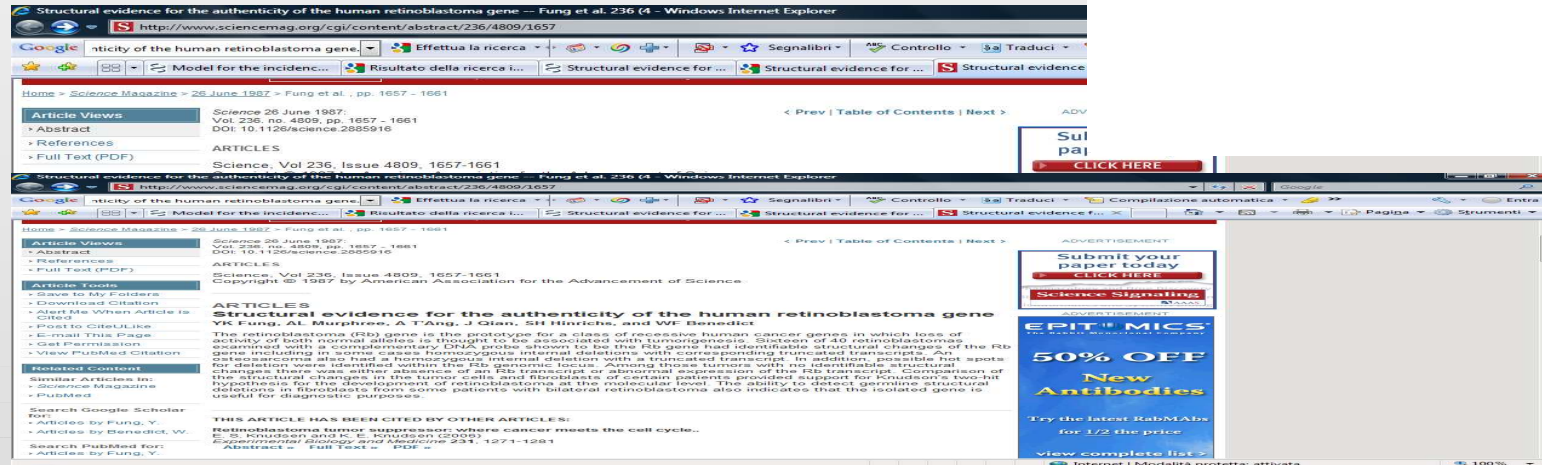
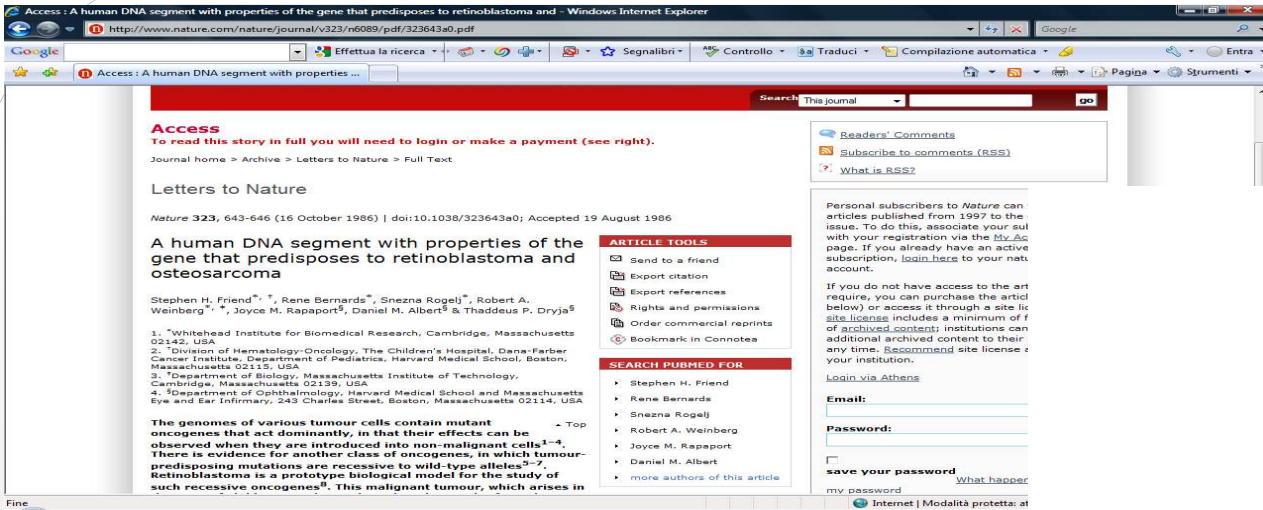
Chromosomal deletion and retinoblastoma



Hudson AG Jr, Meadows AT, Nichols WW, Hill R.

■ **RB1**

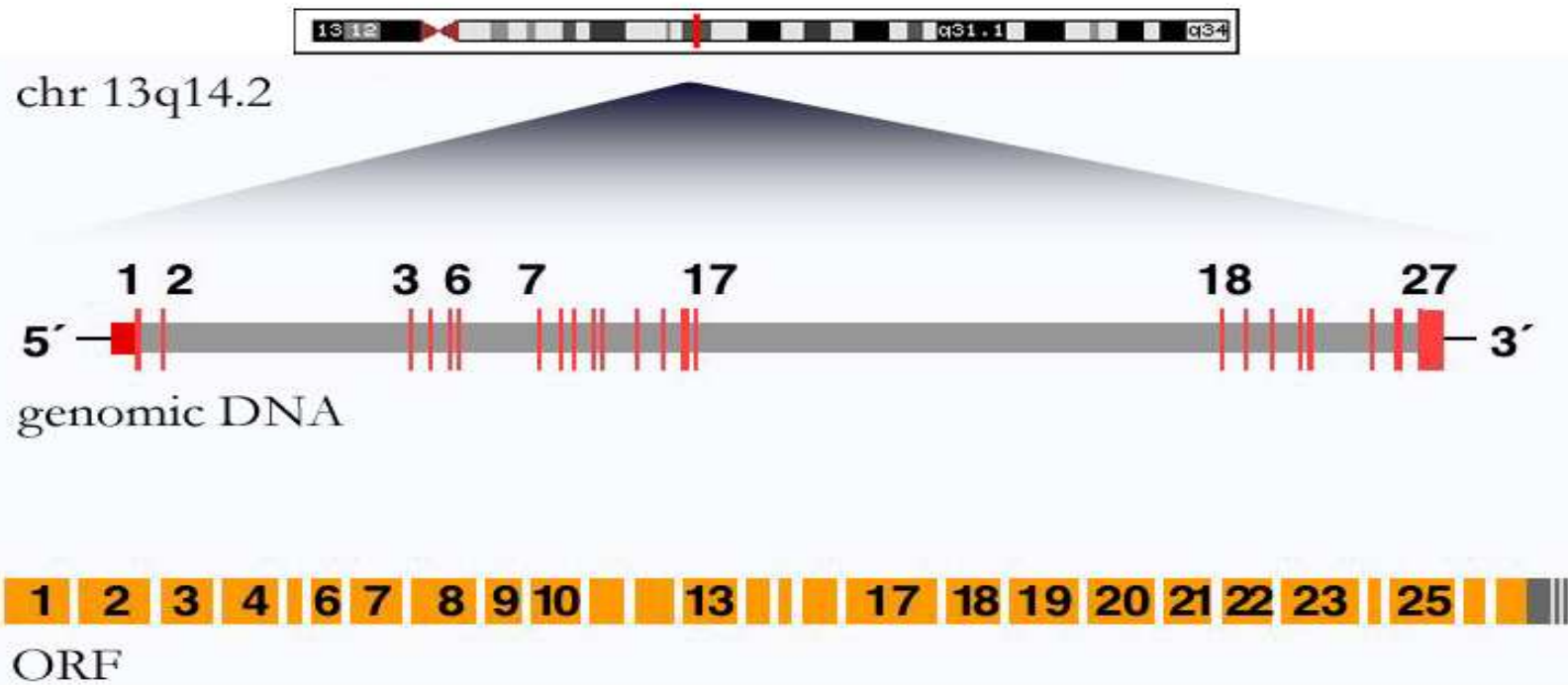
03/11/09



03/11/09

II gene *RB1*

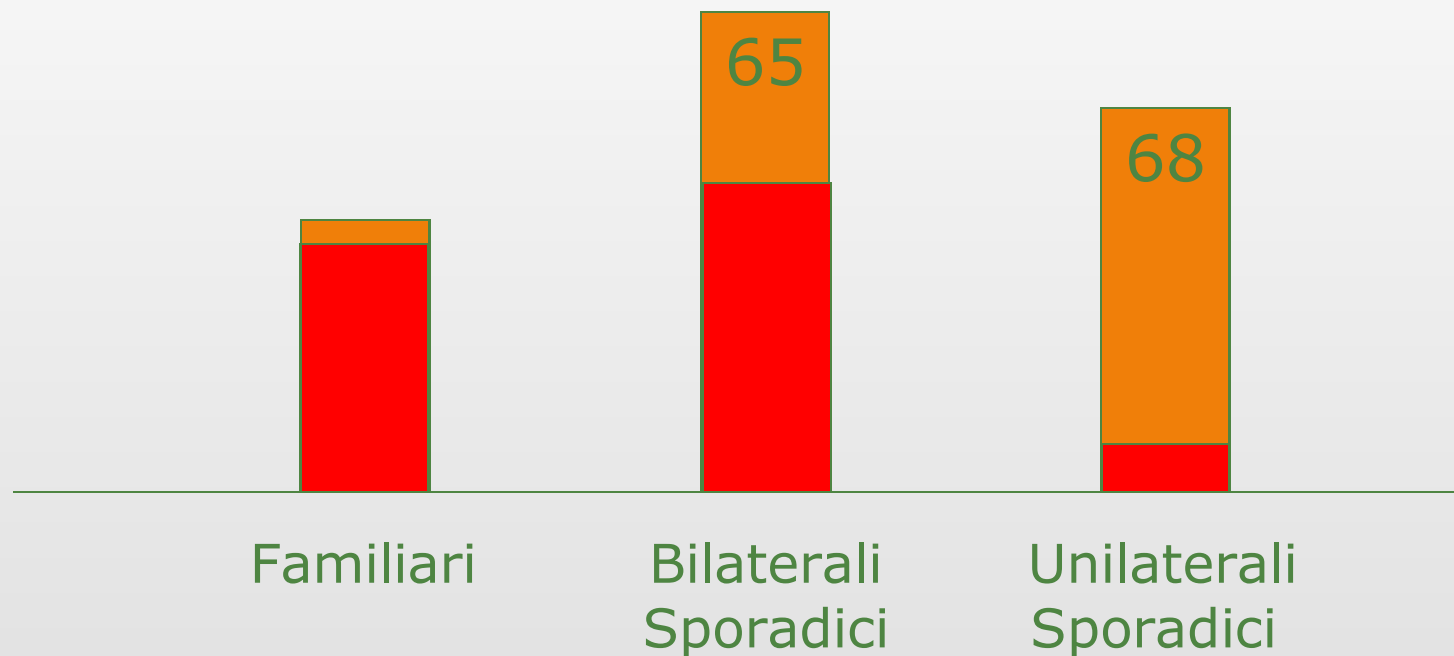
The *RB1* gene



03/11/09

...Novembre 2000

167 famiglie RB



Familiari

Bilaterali
Sporadici

Unilaterali
Sporadici

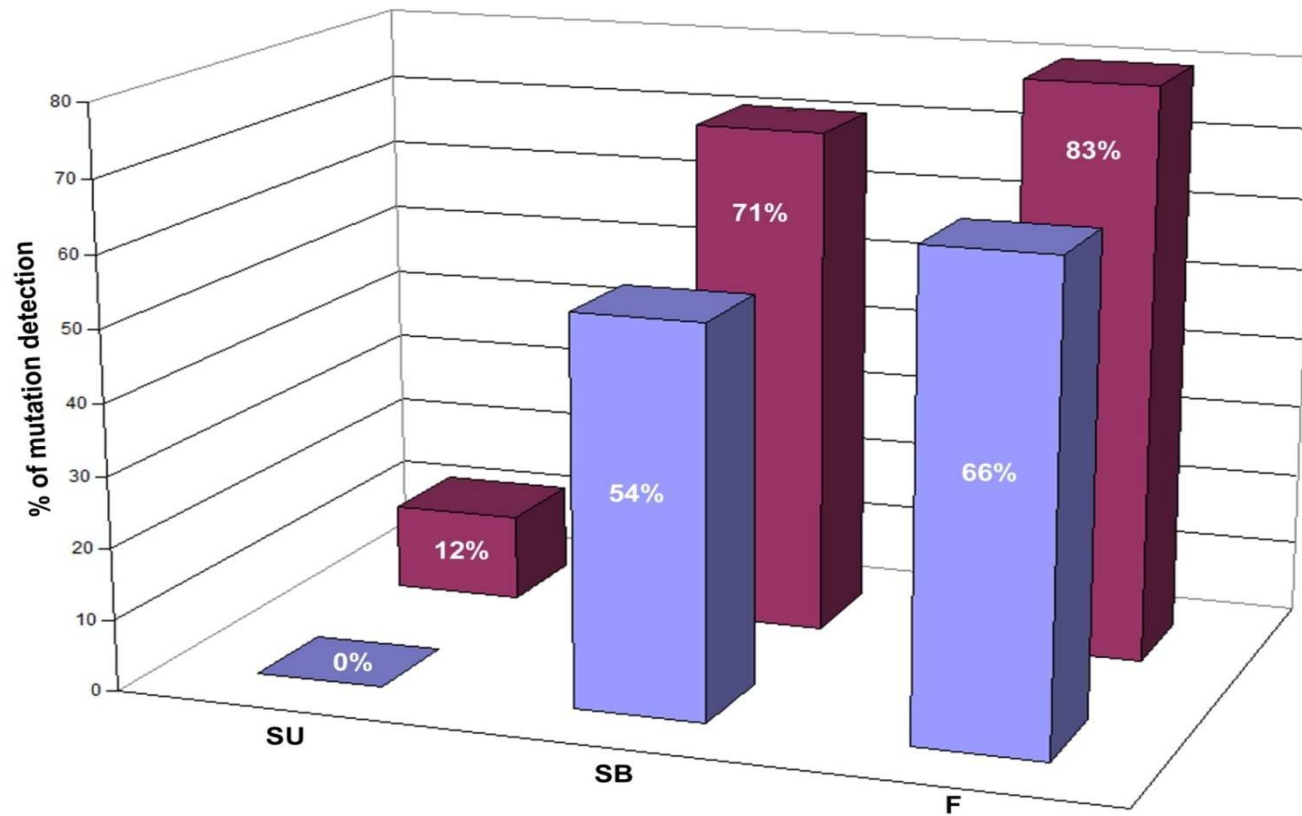
82 mutazioni
RB1

32/35
(91%)

40/64
(63%)
03/11 (27%)

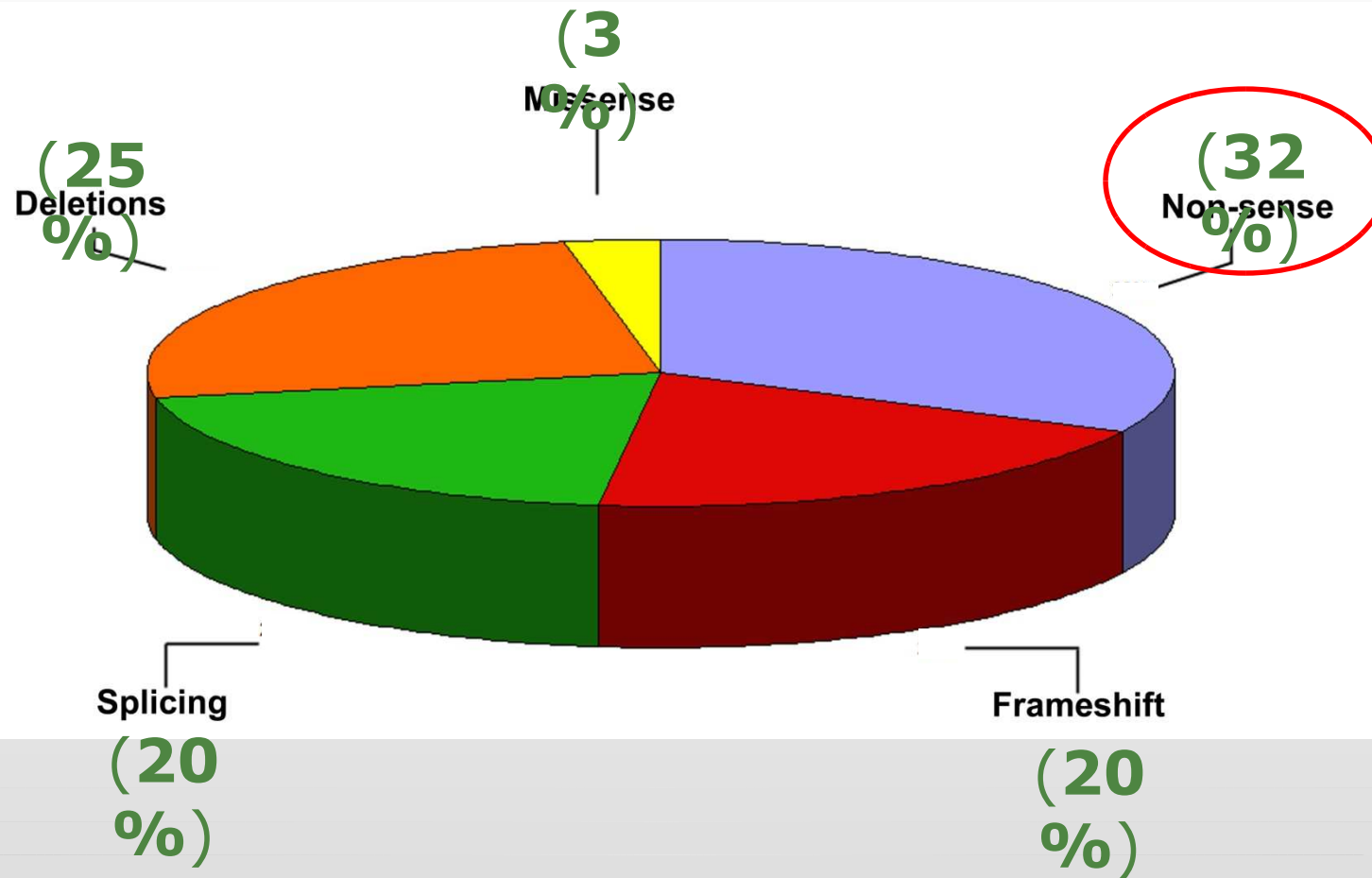
10/68
(15%)

Detection rate



 *Sampieri et al., 2006*
 Multistep analysis

Mutazioni del gene *RB1*



03/11/09

RB database

<http://www.biobank.unisi.it>

The screenshot shows the Retinoblastoma database interface. At the top, there is a navigation bar with the title "Retinoblastoma" and a menu with links for Home, Search, E-Mail, and Back. Below this, there are three main sections: "RB1 point mutations", "RB1 large deletions", and "Search by".

The main content area displays a "list of mutations" and a "graph of mutations". A detailed view of a specific mutation is shown, with the following information:

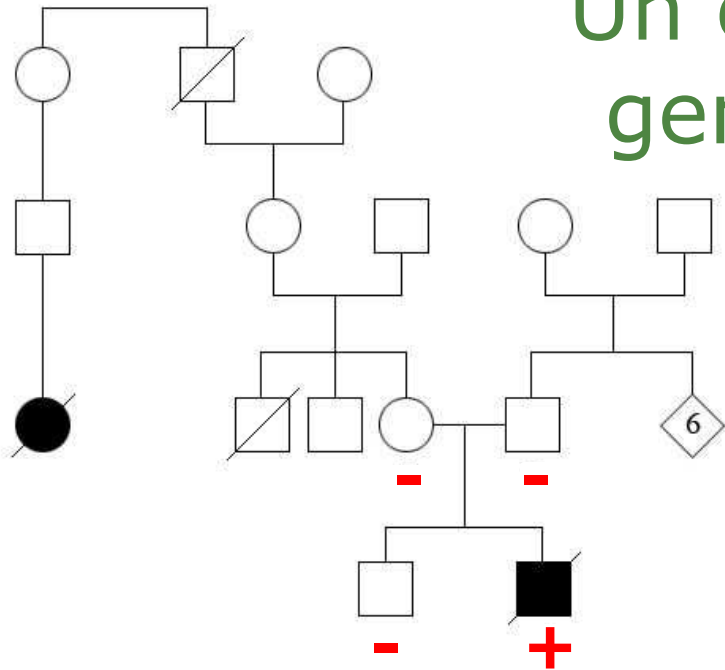
- Details of the Cod:** 309
- Insertion Date:** 03/04/2007
- Last Update:** 24/08/2007
- Additional info:**
 - Age at diagnosis (days): 42
 - Second primary tumors: no
 - Additional analysis:

At the bottom of the screenshot, there is a table with columns for Internal Code, Code, Phenotype, and other details. The table contains the following data:

Internal Code	Code	Phenotype						
1	1,I-1	Unilateral(unknown foci)						
2	2,III-1	RB Bilateral						
5	3,III-1	RB Bilateral	Sporadic	no mutations				DNA 3
8	4,IV-2	RB Bilateral	Sporadic	Splicing	2105del4			DNA 4

03/11/07

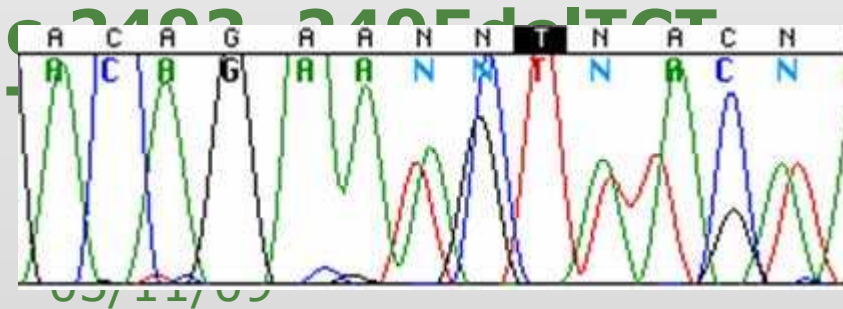
Un esempio di consulenza genetica preconcezionale



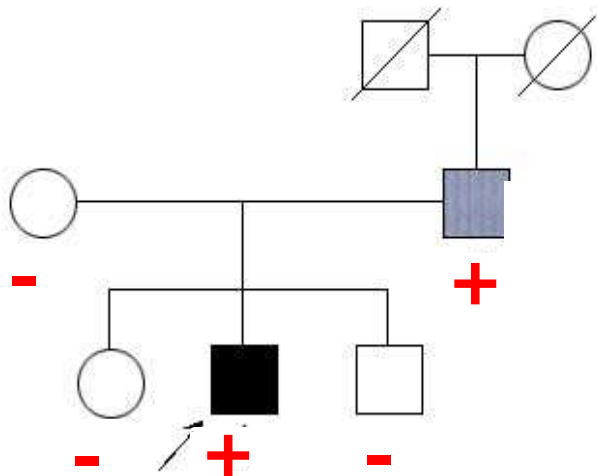
3 aa: RB bilaterale
(enucleazione OS + Chemioterapia)

Sangue cordonale da biobanca

frameshift ,

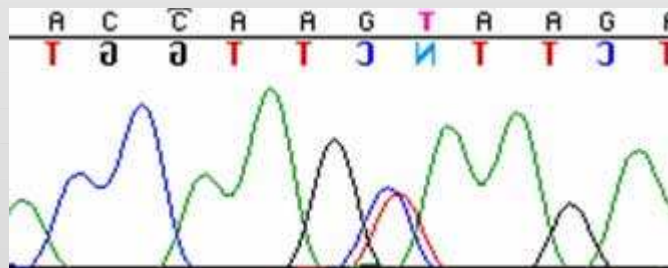


Un caso di retinoma



Retinoma monolaterale
identificato *a posteriori*

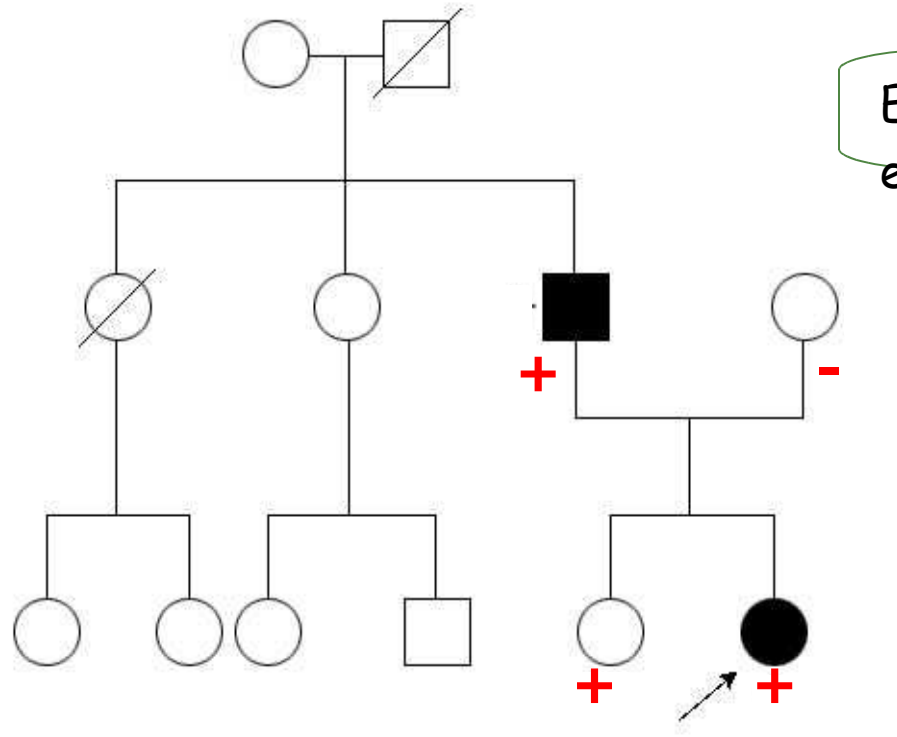
4 m: Enucleazione OD.
Chemioterapia e successiva
enucleazione OS



**Introne
20**

c.2106+2T

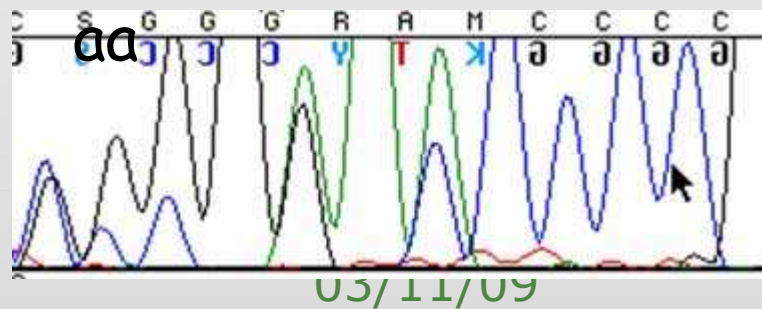
Un caso di non penetranza



Enucleazione
e a 15 m

14 m RB unilaterale

11



**Eson 1
frameshift
c.58delC**

**Retinoblastoma and mental retardation microdeletion syndrome:
clinical characterization and molecular dissection
using array CGH**

R. Caselli · C. Speciale · C. Pescucci · V. Uliana · K. Sampieri ·
M. Bruttini · L. Longo · S. De Francesco · T. Pramparo · O. Zuffardi ·
R. Frezzotti · A. Acquaviva · T. Hadjistilianou · A. Renieri · F. Mari

Caso 1



1a 2m

Caso 2



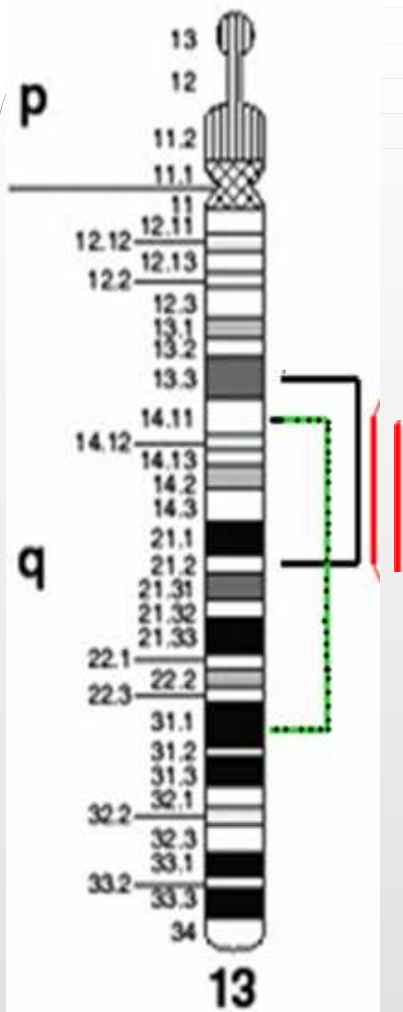
2a 7m

Caso 3



7a6m

Cromosoma



chr13: 45000000 | 50000000 | 55000000

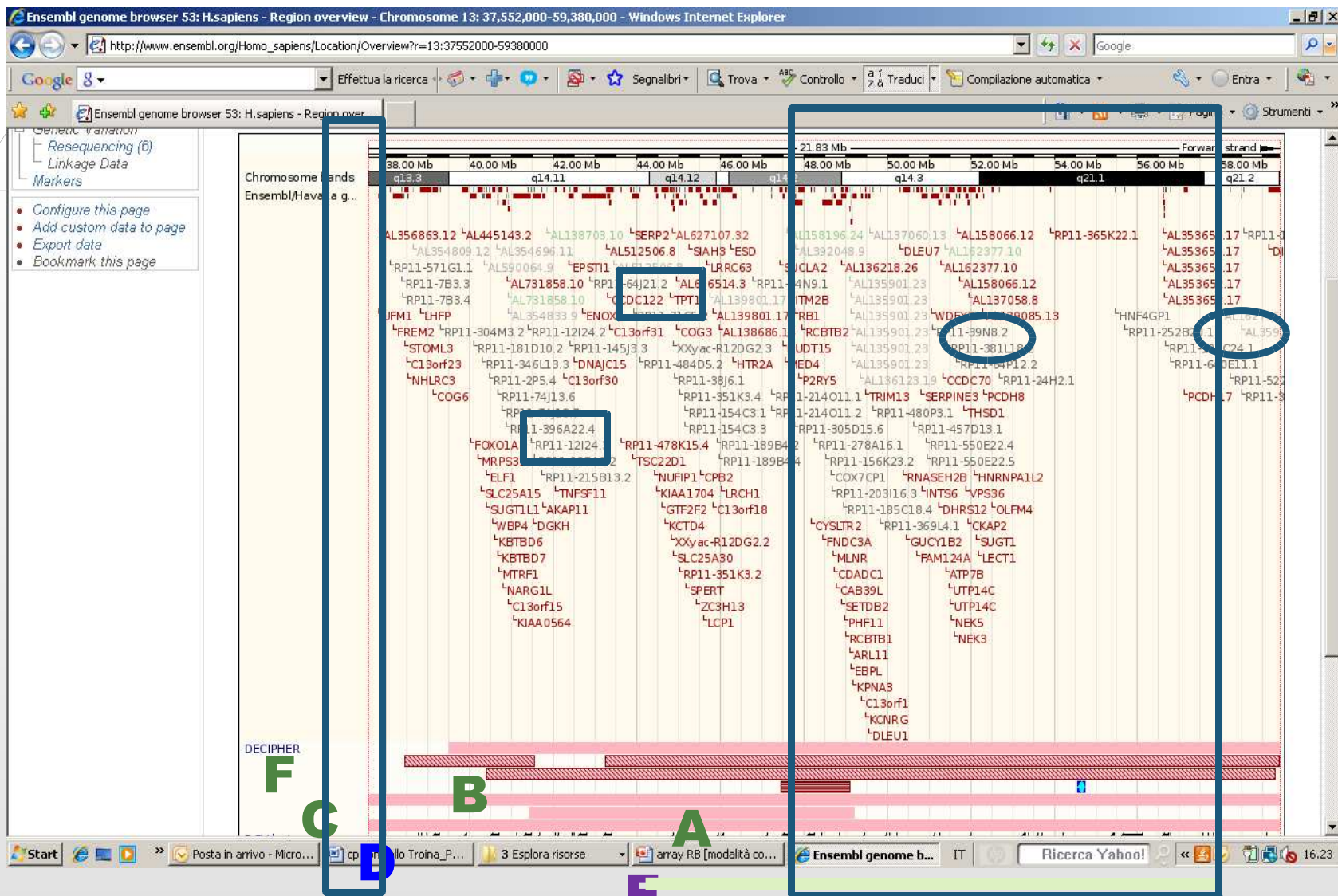
STS Markers on Genetic (blue) and Radiation Hybrid (black) Maps

UCSC Known Genes (June 05) Based on Uniprot, RefSeq, and GenBank mRNA

STS Markers	UCSC Known Genes	UCSC Known Genes	UCSC Known Genes	UCSC Known Genes	UCSC Known Genes
FLJ31846	TPT1	ESD	MEI4	ARL11	DDX26
FLJ38725	COG3	SUCLA2	MLNR	DLEU7	NEK3
BC000668	COG3	SUCLA2	EBFL	WDFY2	
C13orf21	CPB2	SUCLA2	EBFL	AK058149	
C13orf21	CPB2	NUDT25	KPNR3	FLJ13639	
AB082525	LCP1	ITIH2B	RFP2	ATP7B	
TSC22D1	LCP1	M19701	RFP2	ATP7B	
TSC22D1	LRCH1	RB1	KCHRC	AK126503	
TSC22D1	NUFIP1	LRCH1	P2RY5	KCHRC	BC009407
BC017745		HTR2A	RC3TB2	DLEU7	BC063885
BC039586				C13orf1	AK126330
BC039586				AK001904	BC055417
KIARA1704				AK131359	
	GTF2F2			AK123179	DLEU7
	KCTD4				THSD1
BC022436				CYSLTR2	FLJ1712
BC040008				BC0648141	GUCY1B2
AF318337				BC0648141	SUGT1
				BC0648141	LECT1
				BC051771	LECT1
				AK056071	BC051771
					PCDH8
				AK127569	OLFM4
				BC032689	
				AK127569	BC009825
				SLC25A30	
				AK057244	CDADC1
					AK124797
					LOC440138
				NURIT	CAB39L
				BC027609	AK131359
					AL137707
				AY263616	AY358149
				KIARA0853	AK096289
					SETDB2
				BC043488	SETDB2
				BC032311	C13orf9
				C13orf18	BC050439
				AK125950	BC050439
					AY062262
				BC001169	Y15758
					BC010901
					BC010901
					AK001611
					FAM109A
					LOC144983
					DKFIP434K1172
					AY271314
					AY271314
					AY358567

RefSeq Genes

Delezione caso 4



Caso 4 Caselli et al. (47.44-49.10Mb)

Caso 1 Caselli et al. (43.24-79.27Mb)

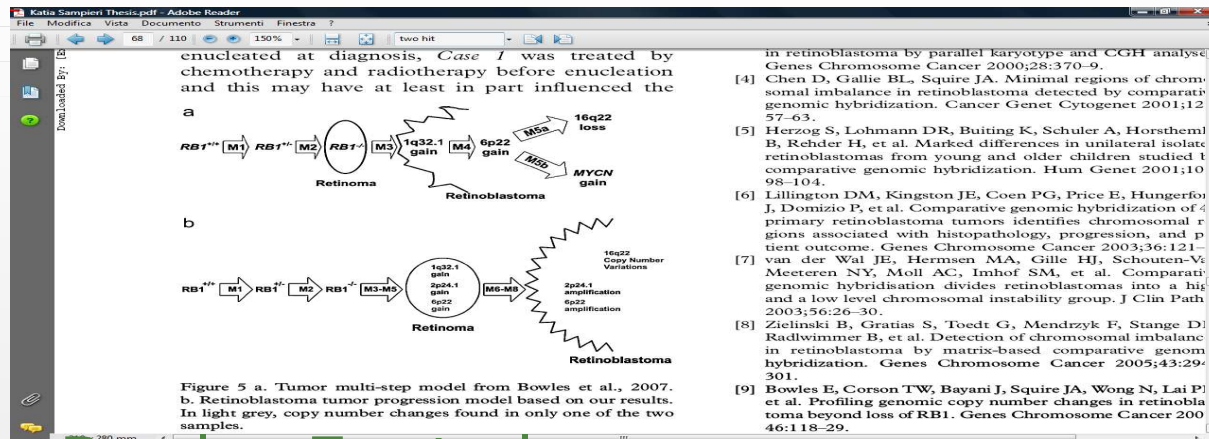
Caso 2 Caselli et al. (40.40-59.28Mb)

D RB355 retinoblastoma unilaterale sporadico, no ritardo (41.41-49.19Mb)

E RB421 retinoblastoma bilaterale, ritardo ? (41.41-49.19Mb)

F RB370 retinoblastoma monolaterale sporadico, ritardo (37.12-71.59Mb)

Modello di progressione tumorale



[4] Chen D, Gallie BL, Squire JA. Minimal regions of chromosomal imbalance in retinoblastoma detected by comparative genomic hybridization. *Cancer Genet Cytogenet* 2001;125:57-63.

[5] Herzog S, Lohmann DR, Buiting K, Schuler A, Horsthemel B, Rehder H, et al. Marked differences in unilateral isolate retinoblastomas from young and older children studied by comparative genomic hybridization. *Hum Genet* 2001;109:98-104.

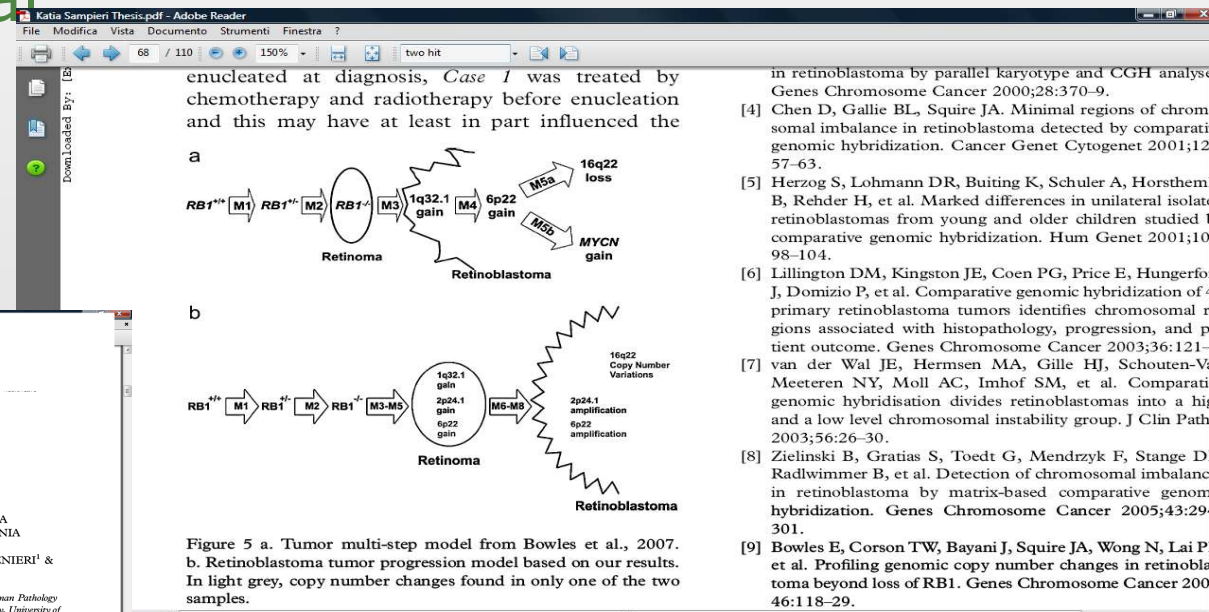
[6] Lillington DM, Kingston JE, Coen PG, Price E, Hungerford J, Domizio P, et al. Comparative genomic hybridization of 4 primary retinoblastoma tumors identifies chromosomal regions associated with histopathology, progression, and patient outcome. *Genes Chromosome Cancer* 2003;36:121-128.

[7] van der Wal JE, Hermesen MA, Gille HJ, Schouten-Ve Meeteren NY, Moll AC, Imhof SM, et al. Comparative genomic hybridisation divides retinoblastomas into a high and a low level chromosomal instability group. *J Clin Pathol* 2003;56:26-30.

[8] Zielinski B, Gratijs S, Toedt G, Mendrzyk F, Stange DJ, Radlwimmer B, et al. Detection of chromosomal imbalance in retinoblastoma by matrix-based comparative genomic hybridization. *Genes Chromosome Cancer* 2005;43:29-301.

[9] Bowles E, Corson TW, Bayani J, Squire JA, Wong N, Lai P, et al. Profiling genomic copy number changes in retinoblastoma beyond loss of RB1. *Genes Chromosome Cancer* 2004;46:118-29.

Bowles E. et al
2007



[4] Chen D, Gallie BL, Squire JA. Minimal regions of chromosomal imbalance in retinoblastoma detected by comparative genomic hybridization. *Cancer Genet Cytogenet* 2001;125:57-63.

[5] Herzog S, Lohmann DR, Buiting K, Schuler A, Horsthemel B, Rehder H, et al. Marked differences in unilateral isolate retinoblastomas from young and older children studied by comparative genomic hybridization. *Hum Genet* 2001;109:98-104.

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[7] van der Wal JE, Hermesen MA, Gille HJ, Schouten-Ve Meeteren NY, Moll AC, Imhof SM, et al. Comparative genomic hybridisation divides retinoblastomas into a high and a low level chromosomal instability group. *J Clin Pathol* 2003;56:26-30.

[8] Zielinski B, Gratijs S, Toedt G, Mendrzyk F, Stange DJ, Radlwimmer B, et al. Detection of chromosomal imbalance in retinoblastoma by matrix-based comparative genomic hybridization. *Genes Chromosome Cancer* 2005;43:29-301.

[9] Bowles E, Corson TW, Bayani J, Squire JA, Wong N, Lai P, et al. Profiling genomic copy number changes in retinoblastoma beyond loss of RB1. *Genes Chromosome Cancer* 2004;46:118-29.

Acta Oncologica, 2008; 47: 1483-1492

ORIGINAL ARTICLE

Genomic differences between retinoma and retinoblastoma

KATIA SAMPIERI¹, MARIA ANTONIETTA MENCARELLI¹, MARIA CARMELA EPISTOLATO², PAOLO TOTI², STEFANO LAZZI², MIRELLA BRUTTINI¹, SONIA DE FRANCESCO³, ILARIA LONGO³, ILARIA MELONI³, FRANCESCA MARI¹, ANTONIO ACQUAVIVA⁴, THEODORA HADJISTILIANOU⁵, ALESSANDRA RENIERI¹ & FRANCESCA ARIANI¹

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Abstract

03/11/09

Sampieri et al 2009.pdf - Adobe Reader

File Modifica Vista Documento Strumenti Finestra 2

1 / 7 133% Trova

Array comparative genomic hybridization in retinoma and retinoblastoma tissues

Katia Sampieri,¹ Mariangela Amenduni,¹ Filomena Tiziana Papa,¹ Eleni Katzaki,¹ Maria Antonietta Mencarelli,¹ Annabella Marozza,¹ Maria Carmela Epistolato,² Paolo Toti,² Stefano Lazzi,² Mirella Bruttini,¹ Roberta De Filippis,¹ Sonia De Francesco,³ Ilaria Longo,¹ Ilaria Meloni,¹ Francesca Mari,¹ Antonio Acquaviva,⁴ Theodora Hadjistilianou,³ Alessandra Renieri^{1,5} and Francesca Ariani¹

¹Medical Genetics, Department of Molecular Biology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100 Siena, Italy, ²Department of Human Pathology and Oncology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100, Siena, Italy, ³Retinoblastoma Referral Center, Department of Ophthalmology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100, Siena, Italy, ⁴Department of Pediatrics, Obstetrics and Reproductive Medicine, Italian retinoblastoma registry, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100, Siena, Italy

(Received September 4, 2008/Revised November 17, 2008/Accepted November 19, 2008/Online publication January 31, 2009)

In retinoblastoma, two *RB1* mutations are necessary for tumor development. Recurrent genomic rearrangements may represent subsequent events required for retinoblastoma progression. Array-comparative genomic hybridization was carried out in 18 eye samples, 10 from bilateral and eight from unilateral retinoblastoma patients. Two unilateral cases also showed areas of retinoma. The most frequent imbalance in retinoblastomas was 6p gain (40%), followed by gains at 1q12-q25.3, 2p24.3-p24.2, 9q22.2, and 9q33.1 and losses at 11q24.3, 13q13.2-q22.3, and 16q12.1-q21. Bilateral cases showed a lower number of imbalances than unilateral cases ($P = 0.002$). Unilateral cases were divided into low-level (≤ 4) and high-level (≥ 7) chromosomal

polymerase chain reaction (PCR) and fluorescence *in situ* hybridization on specific candidate genes, it has also been shown that RN display low-level copy number changes involving higher levels of amplification in adjacent RB.^(4,5) A study by Dimaras *et al.* in RN importantly clarified that the two hits in *RB1* (M1–M2) do not inevitably cause a malignant phenotype but only genomic instability.^(4,6) At some point this instability can lead to further genomic rearrangements (M3–Mn) that result in tumor progression.^(4,8)

Cytogenetic and conventional or microarray comparative genomic hybridization (CGH) studies have detected recurrent

Sampieri et al 2009.pdf - Adobe Reader

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4 / 7 167% Trova

array-comparative genomic hybridization (CGH) analysis was carried out in 18 eye samples, 10 from bilateral and eight from unilateral retinoblastoma patients. Two unilateral cases also showed areas of retinoma. The most frequent imbalance in retinoblastomas was 6p gain (40%), followed by gains at 1q12-q25.3, 2p24.3-p24.2, 9q22.2, and 9q33.1 and losses at 11q24.3, 13q13.2-q22.3, and 16q12.1-q21. Bilateral cases showed a lower number of imbalances than unilateral cases ($P = 0.002$). Unilateral cases were divided into low-level (≤ 4) and high-level (≥ 7) chromosomal

Figure 1. Overview of recurrent genomic imbalances in 18 retinoblastoma samples. The figure shows a series of vertical bars representing chromosomes 1 through 22, with colored segments indicating gains (red) and losses (blue). The most prominent gain is on chromosome 6p, followed by gains on 1q, 2p, 9q, and 9q33.1, and losses on 11q, 13q, and 16q.

Table 1. Recurrent genomic imbalances identified by array-comparative genomic hybridization analysis.

Chromosomal imbalances	Band position	Frequency (%)	No. genes	Oncogenes and tumor suppressors	Other candidate genes
dup(6)q25.3-p11(0201184)	6p25.3-6p11	40	316	ARF, E2F3, MDM1	226 (72%)
dup(1)q12-q25.3(11847)	1q12-1q25.3	23.89	401		363 (90.5%)
dup(9)q22.2-q24.3(11847)	9q22.2-9q24.3	22.22	4	MYCN	2041

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5 / 7 133% Trova

These regions have been studied for gene content in order to identify candidates involved in the RN–RB transition. We searched for known oncogenes and tumor suppressors, for genes related to the pRB pathway, and for genes involved in proliferation, differentiation, apoptosis, or senescence (Table 4).

Discussion

The loss of *RB1* function, by means of two mutational events (M1 and M2), is considered to be the first rate-limiting step in RB development.^(1,6) Several studies have suggested that genomic

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Table 3. Correlation between the number of genomic rearrangements and age at diagnosis in unilateral cases

Case no.	No. rearrangements	Chromosomal instability group	Age at diagnosis (days)
11	2	≤4	90
12	2	≤4	743
13	4	≤4	285
14	4	≤4	480
15	4	≤4	958
16	7	≥7	1326
17	8	≥7	1663
18	24	≥7	1828

imbalance (M3–Mn) involving specific oncogenes and tumor

The rearrangement contains 461 genes, including the three known oncogenes *IRF4*, *DEK*, and *PIM1* (Table 2). We further selected two members of the pRB pathway that have an essential role in G1–S cell-cycle transition: the pRB-regulated transcription factor E2F3 and cyclin CCND3, involved in pRB phosphorylation (Table 2).^(25,26) Previous studies reporting more focused gains at 6p22 led to deep investigation of the genes within this region.⁽¹⁴⁾ By QM-PCR and microarray expression analysis on RB tissues, it has been demonstrated that *DEK* and *E2F3* are the most commonly gained genes and that they show overexpression.^(25,26) Furthermore, *DEK* and *E2F3* are overexpressed in Tag-RB murine tumors.⁽⁹⁾ These results indicate that both *DEK* and *E2F3* represent strong candidates for RB progression and that a combination of genes on 6p, instead of a single one, probably contributes to RB progression.

The MRG on chromosome 1 (dup1q12-q25.3) contains 497 genes (Table 2). We selected *MUC1* as its overexpressed in human carcinomas and certain hematological

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CONSULENZA GENETICA



ANALISI MOLECOLARE

Sporadici
monolaterali

mutazione -
foc

Rassicurare

Casi familiari
+
Sporadici
bilaterali

mutazione +

Definire esatto Rischio di Ricorrenza
Offrire test prenatale
Identificare familiari a rischio