cancer is fundamentally a genetic disease II

Dr. Bilal Azab

Vedio: https://youtu.be/tGrkxuDa4aU
Vedio: https://youtu.be/EdQmkXFCjxw

The Two-Hit Theory of Tumor Suppressor Gene Inactivation in Cancer

Selected Tumor Suppressor Genes Involved in Human Neoplasms

proteins encoded by proto-oncogenes promote cancer when activated or overexpressed

variants in TSGs <u>contribute to malignancy</u> by a different mechanism,
the **<u>loss of function</u>** of both alleles of the gene.

The products of many TSGs have now been isolated and characterized

TABLE 7-8 -- Selected Tumor Suppressor Genes Involved in Human Neoplasms

Subcellular Locations	Gene	Function	Tumors Associated with Somatic Mutations	Tumors Assocated with Inherited Mutations
Cell surface	TGF-β receptor	Growth inhibition	Carcinomas of colon	Unknown
	E-cadherin	Cell adhesion	Carcinoma of stomach	Familial gastric cancer
Inner aspect of plasma membrane	*NF1*	Inhibition of RAS signal transduction and of p21 cell cycle inhibitor	Neuroblastomas	Neurofibromatosis type 1 and sarcomas
Cytoskeleton	*NF2*	Cytoskeletal stability	Schwannomas and meningiomas	Neurofibromastosis type 2, acoustic schwannomas, and meningiomas
Cytosol	*APC*/β-catenin	Inhibition of signal transduction	Carcinomas of stomach, colon, pancreas; melanoma	Familial adenomatous polyposis coli/colon cancer
	PTEN	PI3 kinase signal transduction	Endometrial and prostate cancers	Cowden syndrome
	SMAD2 and *SMAD4*	TGF-β signal transduction	Colon, pancreas tumors	Unknown
Nucleus	*RB1*	Regulation of cell cycle	Retinoblastoma; osteosarcoma carcinomas of breast, colon, lung	Retinoblastomas, osteosarcoma
	p53	Cell cycle arrest and apoptosis in response to DNA damage	Most human cancers	Li-Fraumeni syndrome; multiple carcinomas and sarcomas
	WT1	Nuclear transcription	Wilms' tumor	Wilms' tumor
	P16/INK4a	Regulation of cell cycle by inhibition of cyclindependent kinases	Pancreatic, breast, and esophageal cancers	Malignant melanoma
	BRCA1 and *BRCA2*	DNA repair	Unknown	Carcinomas of female breast and ovary; carcinomas of male breast

PI3 kinase, phosphatidylinositol 3-kinase.

NON-HEREDITARY CANCER *By Chance – Most Common*

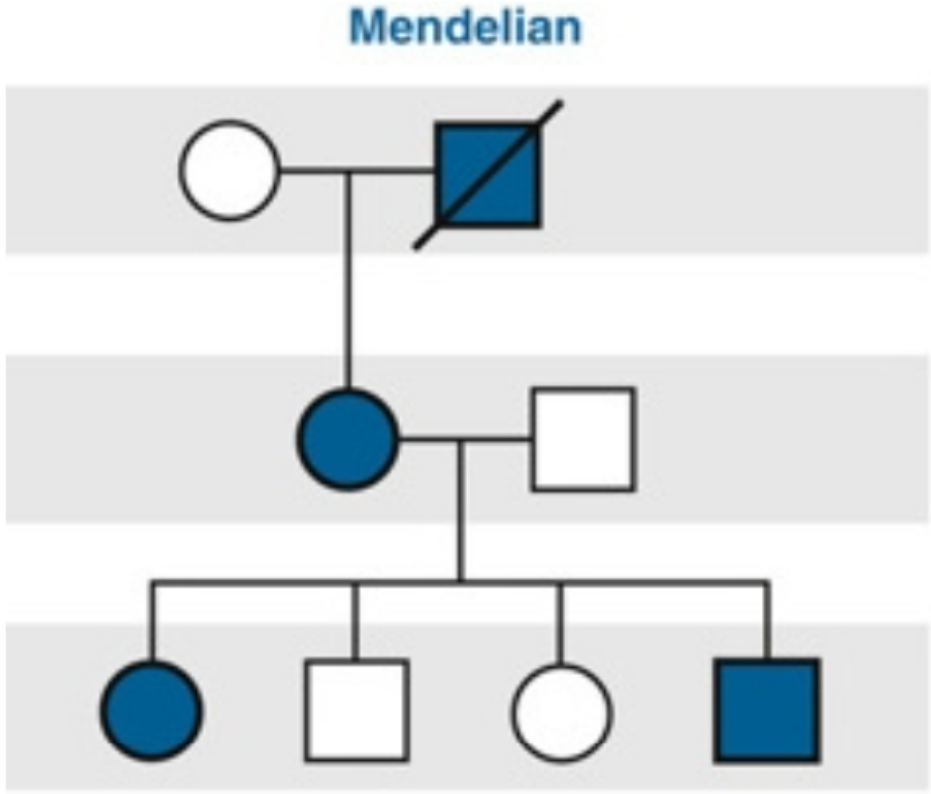
HEREDITARY CANCER *Passed Through Family – Rare*

Retinoblastoma familial

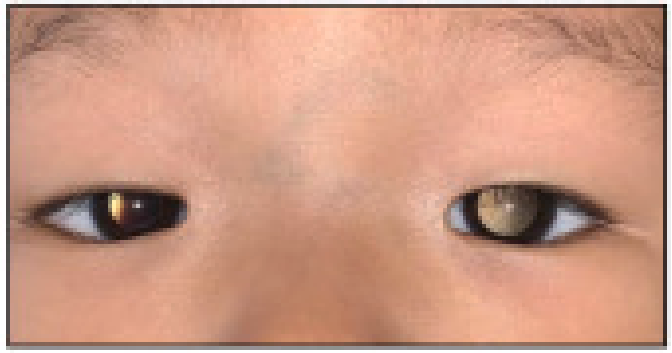
It was suggested that the hereditary form of the childhood cancer **retinoblastoma** might be initiated when a cell in a person heterozygous for a germline mutation in the RB1 TSG

undergoes a second, somatic event that inactivates the other retinoblastoma gene allele.

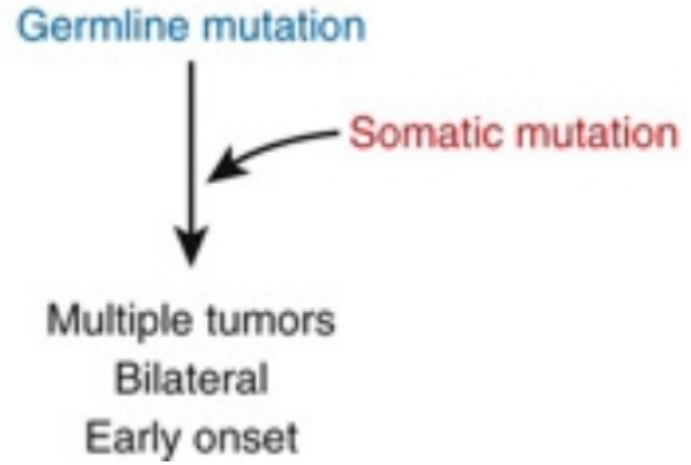
As a consequence of this second somatic event, the cell loses function of both alleles, giving rise to a tumor.



Bilateral

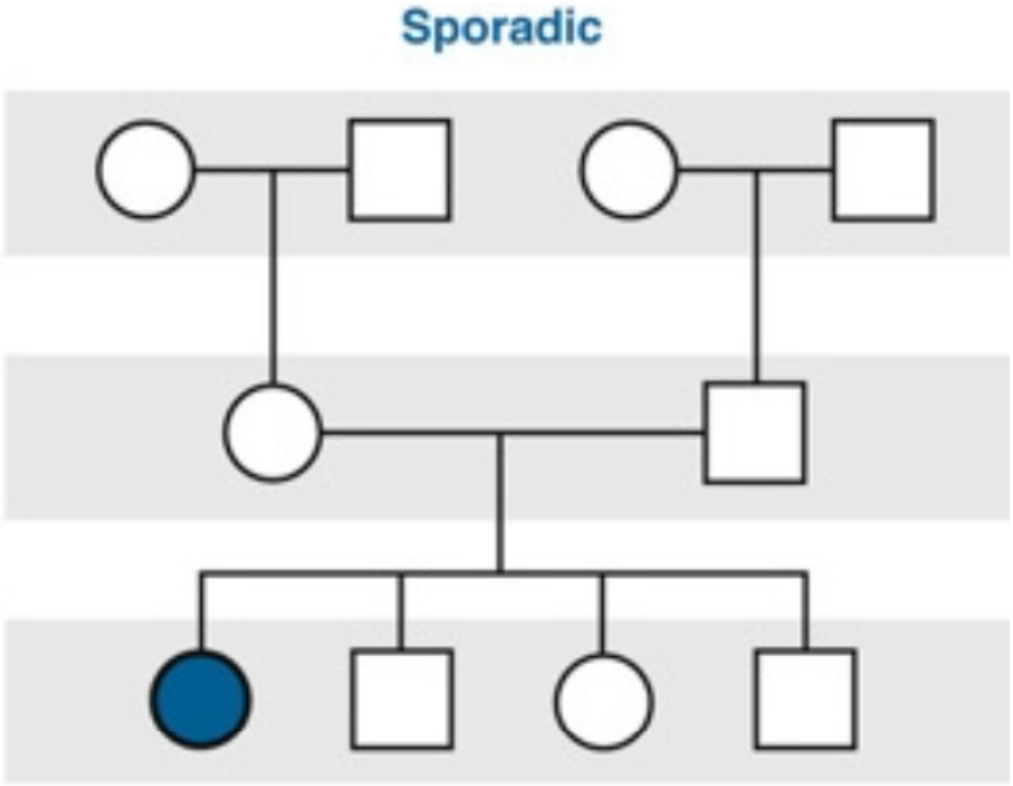


36/39 (92.3%)
Germline *RB1* mutated



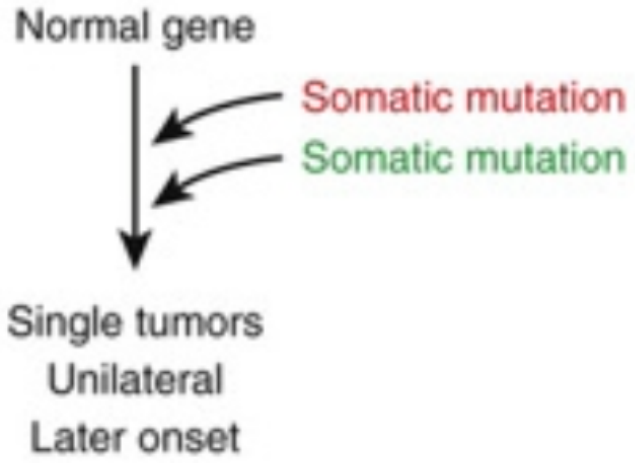
Retinoblastoma sporadic

In the sporadic form of retinoblastoma, both alleles are also inactivated, but in this case, the inactivation results from two somatic events occurring in the same cell.



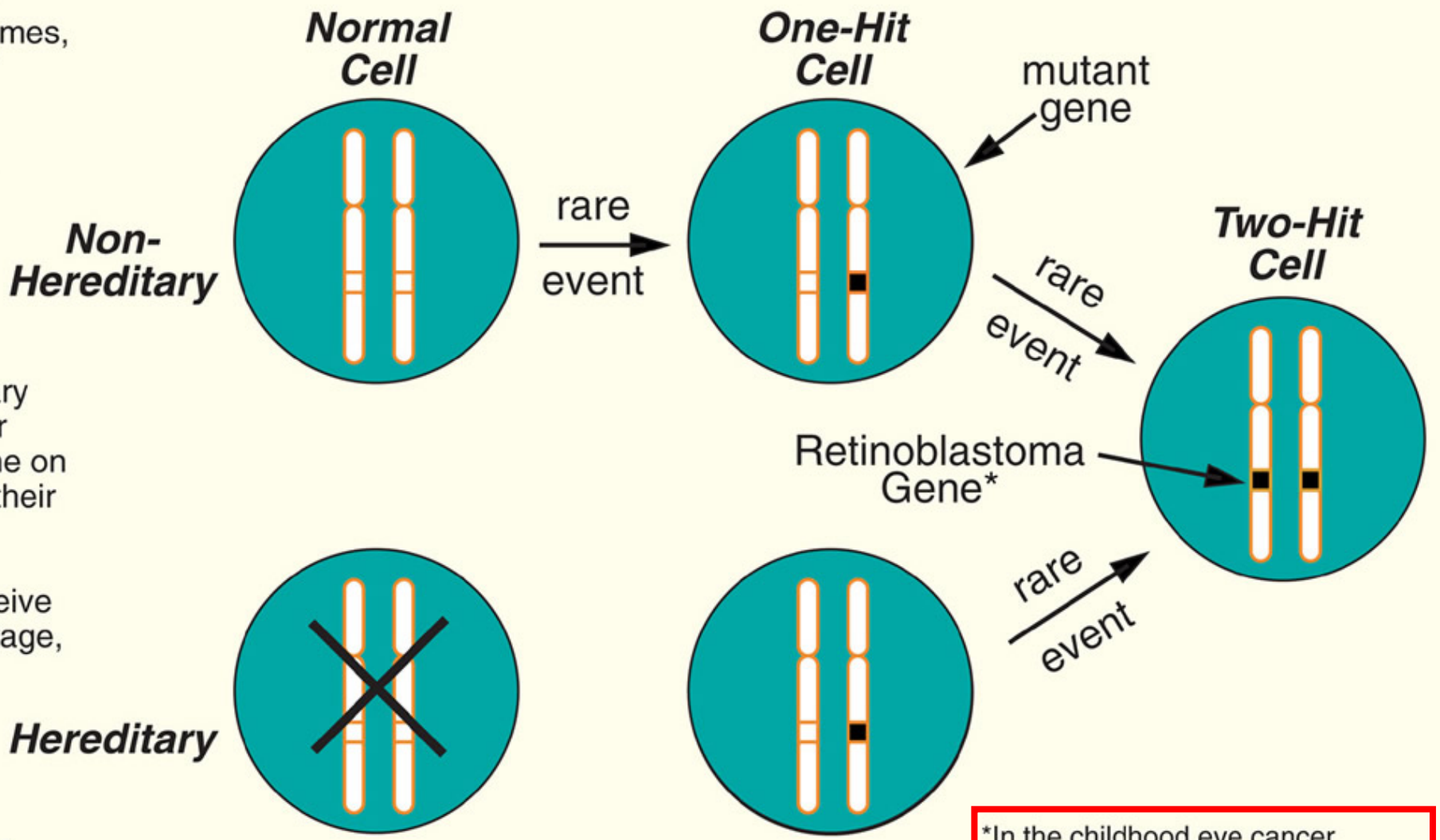
Unilateral

18/106 (17.0%)
Germline *RB1* mutated



Two-Hit Theory of Cancer Causation

Normal cells have two undamaged chromosomes, one inherited from our mother and one from our father. These chromosomes contain thousands of genes.



People with a hereditary susceptibility to cancer inherit a damaged gene on one chromosome, so their first "hit," or mutation, occurs at conception. Other people may receive the first hit at a later stage, before or after birth.

In either case, if a cell receives damage to the same gene on the second chromosome, that cell can produce a cancer.

*In the childhood eye cancer retinoblastioma, people who inherit the first hit are 100,000 times more likely to develop a second, cancer-causing mutation.

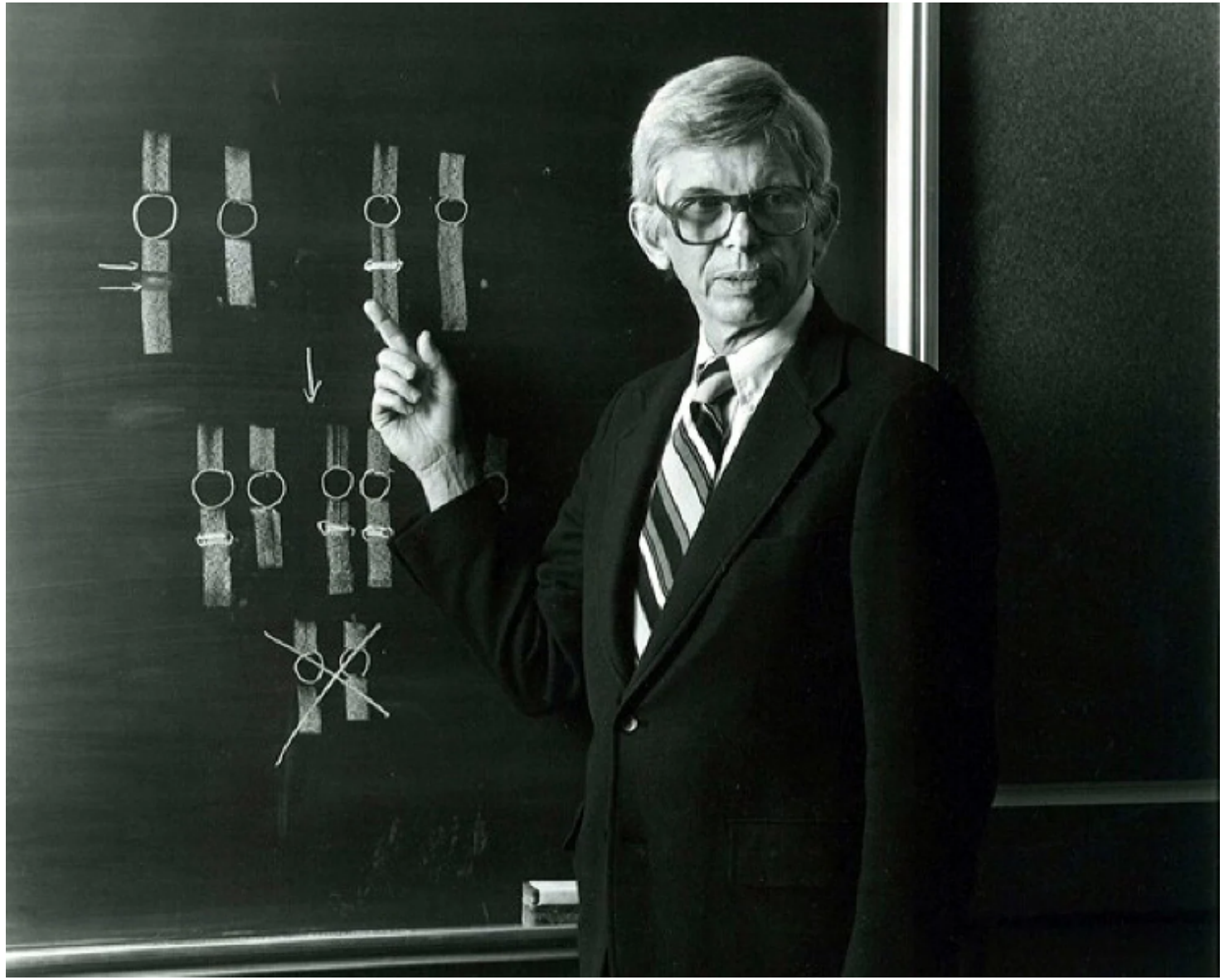
Most Tumor Suppressor Genes Require Both Alleles To Be Inactivated To Cause A Phenotypic Change

https://www.youtube.com/watch?v=h_sfOYFJTfU&t=51s

In 1971
Knudson performed a statistical analysis on cases of retinoblastoma.

He noted that inherited retinoblastoma occurs at a younger age than the sporadic disease.

In addition, the children with inherited retinoblastoma often developed the tumor in both eyes, suggesting an underlying predisposition.


Alfred Knudson

most tumor suppressor genes require both alleles to be inactivated to cause a phenotypic change

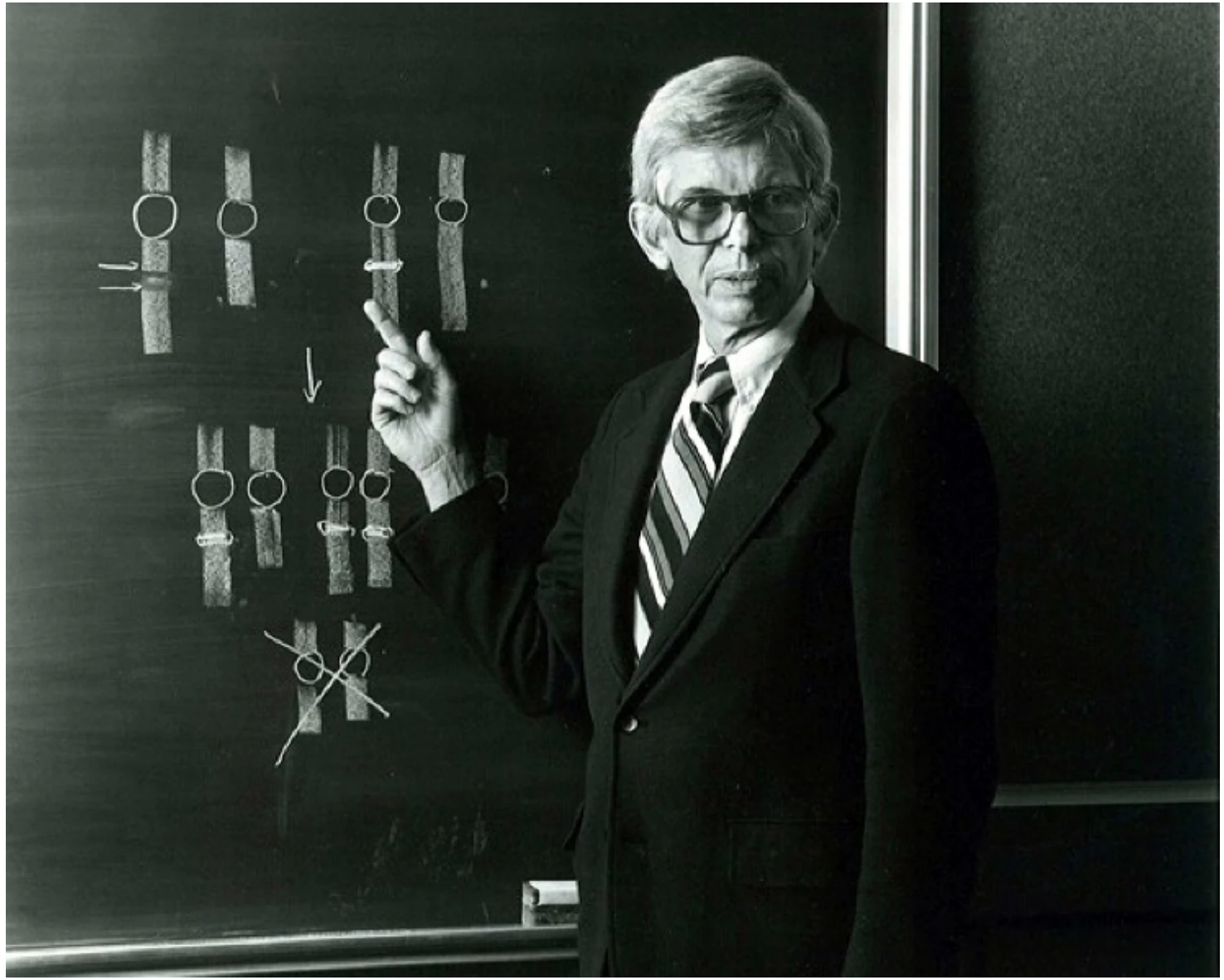
https://www.youtube.com/watch?v=h_sfOYFJTfU&t=51s

Alfred Knudson

Knudson suggested that two "hits" to DNA were necessary to cause the cancer.

In the children with inherited retinoblastoma, the first mutation in what later came to be identified as the RB1 gene, was inherited, the second one acquired.

In non-inherited retinoblastoma, instead two hits, had to take place before a tumor could develop, explaining the later onset.



In 1986, RB gene was the first TSG to be identified in medical history

The two-hit model is now widely accepted as the explanation for many hereditary cancers in addition to retinoblastoma, including

familial polyposis coli

familial breast cancer

neurofibromatosis type 1 (NF1)

Lynch syndrome

Li-Fraumeni

https://www.youtube.com/watch?v=PaEeKZPFuZo

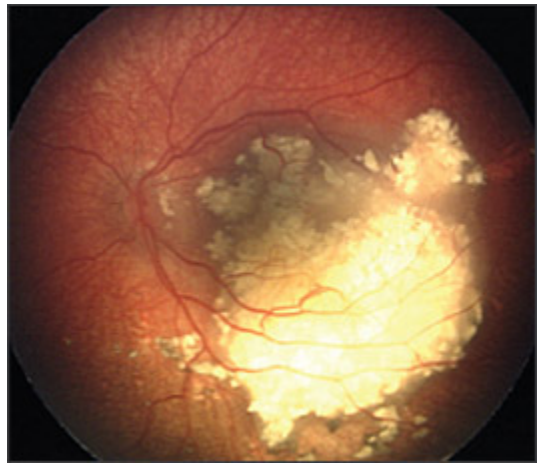
Tumor Suppressor Genes in Autosomal Dominant Cancer Syndromes

Retinoblastoma

The prototype of diseases caused by variant in a TSG

Rare malignant tumor of the retina in infants, with an incidence of approximately 1 in 20,000 births

Diagnosis of a retinoblastoma must usually be followed by removal of the affected eye, although smaller tumors, diagnosed at an early stage, can be treated by local therapy so that vision can be preserved



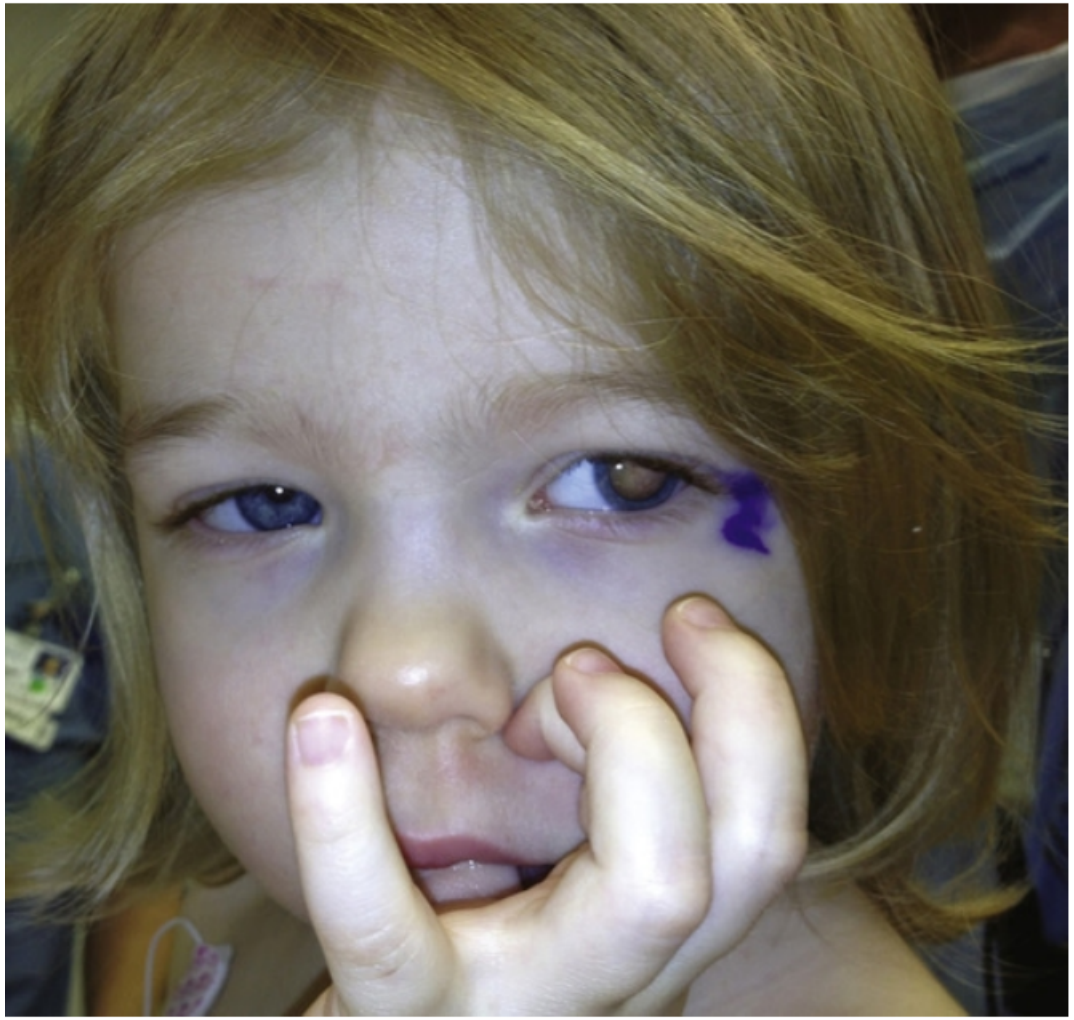


FIGURE 15-7 Retinoblastoma in a young girl, showing as a white reflex in the affected left eye when light reflects directly off the tumor surface. *See Sources & Acknowledgments.*

Approximately 40% of cases of retinoblastoma are of the heritable form, in which the child inherits one mutant allele at the retinoblastoma locus (RB1) through the germline from either a heterozygous parent
Or
more **rarely**, from a parent with **germline mosaicism** for an RB1 variant

In these children, retinal cells, which like all the other cells of the body are already carrying one inherited defective RB1 allele
suffer a somatic mutation or other alteration in the remaining normal allele, leading to loss of both copies of the RB1 gene and initiating development of a tumor in each of those cells

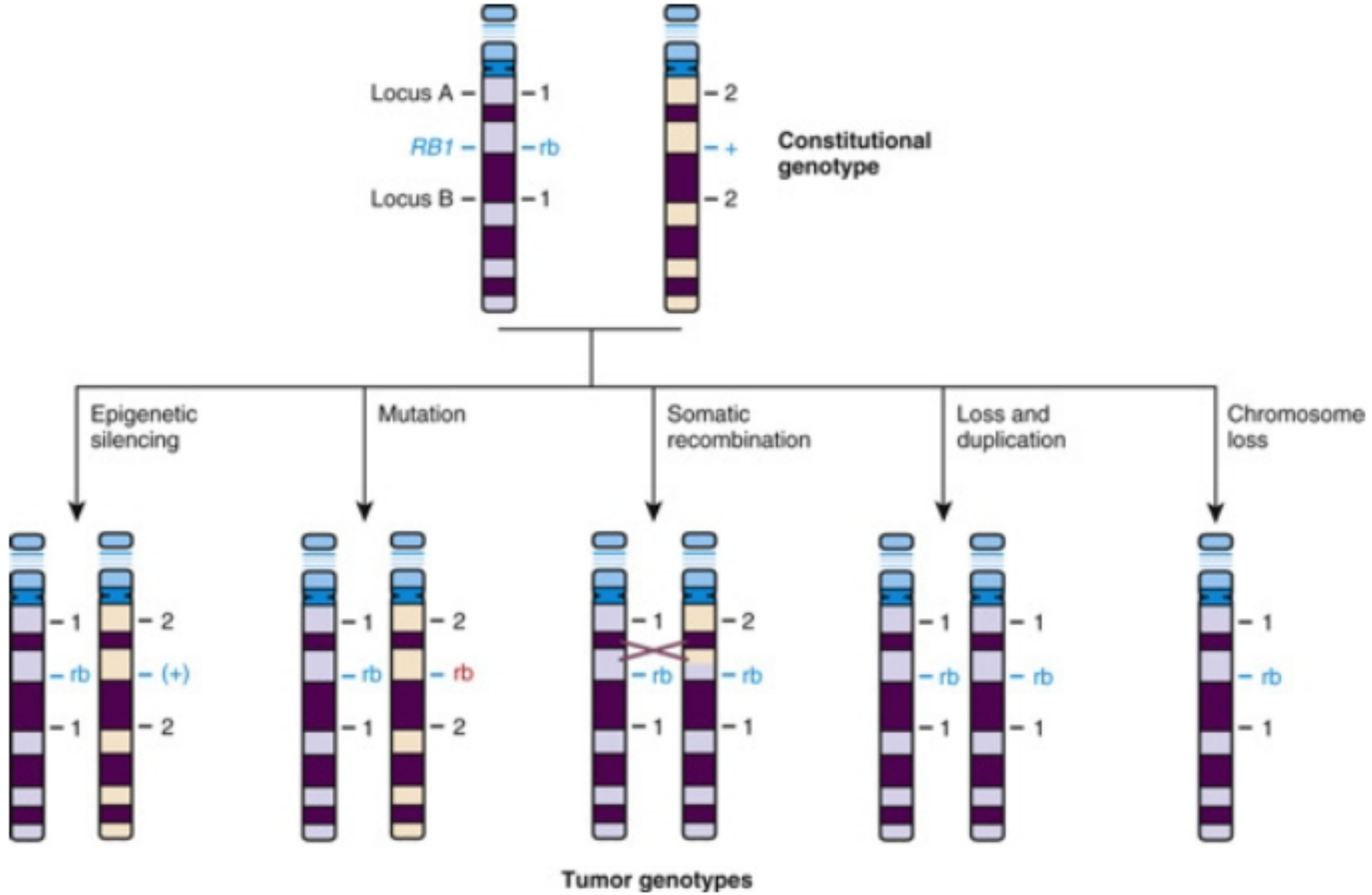
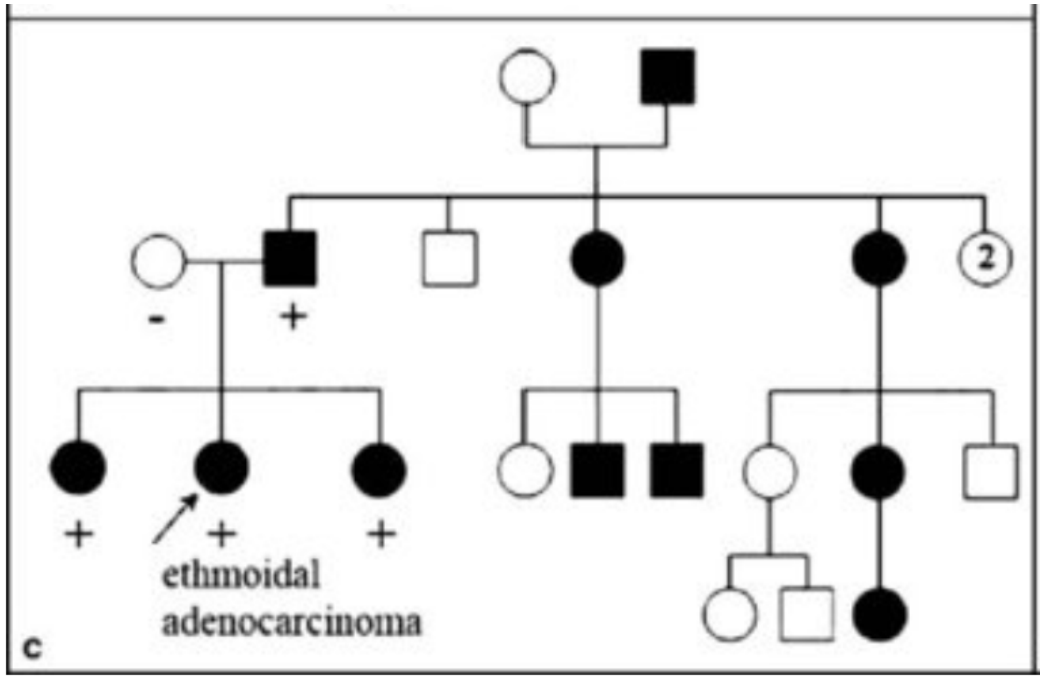


FIGURE 15-8 **Chromosomal mechanisms that could lead to loss of heterozygosity for DNA markers at or near a tumor suppressor gene in an individual heterozygous for an inherited germline mutation. The figure depicts the events that constitute the "second hit" that leads to retinoblastoma with loss of heterozygosity (LOH). Local events such as mutation, gene conversion, or transcriptional silencing by promoter methylation, however, could cause loss of function of both *RB1* genes without producing LOH. +, normal allele, rb, the mutant allele.**

The disorder appears to be inherited as a dominant trait

because the large number of primordial retinoblasts and their rapid rate of proliferation make it very likely that a somatic mutation will occur as a second hit in one or more of the more than10^6 retinoblasts already carrying an inherited RB1 mutation.



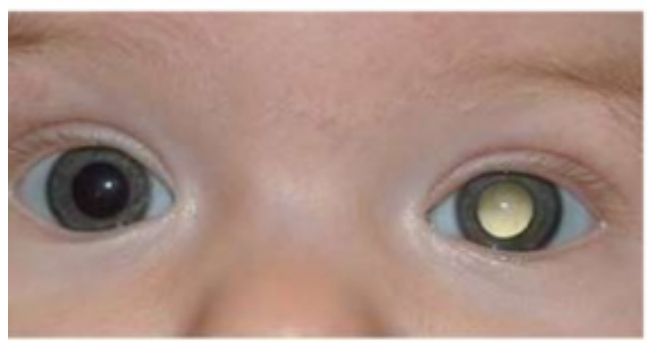


Fig.3 white color in the center circle of the eye

Because the chance of a second hit is so great, it occurs frequently in more than one cell

Thus heterozygotes for the disorder often have tumors arising at multiple sites, such as multifocal tumors in one eye, in both eyes (bilateral retinoblastoma), as well as in the pineal gland (referred to as “trilateral” retinoblastoma).

The occurrence of a second hit is a matter of chance and does not occur 100% of the time; the penetrance of retinoblastoma therefore, although greater than 90%, is not complete.

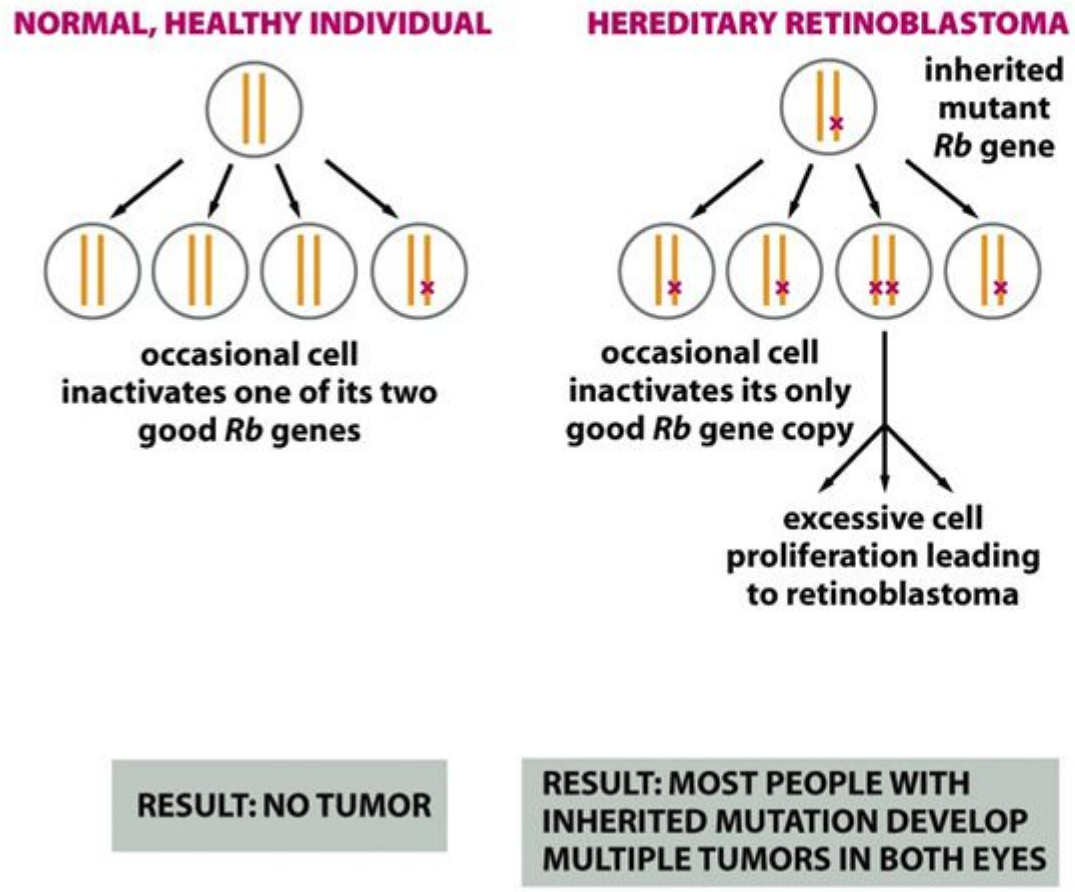


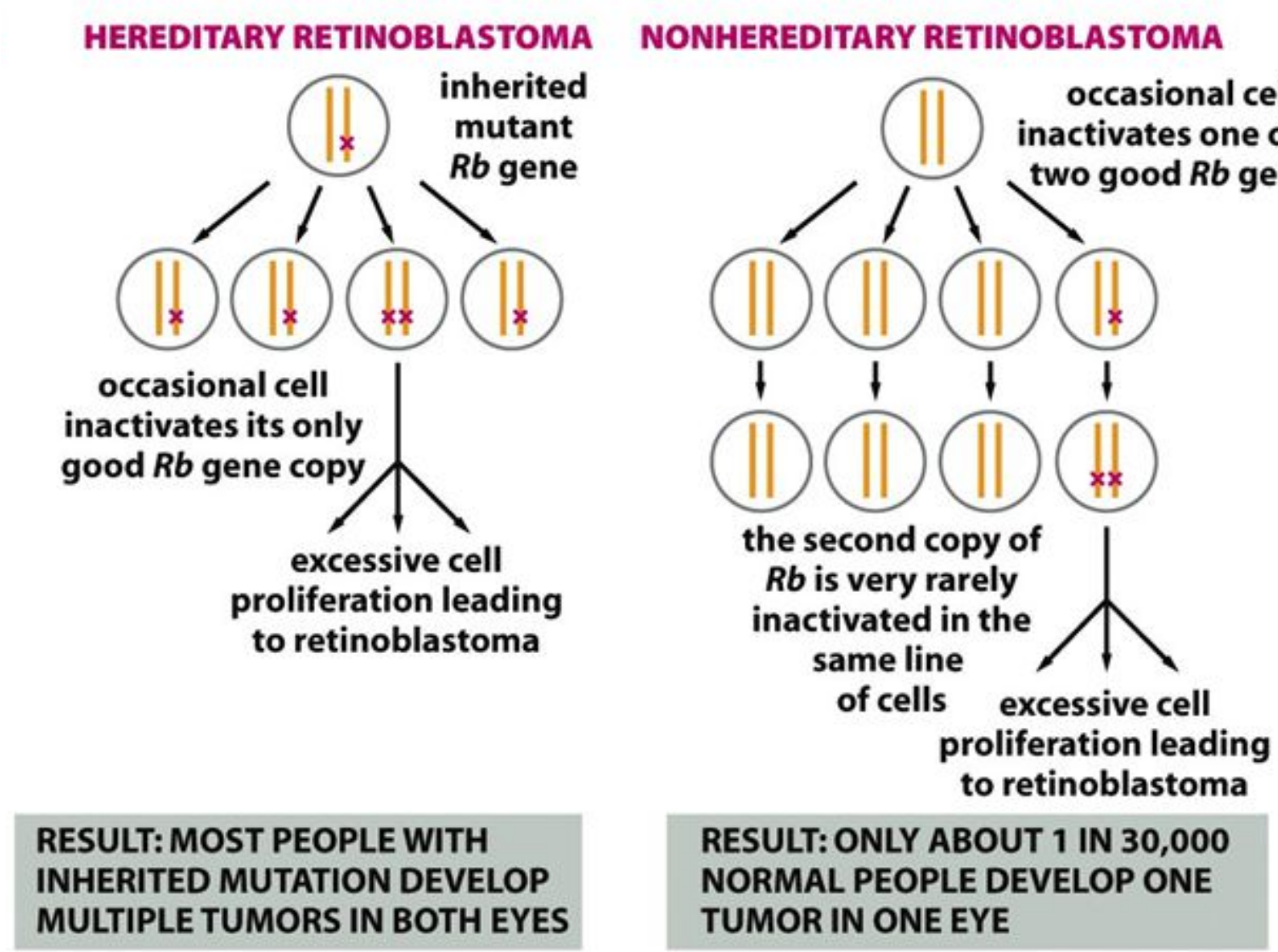
Figure 20-30 *Molecular Biology of the Cell* (© Garland Science 2008)

The other 60% of cases of retinoblastoma are nonhereditary

Both RB1 alleles in a single retinal cell have been inactivated independently by chance

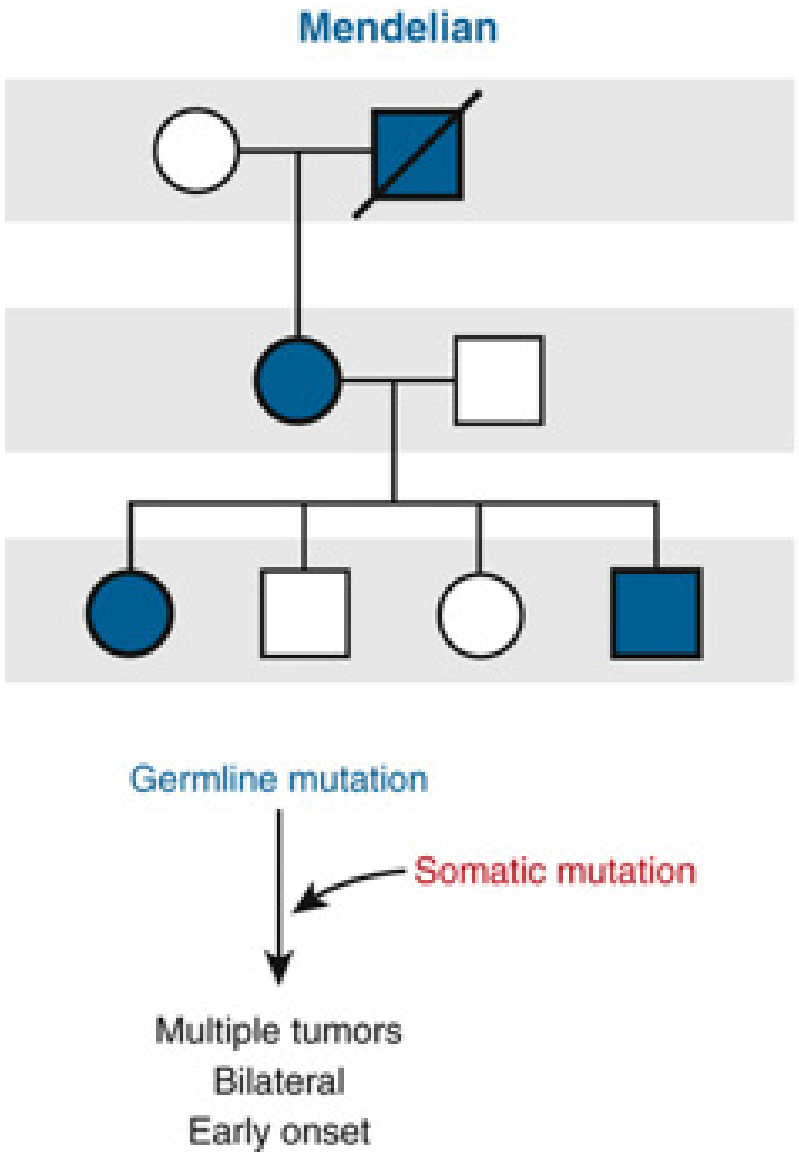
Because two hits in the same cell is a statistically rare event, there is usually only a single clonal tumor, and the retinoblastoma is found at one location (unifocal) in one eye only.

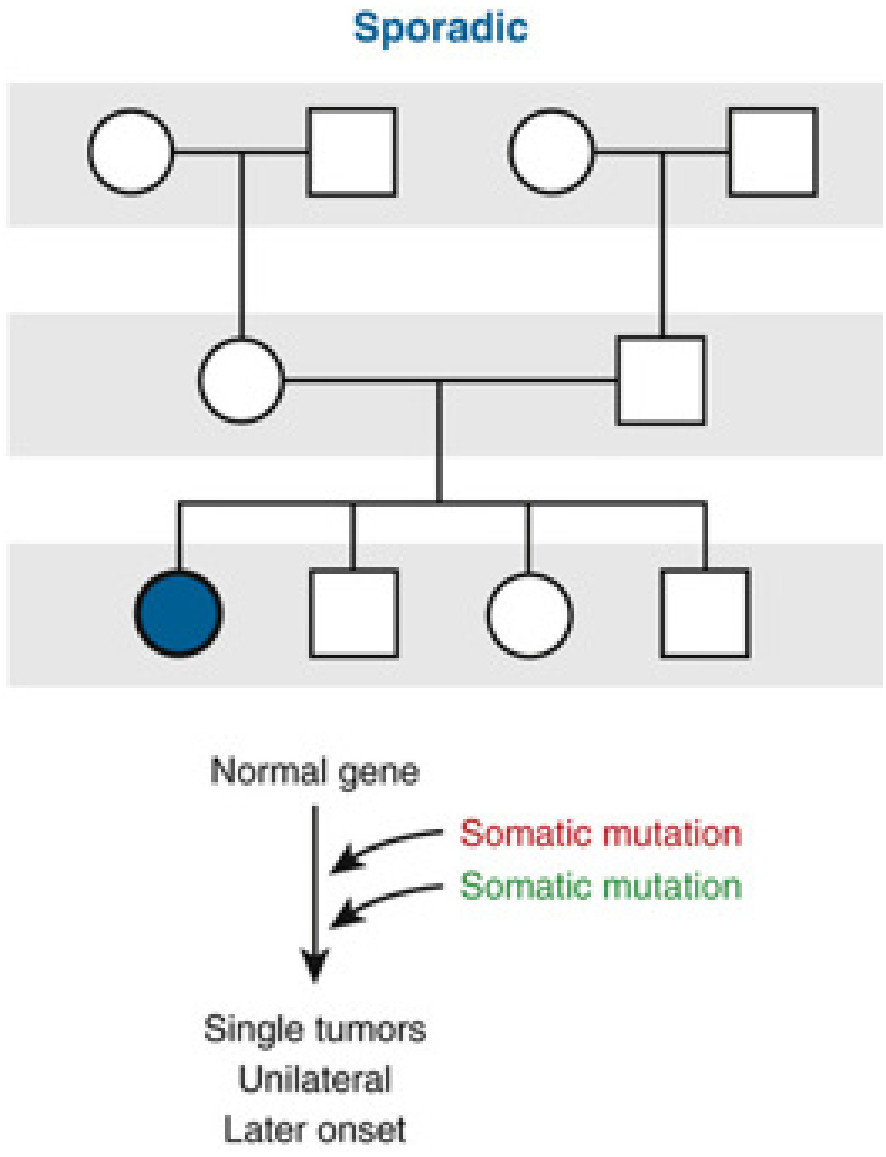
Unilateral tumor is no guarantee that the child does not have the heritable form of retinoblastoma, however, because 15% of patients with the heritable type develop a tumor in only one eye.



Another difference between hereditary and sporadic tumors is that the average **age at onset** of the sporadic form is in early <u>childhood</u>, later than in <u>infants</u> with the heritable form

reflecting the longer time needed on average for two mutations, rather than one, to occur.





In a small percentage of patients with retinoblastoma, the variant responsible is a cytogenetically detectable deletion or translocation of the portion of chromosome 13 that contains the RB1 gene.

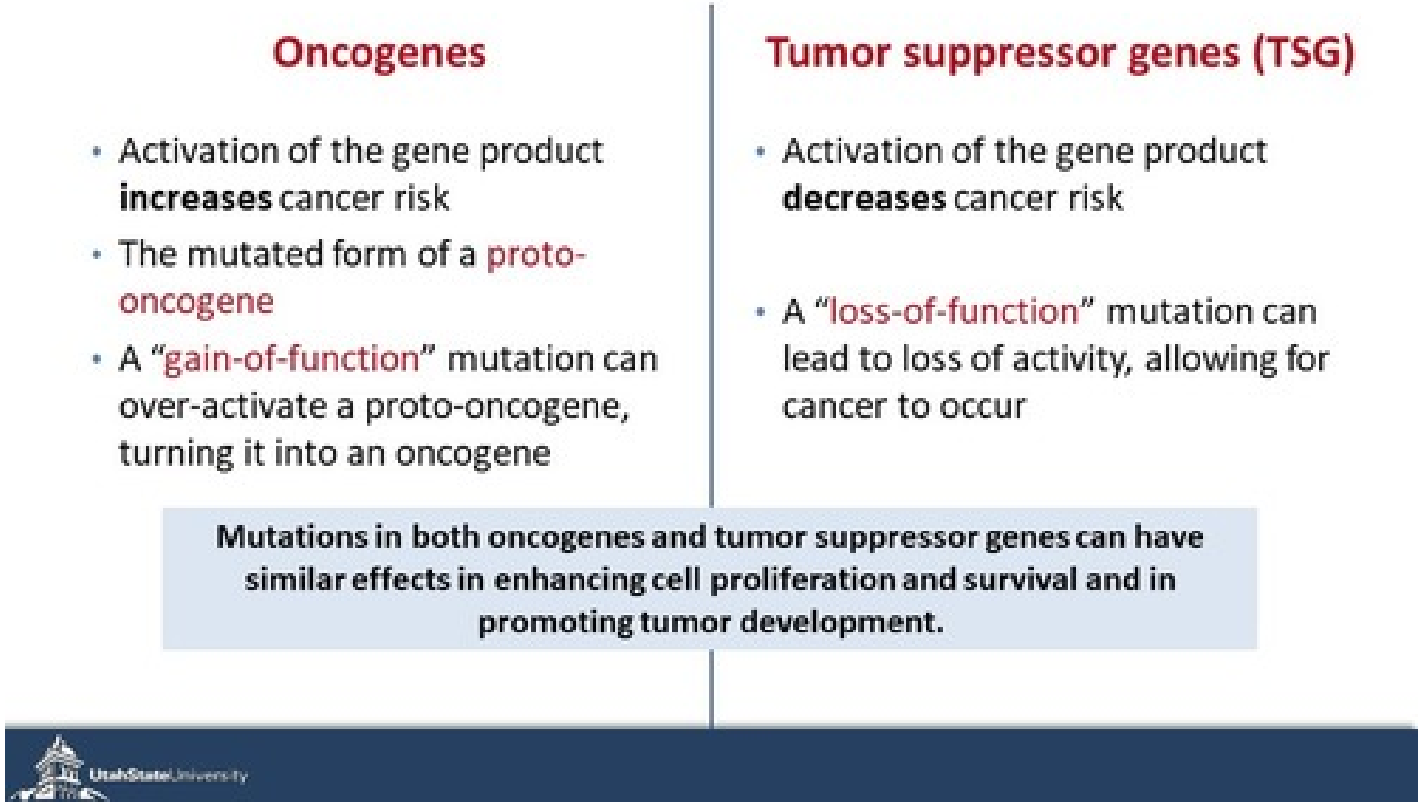
Such chromosomal changes, if they also disrupt genes adjacent to RB1, may lead to **dysmorphic features in addition** to retinoblastoma.

Nature of the Second Hit

Typically, for retinoblastoma as well as for the other hereditary cancer syndromes, the first hit is an inherited mutation, that is, a change in the DNA sequence.

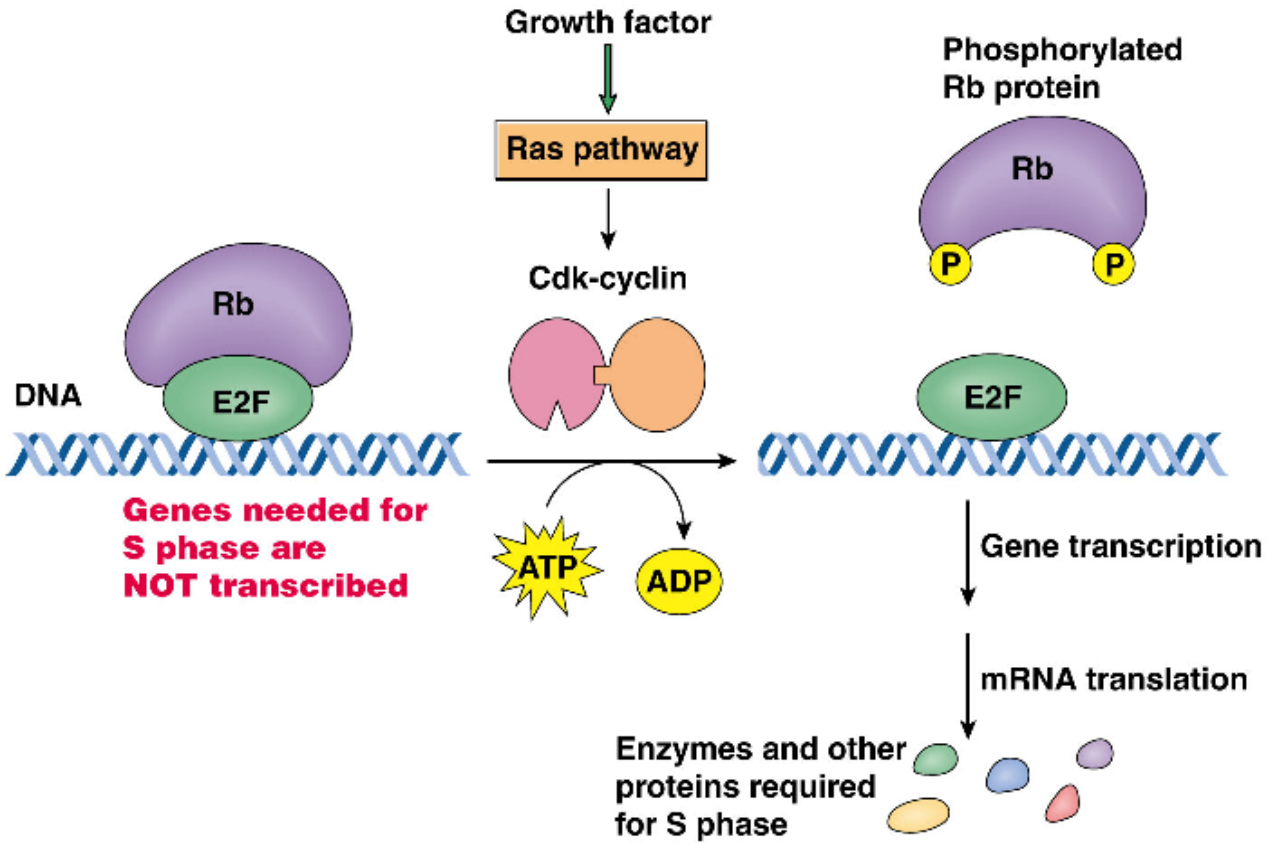
The second hit, however, can be caused by a variety of genetic, epigenetic, or genomic mechanisms

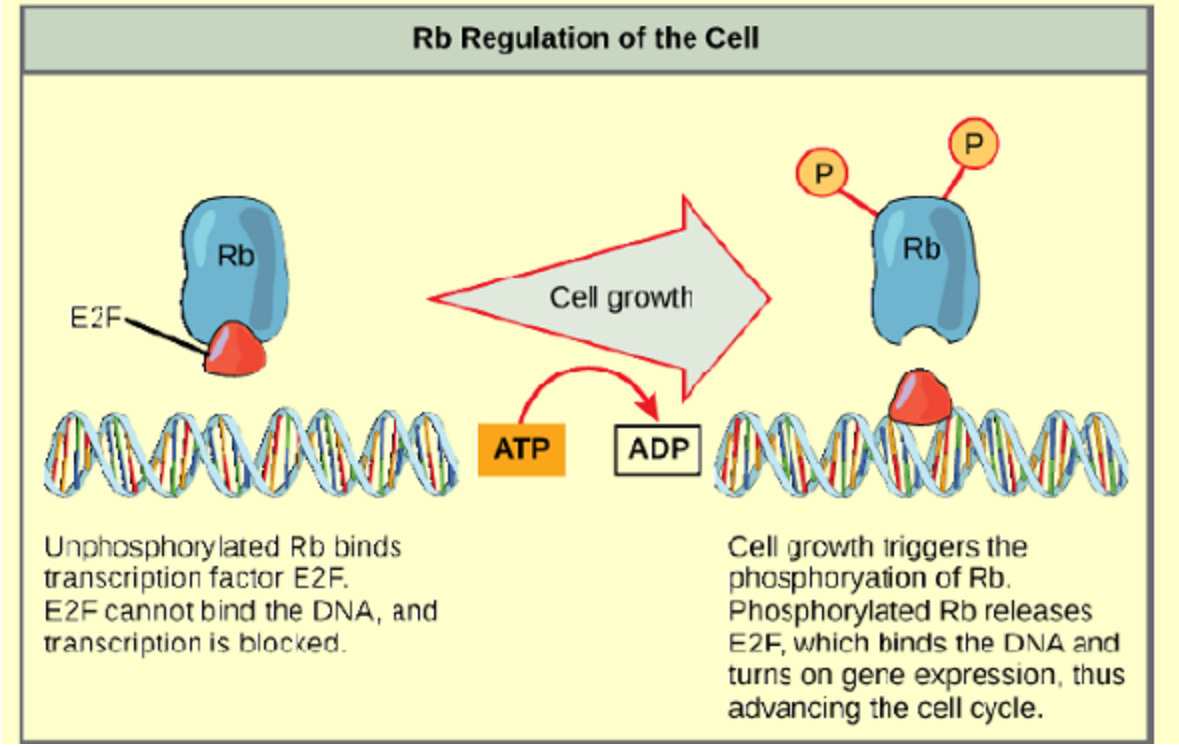
Although a number of mechanisms have been documented, the common theme is **loss of function** of RB1



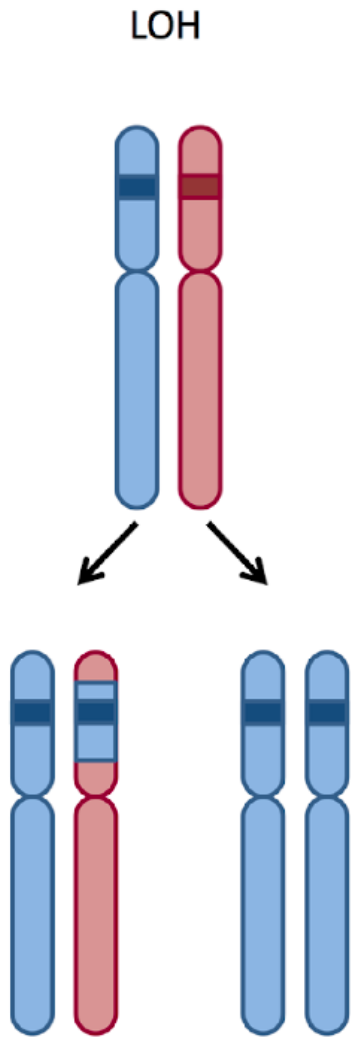
The RB1 gene product, p110 Rb1, is a phosphoprotein that normally regulates entry of the cell into the S phase of the cell cycle.

Thus loss of the RB1 gene and/or absence of the normal RB1 gene product deprives cells of an important checkpoint and allows uncontrolled proliferation.





Loss of Heterozygosity



In addition to mutations and epigenetic silencing

a novel genomic mechanism was uncovered when geneticists made an unusual but highly significant discovery when they
compared DNA polymorphisms at the RB1 locus in DNA from normal cells to those in the retinoblastoma tumor from the same patient.

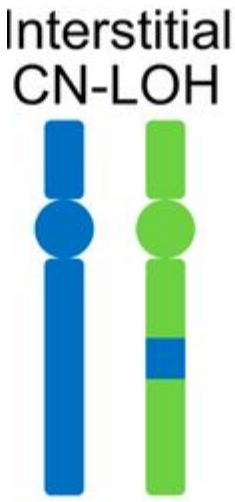
Individuals with retinoblastoma who were heterozygous at polymorphic loci flanking the RB1 locus in **normal tissues** had tumors that contained **alleles from only one of their two chromosome** 13 homologues, revealing a loss of heterozygosity (LOH) in tumor DNA in and around the RB1 locus.

Loss of Heterozygosity

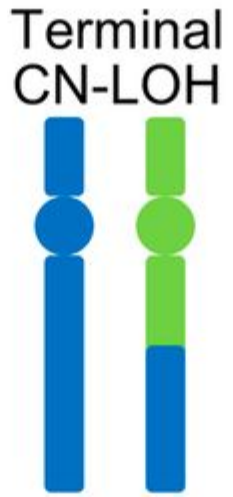
Furthermore, in **familial** cases, the retained chromosome 13 markers were the ones inherited from the affected parent, that is, the chromosome with the abnormal RB1 allele.

Thus, in these cases, **LOH represents the second hit of the remaining allele**.

LOH may occur by interstitial deletion, but there are other mechanisms as well, such as mitotic recombination or monosomy 13 due to nondisjunction



- Copy neutral loss of heterozygosity (CN-LOH) is the most common class of structural mutation.
- Interstitial events are more abundant than Terminal CN-LOH, but affect smaller genomic regions.



- CN-LOH mutation mechanisms are universal to diploid genomes, and play a key role in humans, both in cancer tumor suppressor loss and somatic mosaicism.