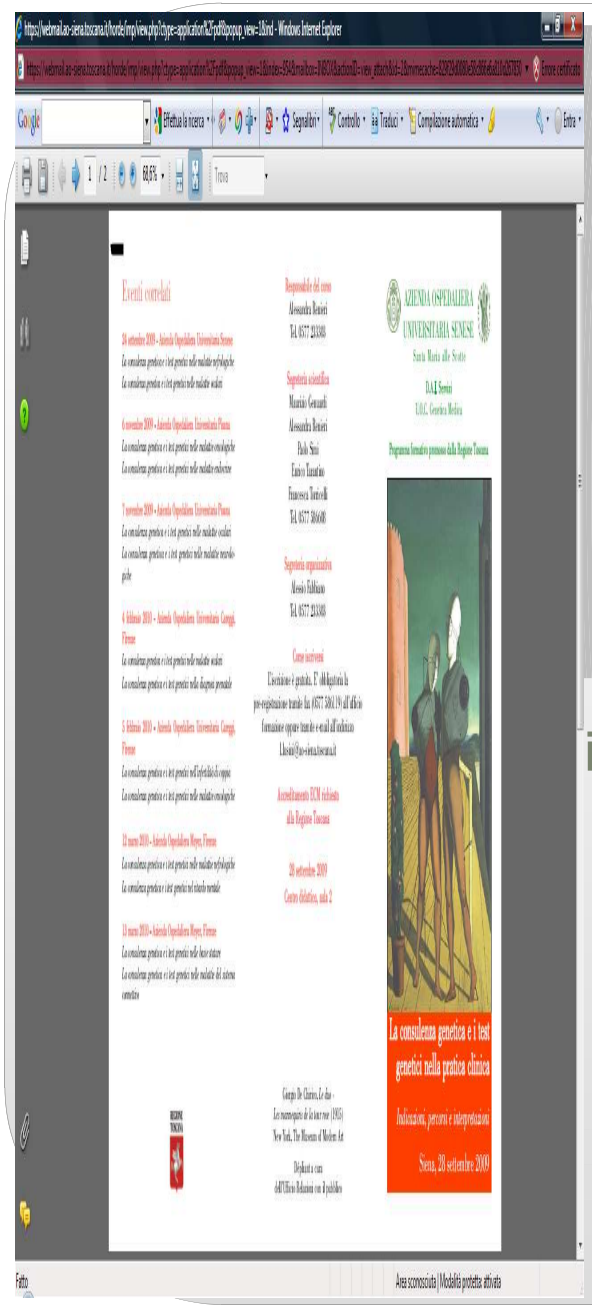


Retinoblastoma

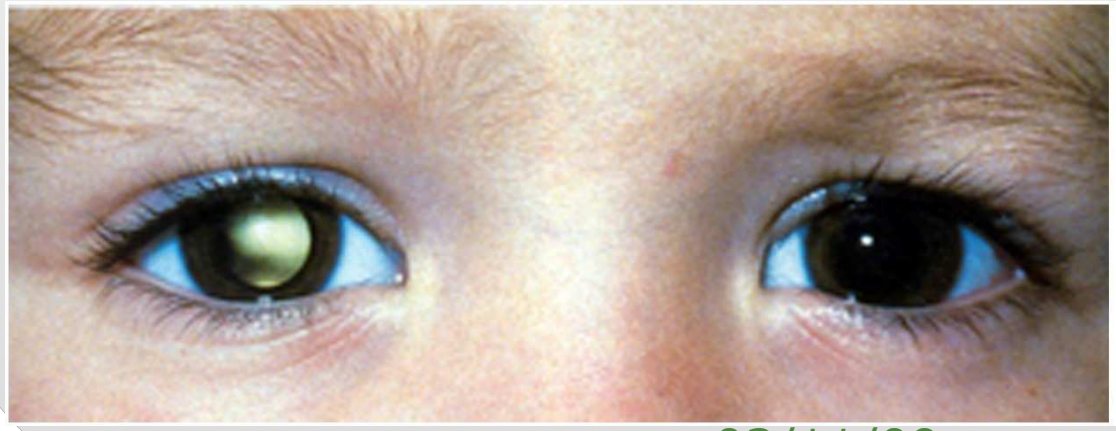
Maria Antonietta Mencarelli
Genetica Medica, AOUS

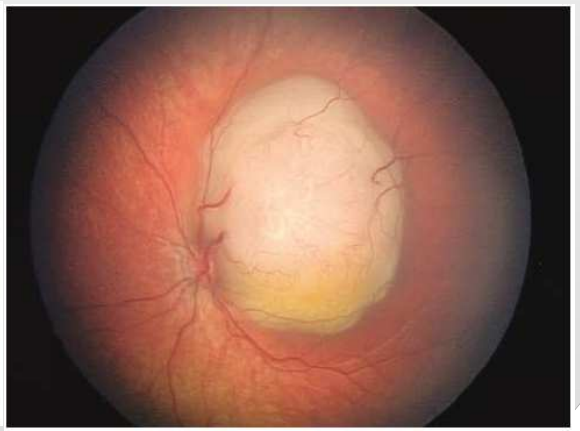
Mantenere lo stile del titolo dello schema

03/11/09

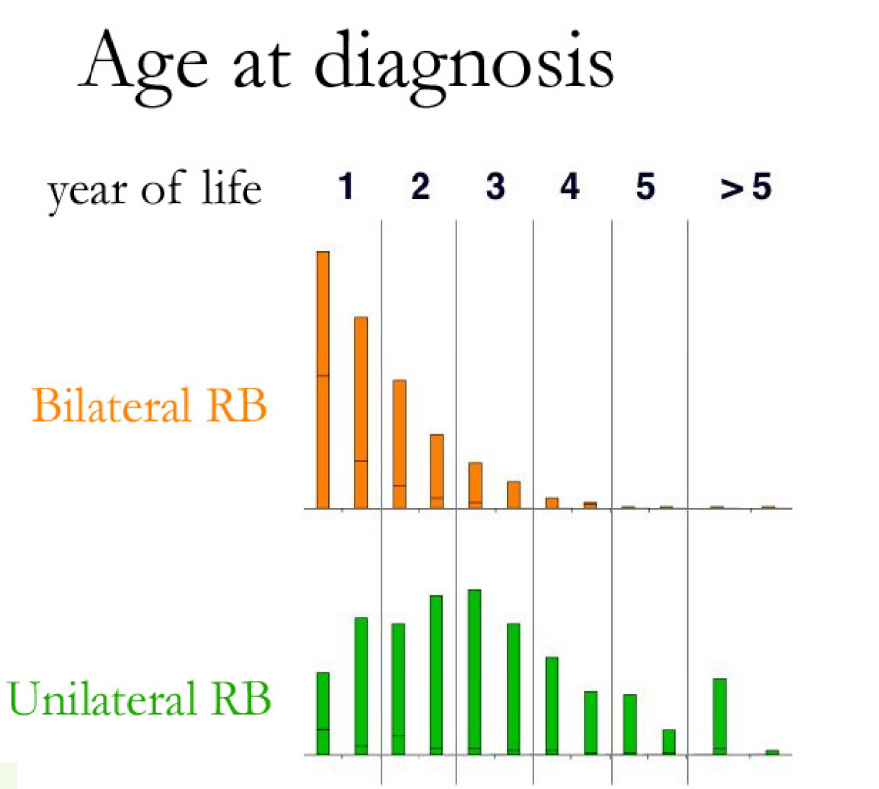
Tumore embrionale maligno, endooculare, che origina dalle cellule della retina

Incidenza: 1:15.000 - 1:20.000





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



4% delle neoplasie del bambino

~1% di tutti i tumori

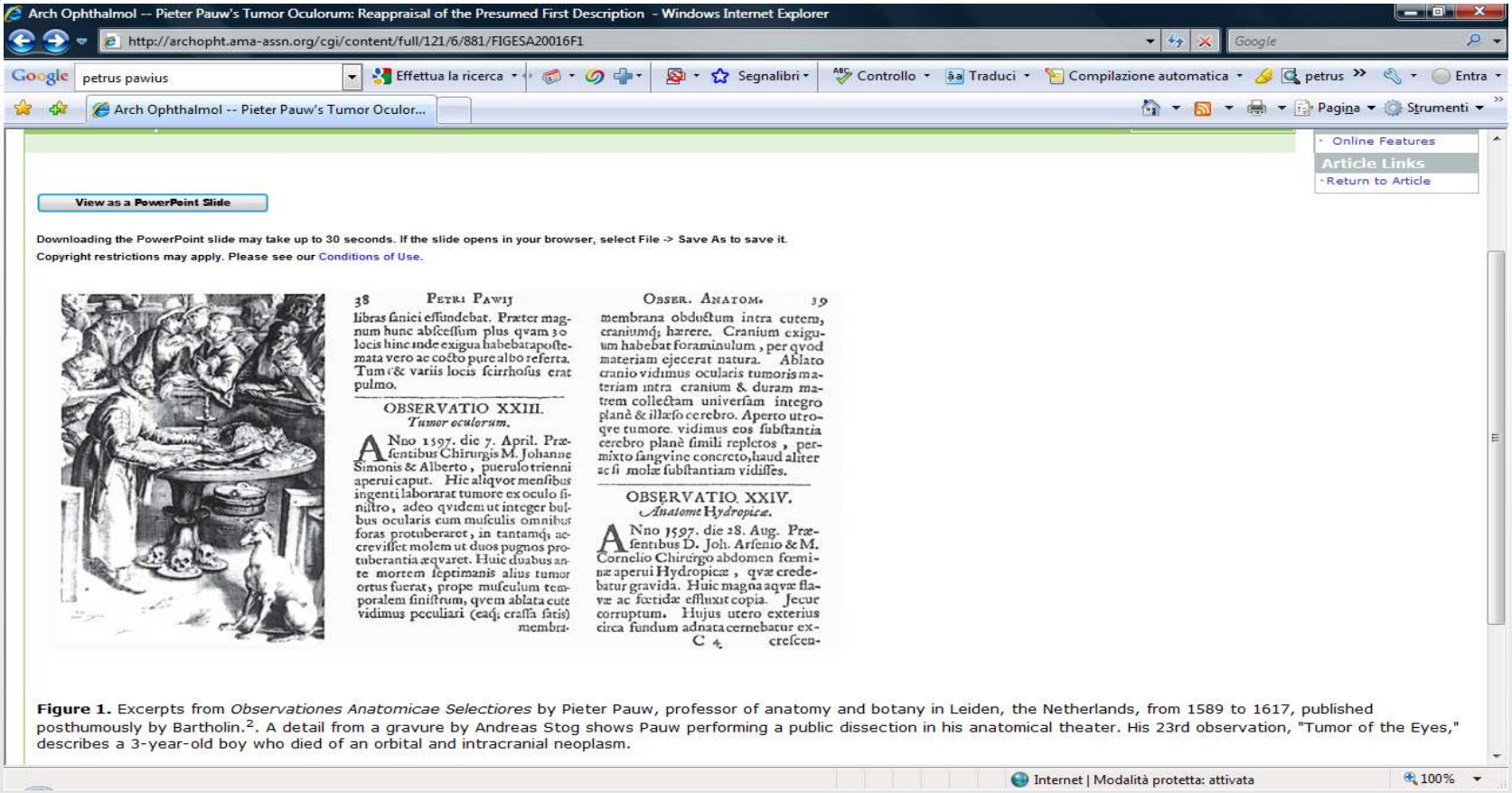


Figure 1. Excerpts from *Observationes Anatomicae Selectiores* by Pieter Pauw, professor of anatomy and botany in Leiden, the Netherlands, from 1589 to 1617, published posthumously by Bartholin.[2]. A detail from a gravure by Andreas Stog shows Pauw performing a public dissection in his anatomical theater.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

1597 Petrus Pawius

Observationes Anatomicae Selectiores

03/11/09

Mutation and Cancer: Statistical Study of Retinoblastoma - Windows Internet Explorer

http://www.pubmedcentral.nih.gov/pagerender.fcgi?artid=389051&pageindex=1

Page 820 | 821 | 822 | 823

PNAS

Proc. 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 via 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 for the first, and the somatic rate for the second, mutation, 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. Ashley (1)

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 patients 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:

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Mutation and Cancer: Statistical Study of Retinoblastoma - Windows Internet Explorer

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PNAS

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 $\ln S = -kt$, 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 Burch (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^{-7} 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

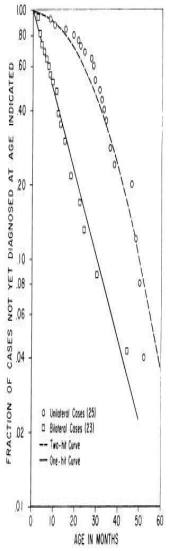

FIG. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -t/30$, the two-hit curve from $\log S = -4 \times 10^{-4} t^2$.

Fine | Internet | Modalità protetta: attivata | 100%

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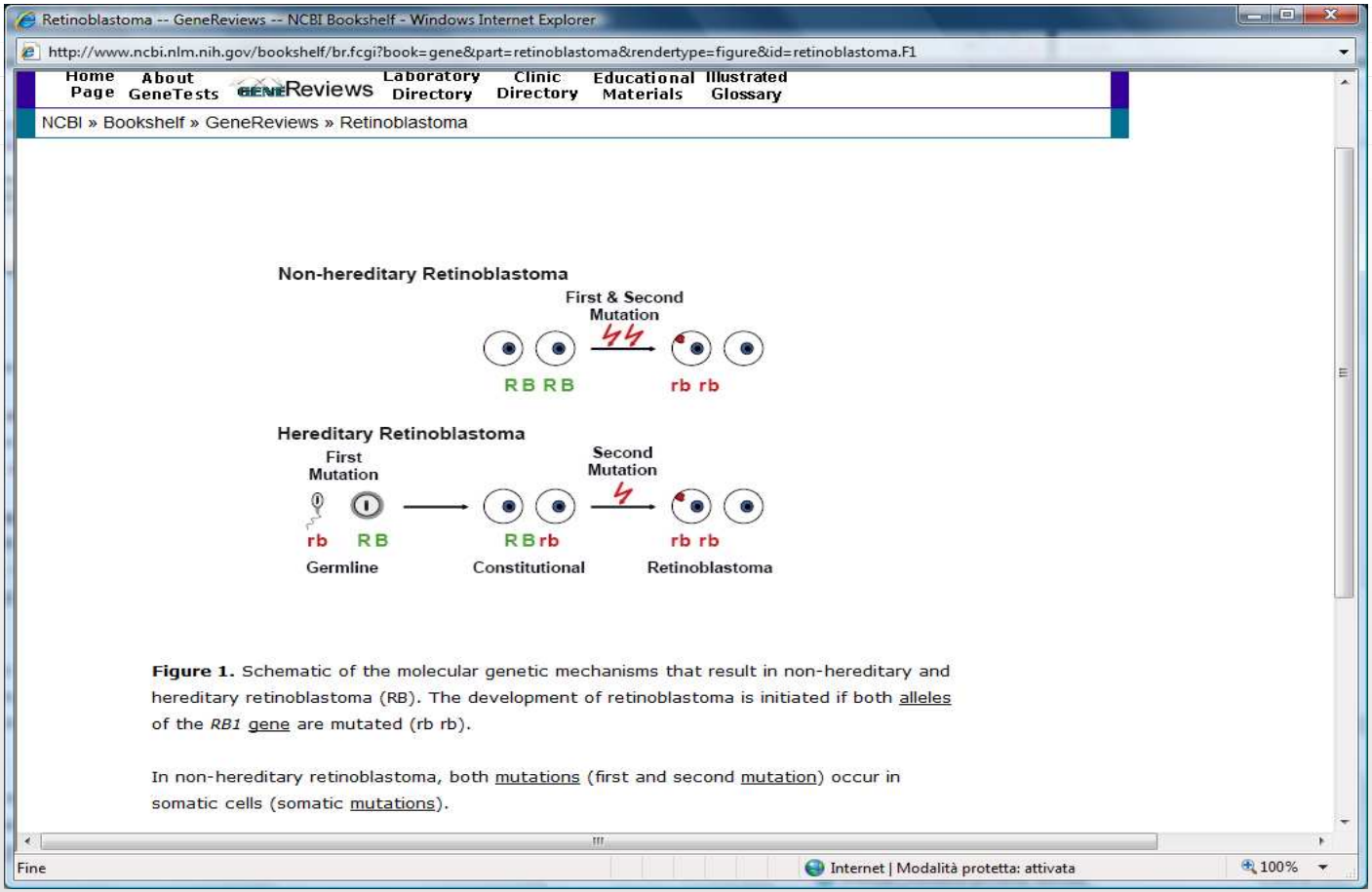
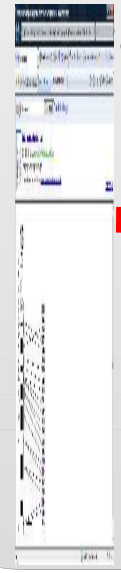


TWO HIT HYPOTHESIS

03/11/09

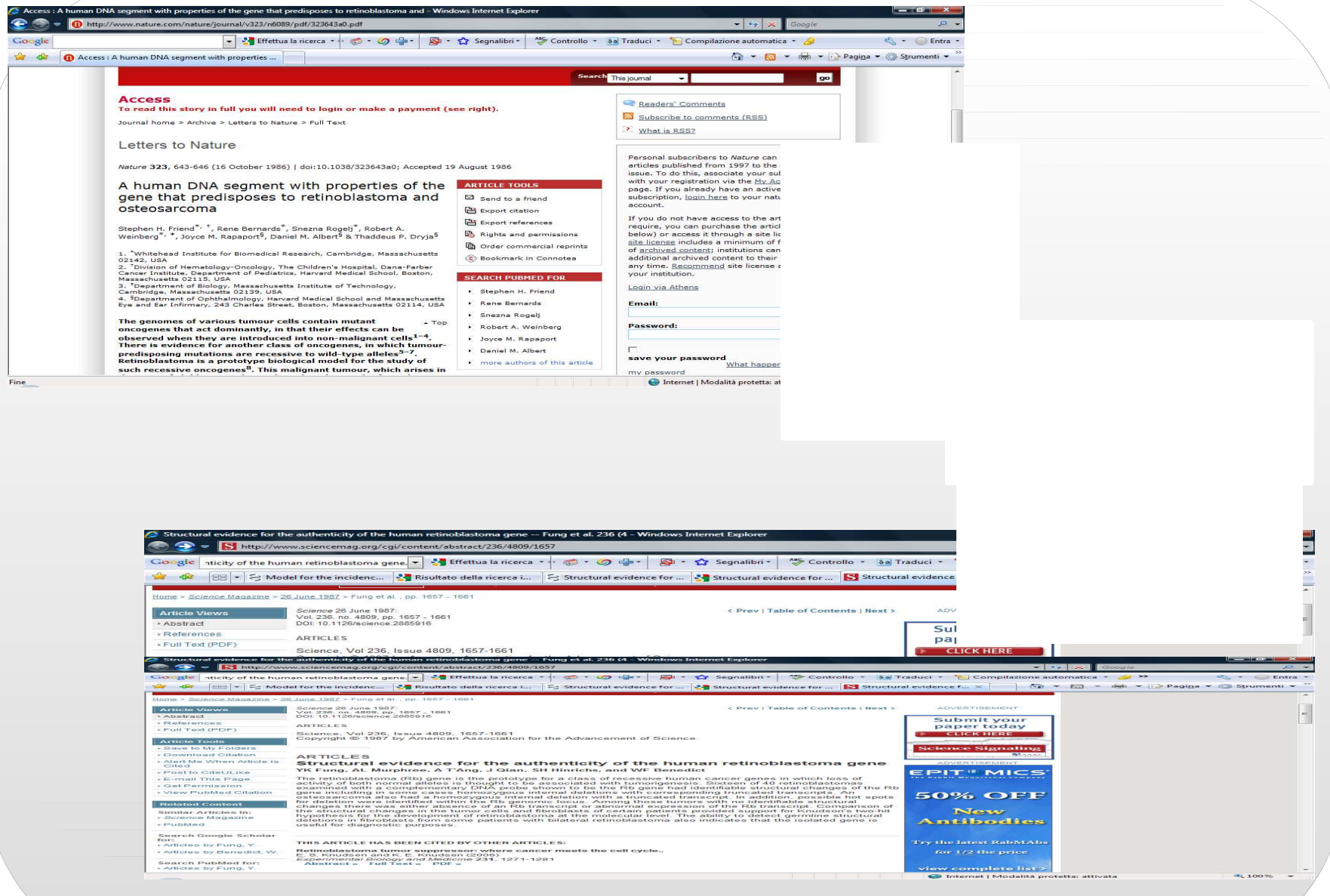
Volume 295:1120-1123 November 11, 1976
Number 20

Chromosomal deletion and retinoblastoma



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

- ***RB1***


Access : A human DNA segment with properties of the gene that predisposes to retinoblastoma and - Windows Internet Explorer
http://www.nature.com/nature/journal/v323/n6089/pdf/323643a0.pdf
Access
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Letters to Nature
A human DNA segment with properties of the gene that predisposes to retinoblastoma and osteosarcoma
Stephen H. Friend, Rene Bernards, Snezna Rogelj, Robert A. Weinberg, Joyce M. Rapaport, Daniel M. Albert & Thaddeus P. Dryja
The genomes of various tumour cells contain mutant oncogenes that act dominantly, in that their effects can be observed when they are introduced into non-malignant cells.
There is evidence for another class of oncogenes, in which tumour-predisposing mutations are recessive to wild-type alleles.
Retinoblastoma is a prototype biological model for the study of such recessive oncogenes. This malignant tumour, which arises in
ARTICLE TOOLS
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Structural evidence for the authenticity of the human retinoblastoma gene -- Fung et al. 236 (4 - Windows Internet Explorer
http://www.sciencemag.org/cgi/content/abstract/236/4809/1657
Science, Vol 236, Issue 4809, 1657-1661
ARTICLES
Structural evidence for the authenticity of the human retinoblastoma gene
YK Fung, AL Murphree, A T'Ang, J Qian, SH Hinrichs, and WF Benedict
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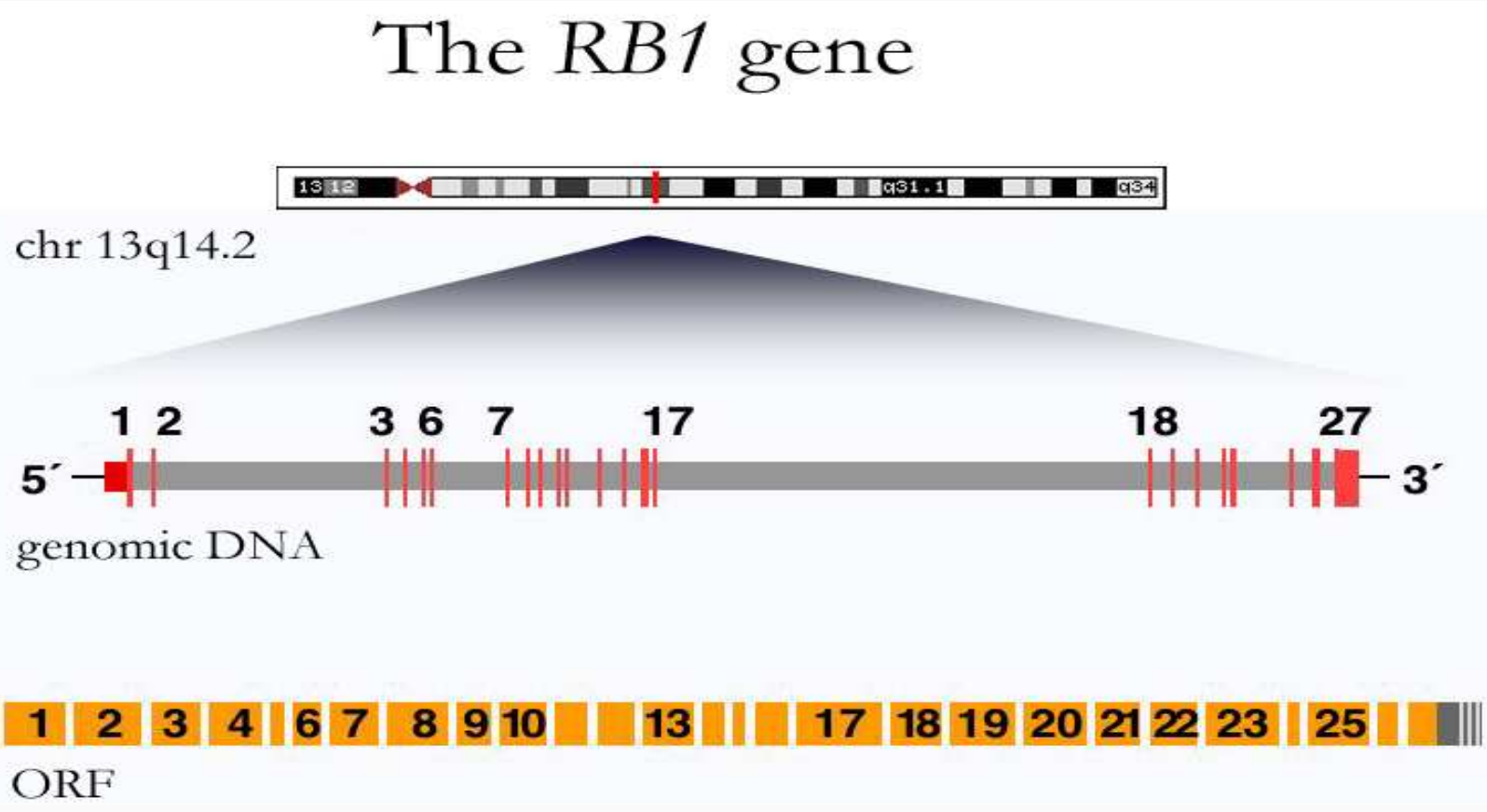
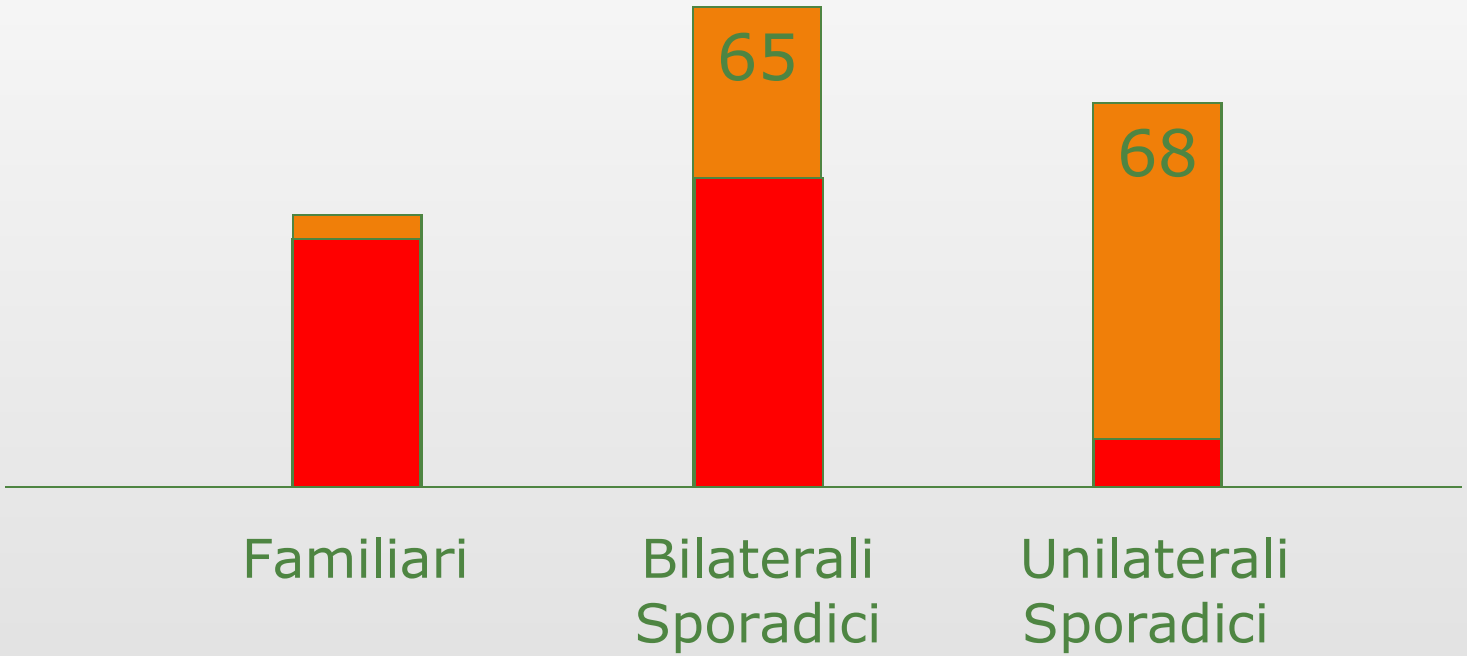
Il gene *RB1*


The RB1 gene
13q12
q31.1
q34
chr 13q14.2
1 2
3 6
7
17
18
27
5´
3´
genomic DNA
1 2 3 4 6 7 8 9 10 13 17 18 19 20 21 22 23 25
ORF

…Novembre 2000

167 famiglie RB



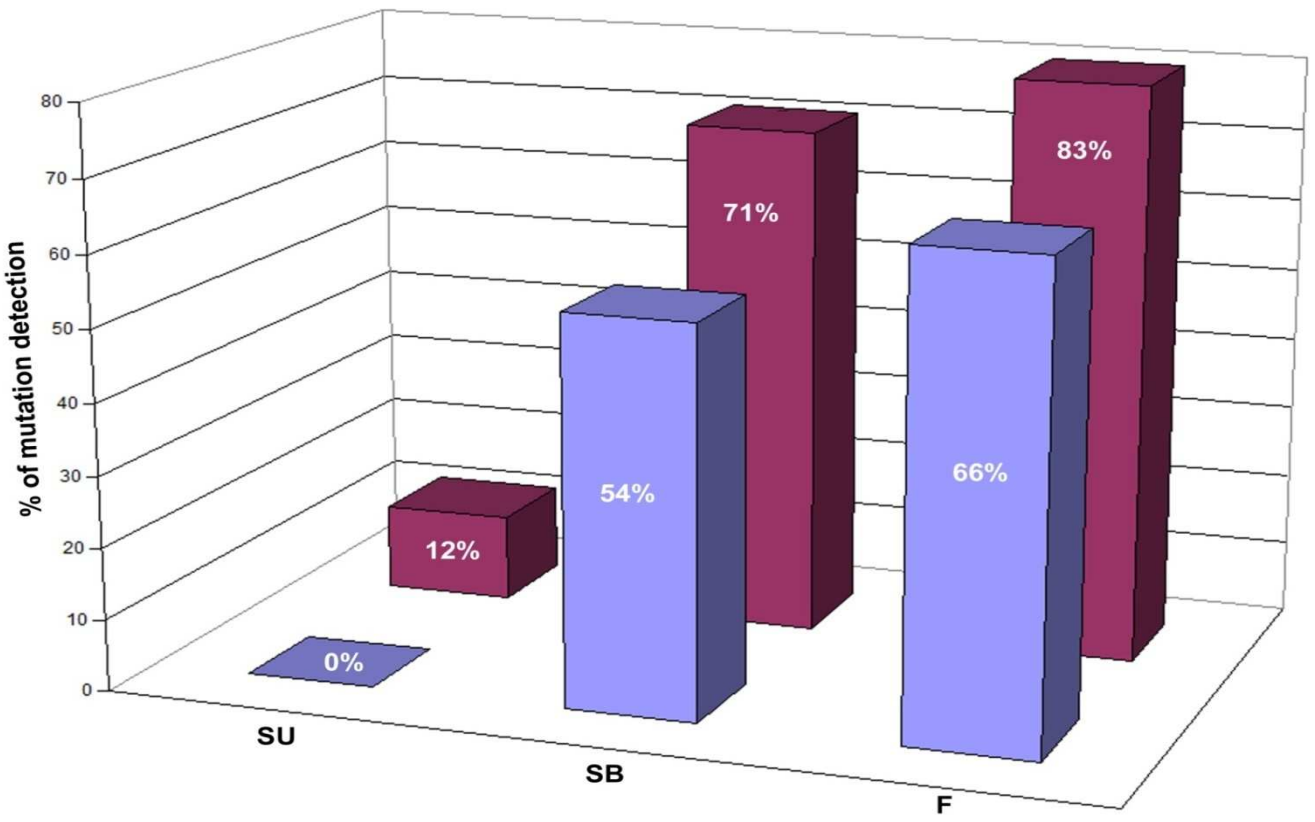
82 mutazioni *RB1*

32/35 (91%)

40/64 (63%)

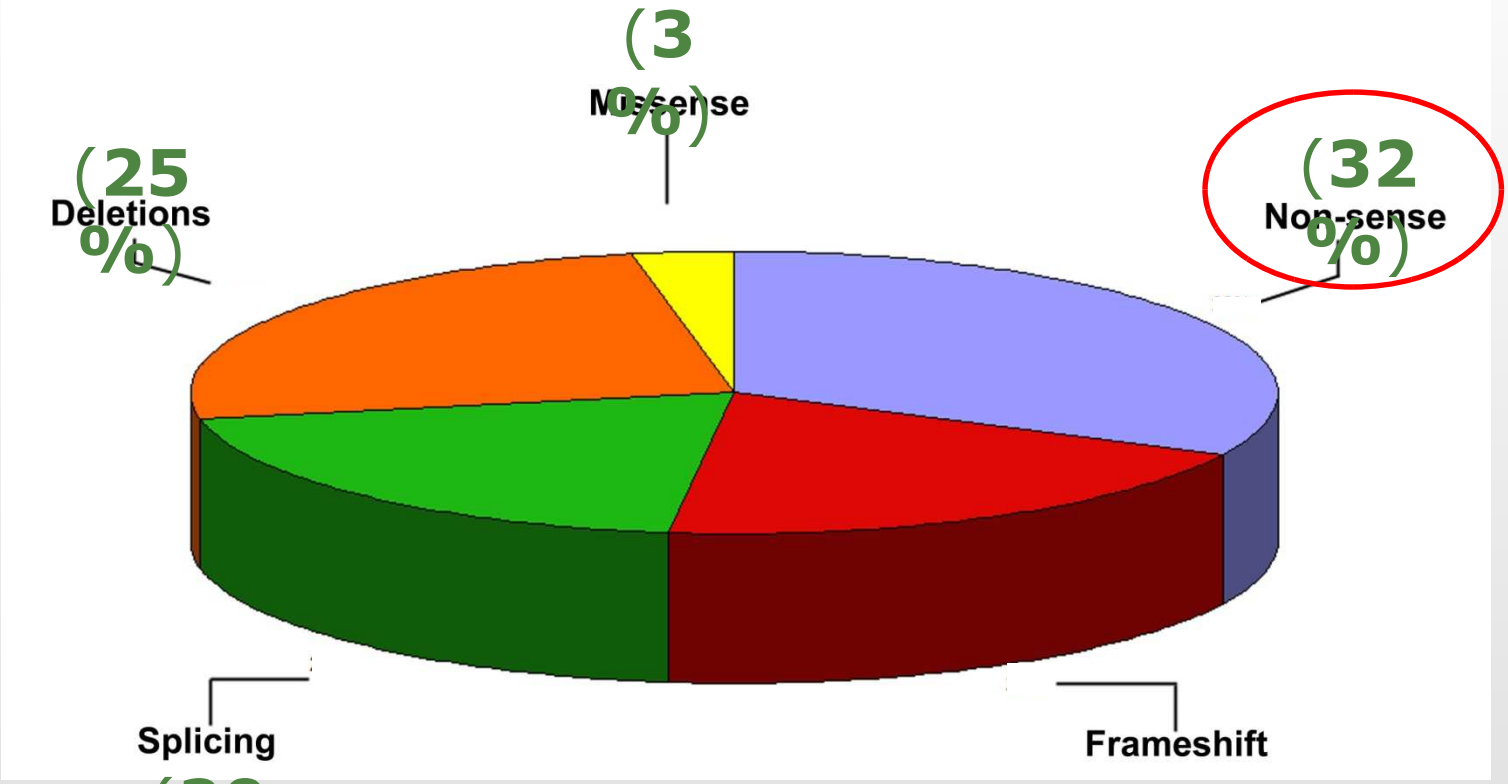
10/68 (15%)

Detection rate



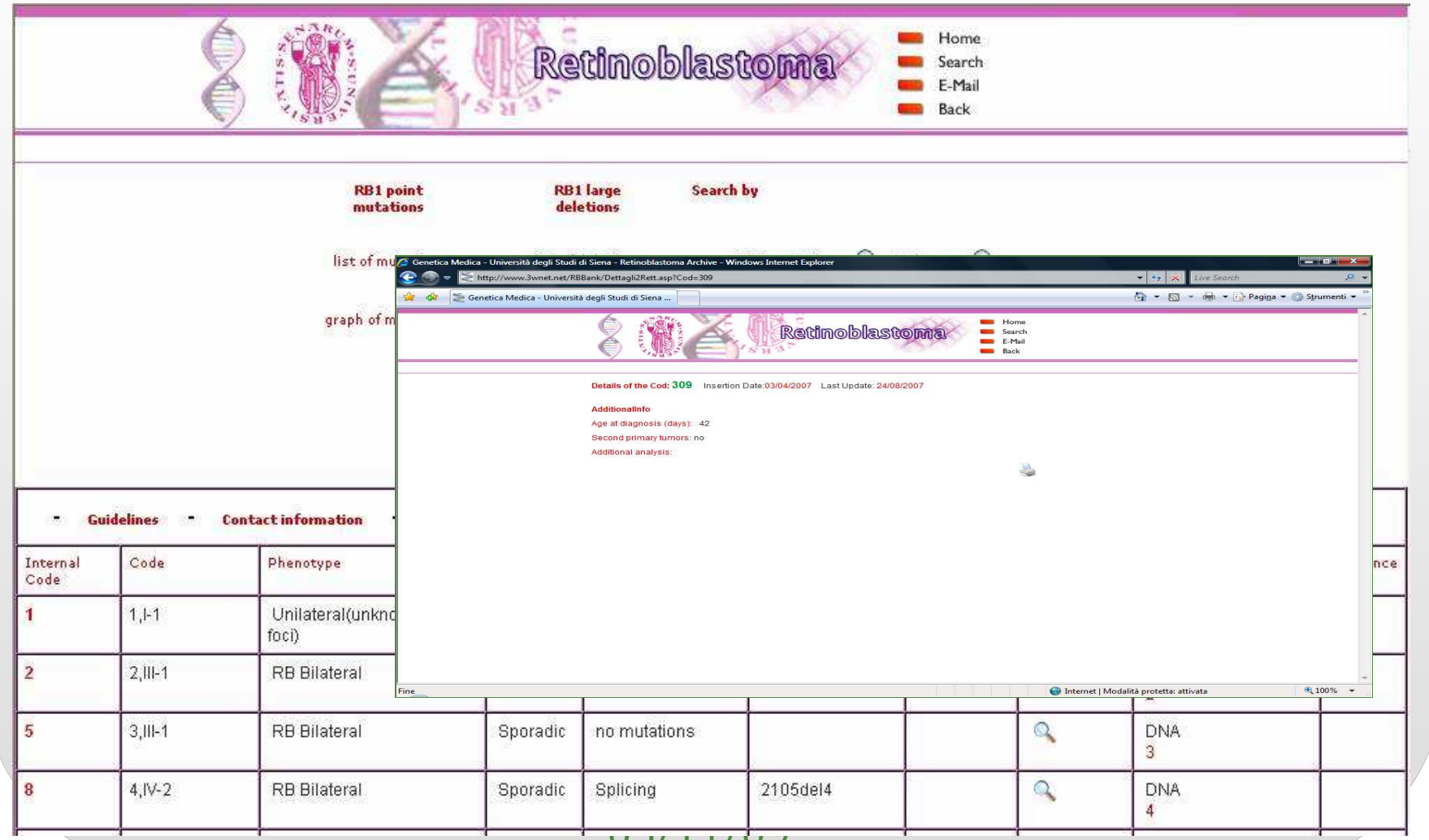
Sampieri et al., 2006
Multistep analysis

Mutazioni del gene *RB1*

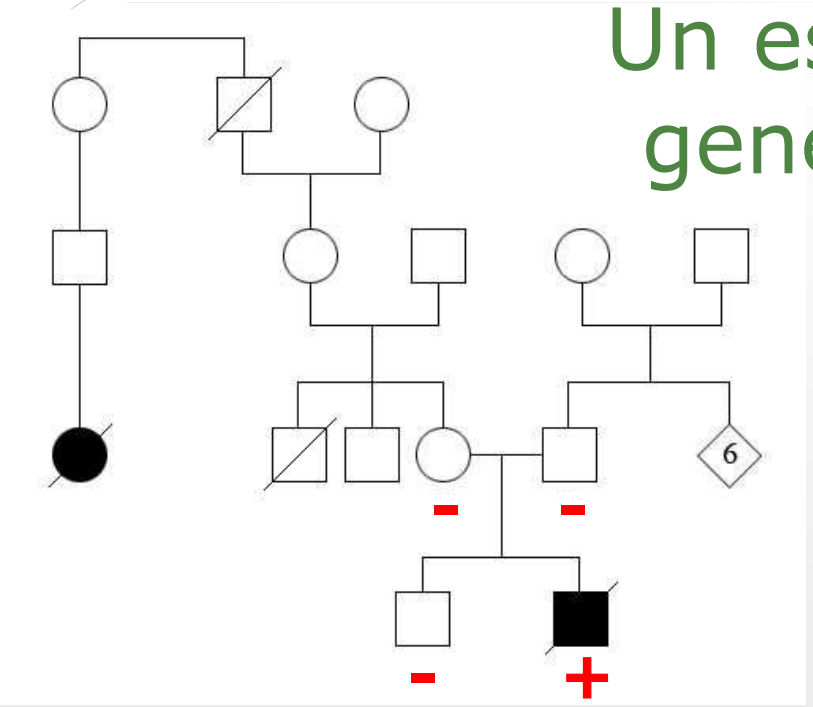


RB database

http://www.biobank.unisi.it



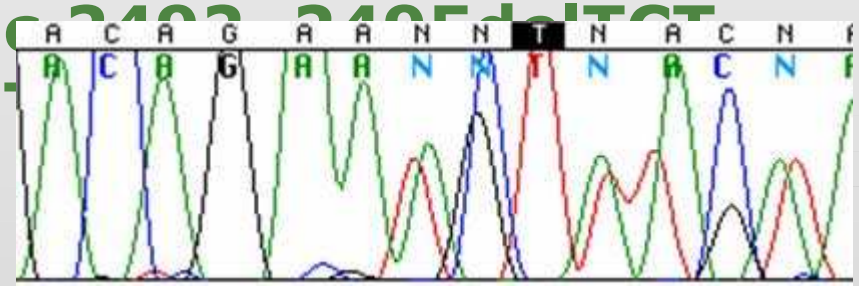
Un esempio di consulenza genetica preconcezionale



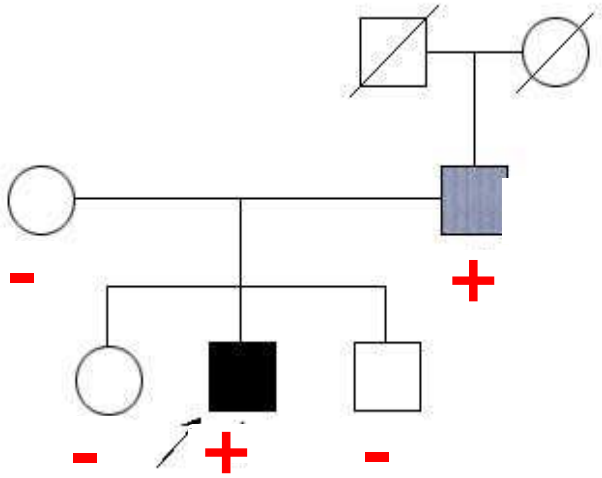
3 aa: RB bilaterale
(enucleazione OS + Chemioterapia)

Sangue cordonale da biobanca

frameshift ,

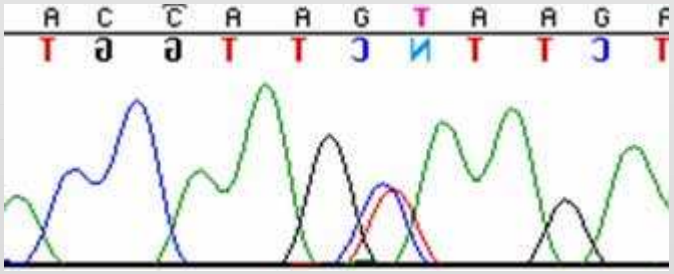


Un caso di retinoma



Retinoma monolaterale identificato *a posteriori*

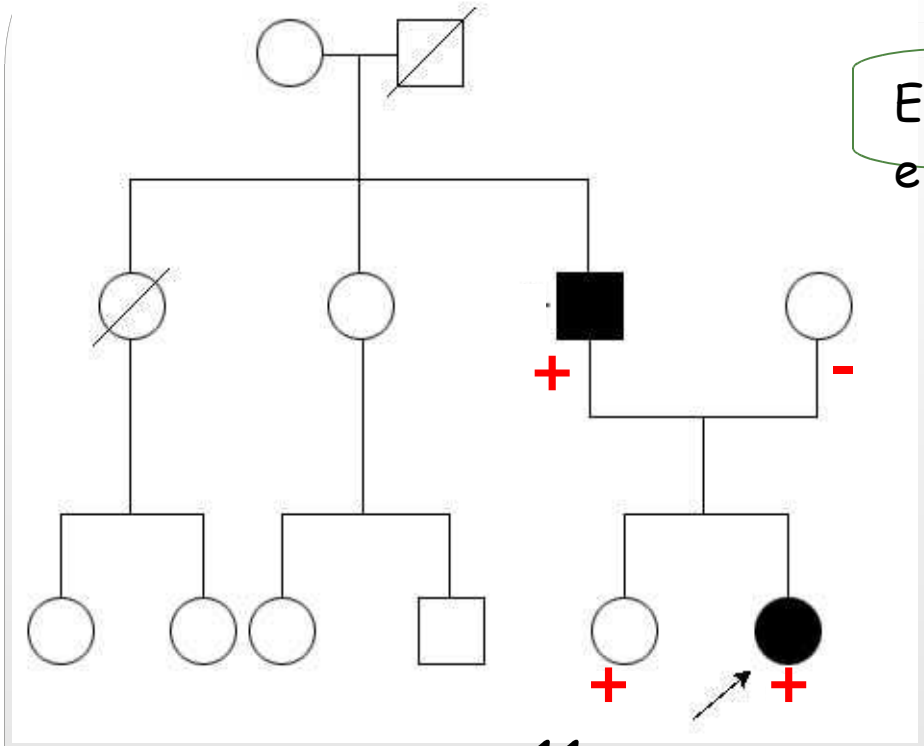
4 m: Enucleazione OD. Chemioterapia e successiva enucleazione OS



Introne 20

c.2106+2T

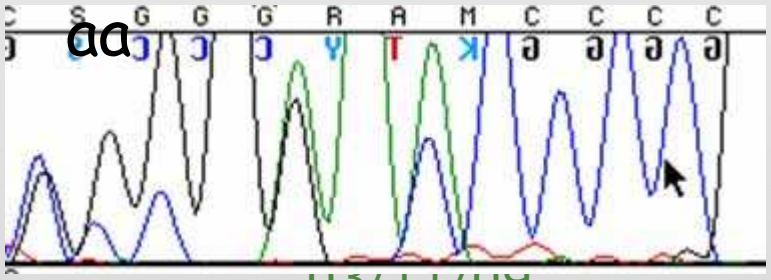
Un caso di non penetranza



Enucleazion
e a 15 m

14 m RB unilaterale

11
aa



Esone 1
frameshift
c.58delC

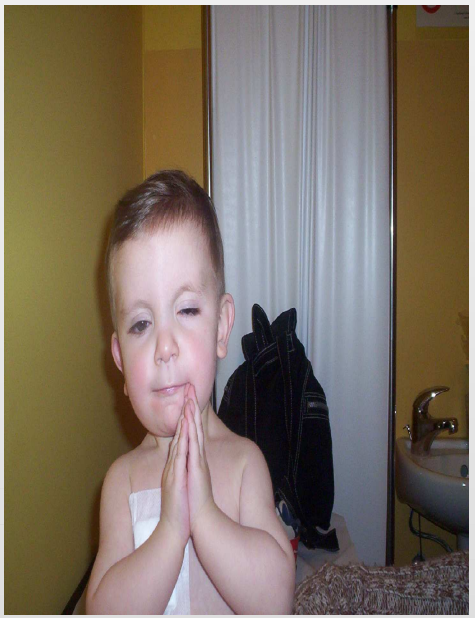
J Hum Genet
DOI 10.1007/s10038-007-0151-4

ORIGINAL ARTICLE

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

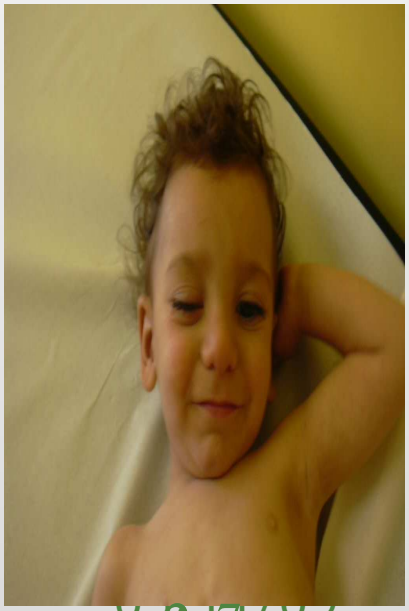
R. Caselli · C. Speciale · C. Pescucci · V. Uliana · K. Sampieri · M. Bruttini · I. Longo · S. De Francesco · T. Pramparo · O. Zuffardi · R. Frezzotti · A. Acquaviva · T. Hadjistilianou · A. Renieri · F. Mari

Caso 1



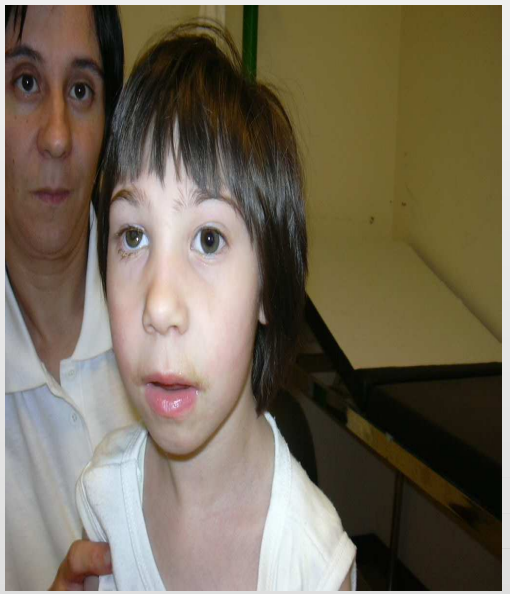
1a 2m

Caso 2



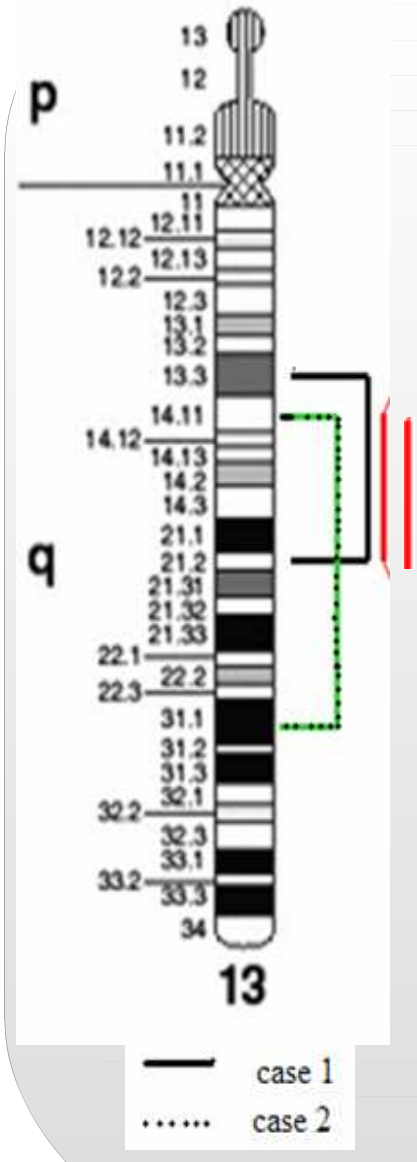
2a7m

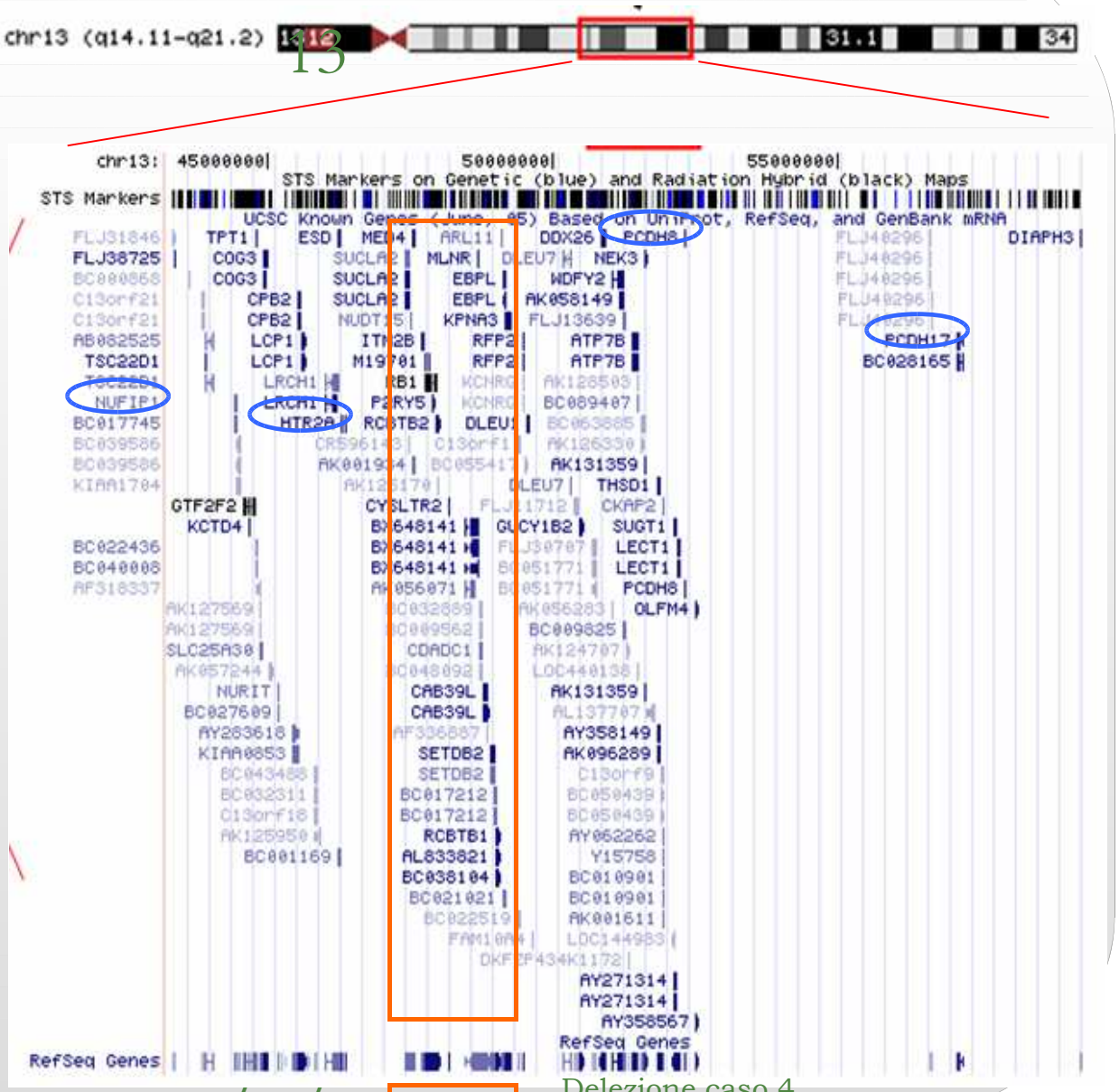
Caso 3



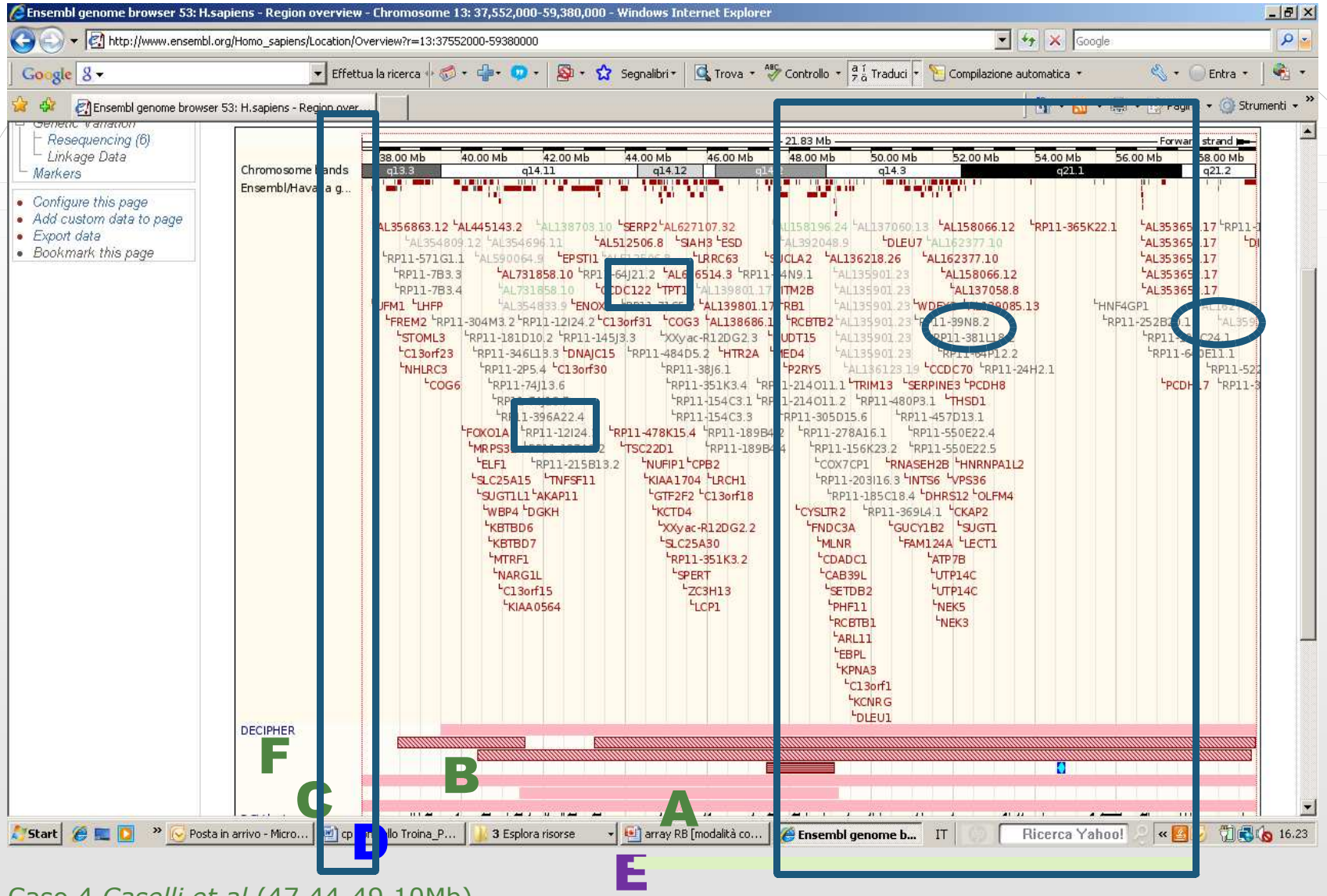
7a6m

Cromosoma 13





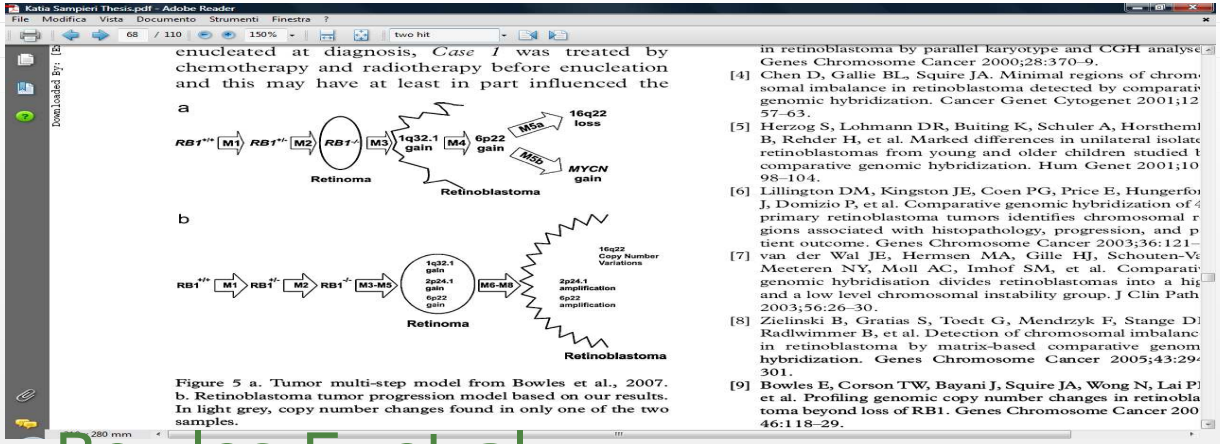
Delezione caso 4



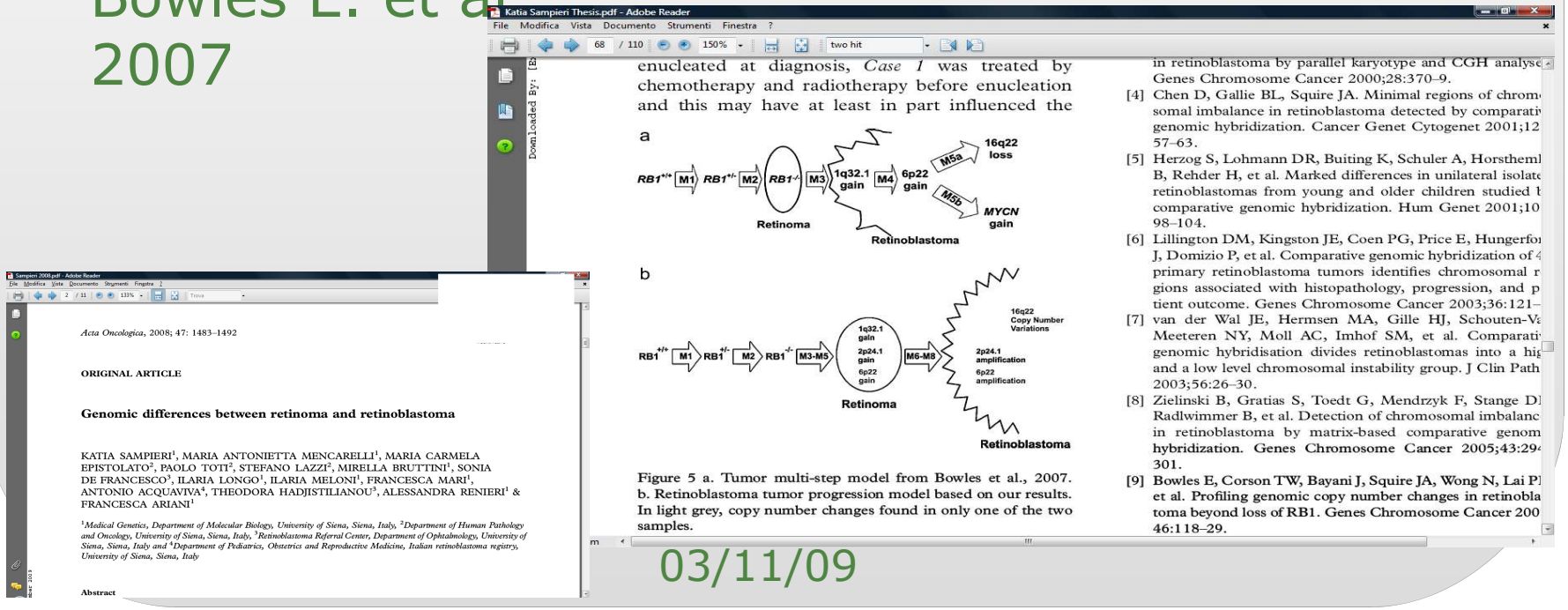
Caso 4 *Caselli et al.*(47.44-49.10Mb)
Caso 1 *Caselli et al.*(43.24-79.27Mb)
Caso 2 *Caselli et al.*(40.40-59.28Mb)
D RB355 retinoblastoma unilaterale sporadico, no ritardo (41.41-49.19Mb)
E RB421 retinoblastoma bilaterale, ritardo ?(46.25-57.29Mb)
F RB370 retinoblastoma monolaterale sporadico, ritardo (37.12-71.59Mb)

03/11/09

Modello di progressione tumorale



Bowles E. et al 2007



Acta Oncologica, 2008; 47: 1483–1492

ORIGINAL ARTICLE

Genomic differences between retinoma and retinoblastoma

KATIA SAMPIERI[1], MARIA ANTONIETTA MENCARELLI[1], MARIA CARMELA EPISTOLATO[2], PAOLO TOTI[2], STEFANO LAZZI[2], MIRELLA BRUTTINI[1], SONIA DE FRANCESCO[3], ILARIA LONGO[1], ILARIA MELONI[1], FRANCESCA MARI[1], ANTONIO ACQUAVIVA[4], THEODORA HADJISTILIANOU[3], ALESSANDRA RENIERI[1] & FRANCESCA ARIANI[1]

[1]*Medical Genetics, Department of Molecular Biology, University of Siena, Siena, Italy,* [2]*Department of Human Pathology and Oncology, University of Siena, Siena, Italy,* [3]*Retinoblastoma Referral Center, Department of Ophtalmology, University of Siena, Siena, Italy and* [4]*Department of Pediatrics, Obstetrics and Reproductive Medicine, Italian retinoblastoma registry, University of Siena, Siena, Italy*

Abstract

03/11/09

Sampieri et al 2009.pdf - Adobe Reader

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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 Ariani[1]

[1]Medical Genetics, Department of Molecular Biology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100 Siena, Italy, [2]Department of Human Pathology and Oncology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100, Siena, Italy, [3]Retinoblastoma Referral Center, Department of Ophtalmology, University of Siena, Policlinico Le Scotte, viale Bracci 2, 53100, Siena, Italy, [4]Department 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] 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

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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).

doi: 10.1111/j.1349-7006.2008.01070.x

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

imbalances (M3–Mn) involving specific oncogenes and tumor

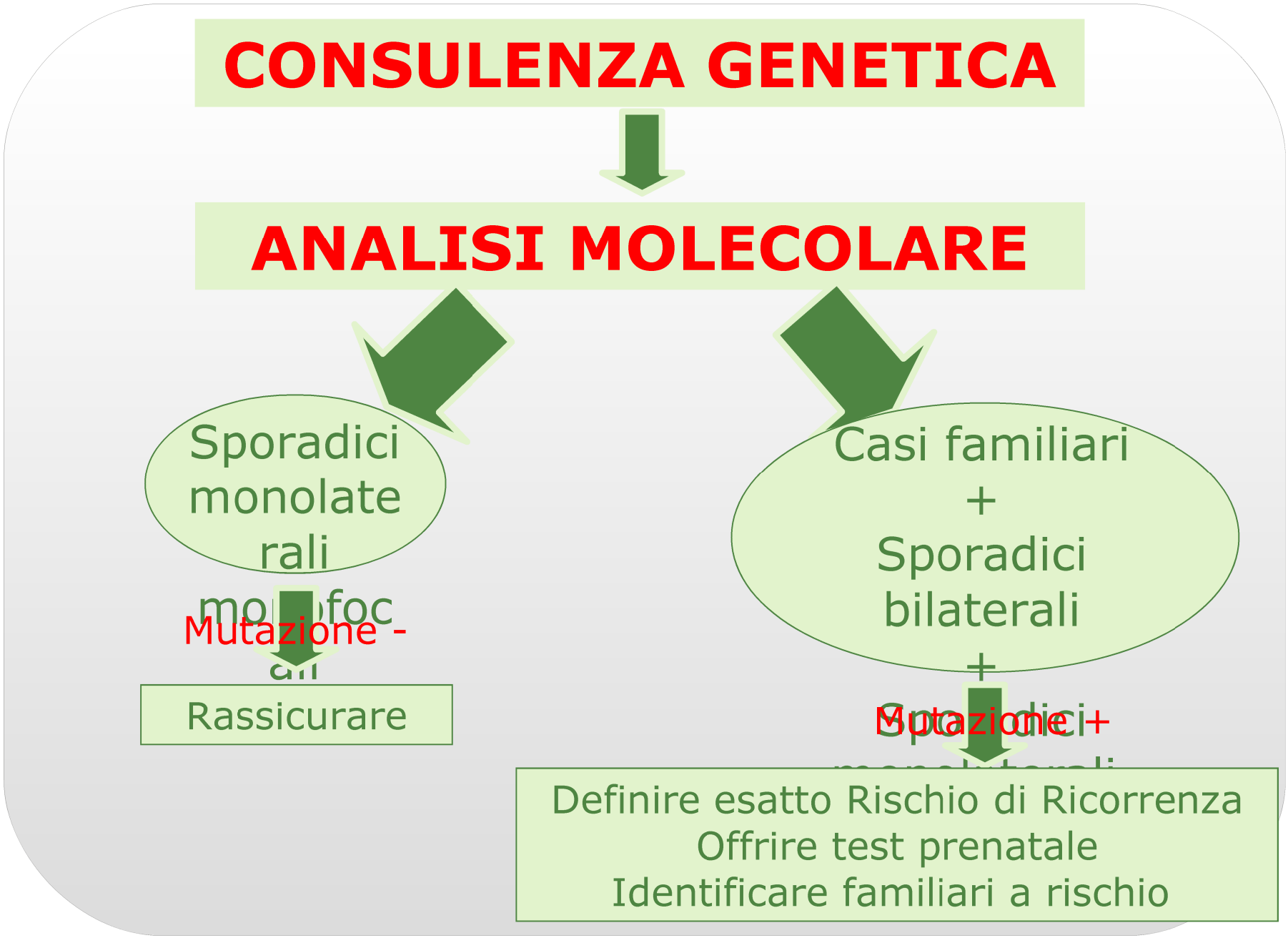
Discussion

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.[1,4] Several studies have suggested that genomic

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).[23,24] 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 overexpres in human carcinomas and certain hematological

domenica 27 settembre 2009


CONSULENZA GENETICA
ANALISI MOLECOLARE
Sporadici monolaterali
Casi familiari + Sporadici bilaterali +
Mutazione -
Mutazione +
Rassicurare
Definire esatto Rischio di Ricorrenza
Offrire test prenatale
Identificare familiari a rischio