Genetics and Cancer

A Statistical Study of Retinoblastoma

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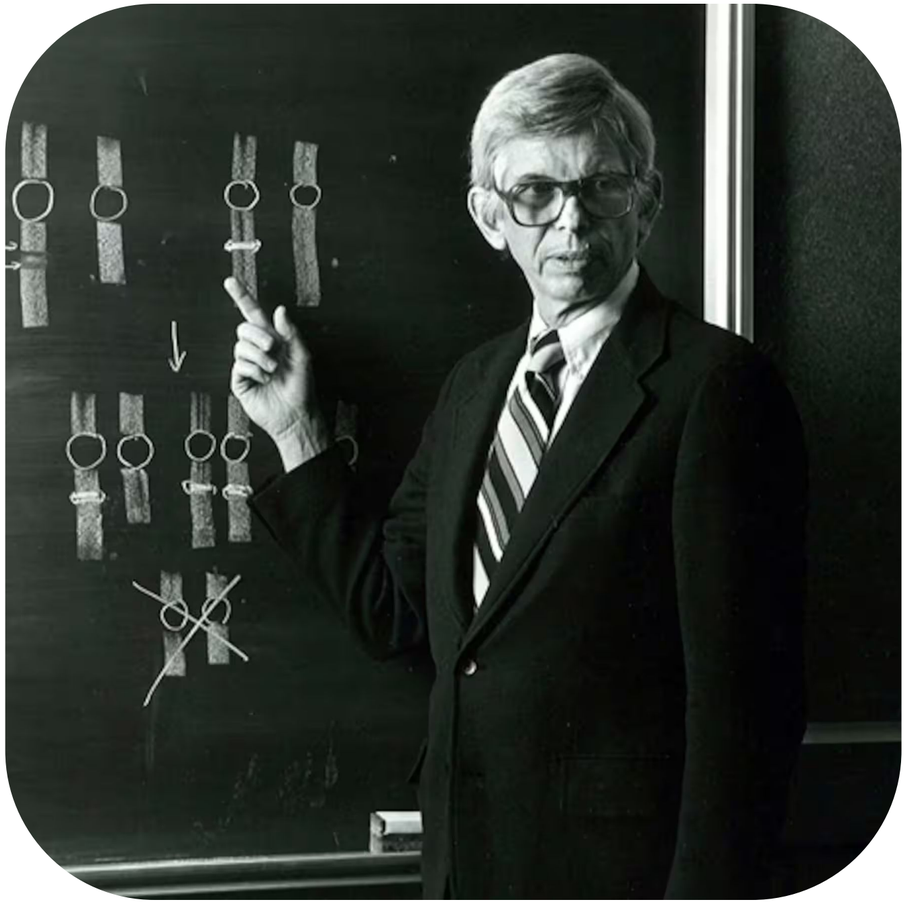
Background

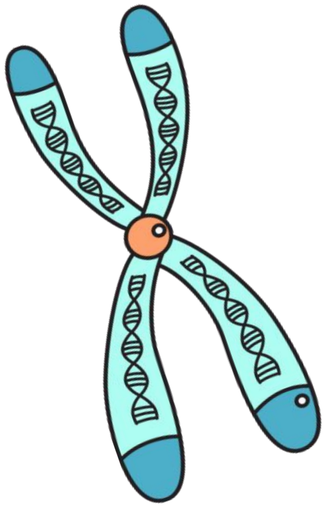
- **Alfred G. Knudson, Jr.** (1922-2016)
- American physician and geneticist
    - “Mendel of Cancer Genetics”
- M.D., Ph.D.
- Received many awards (1988-2005)
- Pediatrics → **Oncology**
- Studied **retinoblastoma**

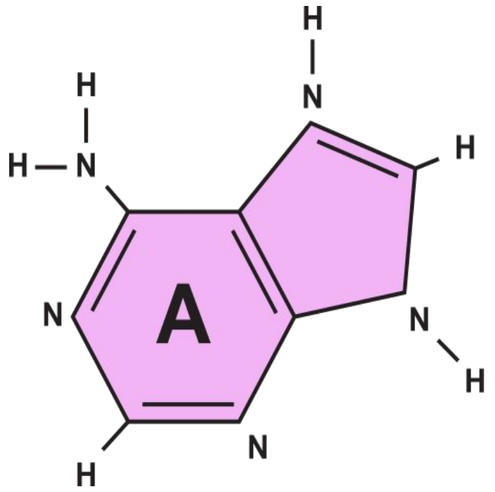


Alfred G. Knudson Jr. presenting genetic concepts using chalkboard illustrations (The Washington Post, 2016)

Genetics in the 1970's

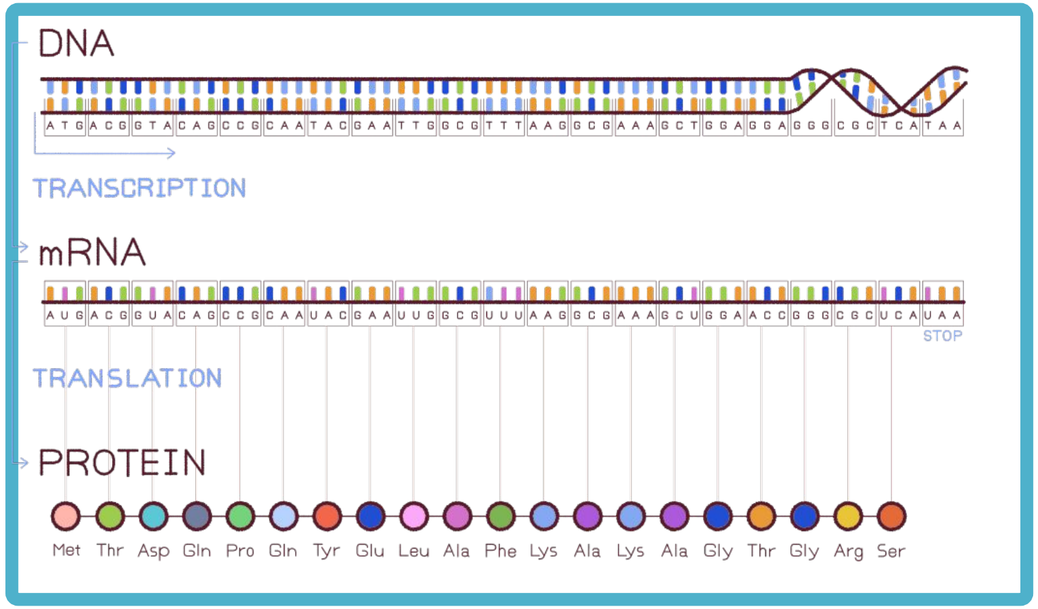
- **Descriptive** → **Molecular** and **Statistical**
  - Phenotypes and abnormalities to recombination and restriction enzymes (National Human Genome Research Institute)
- People wondered *how many* events are necessary to make cancer. I wanted to know the *least number* that it could be" (American Association for Cancer Research, 2013)





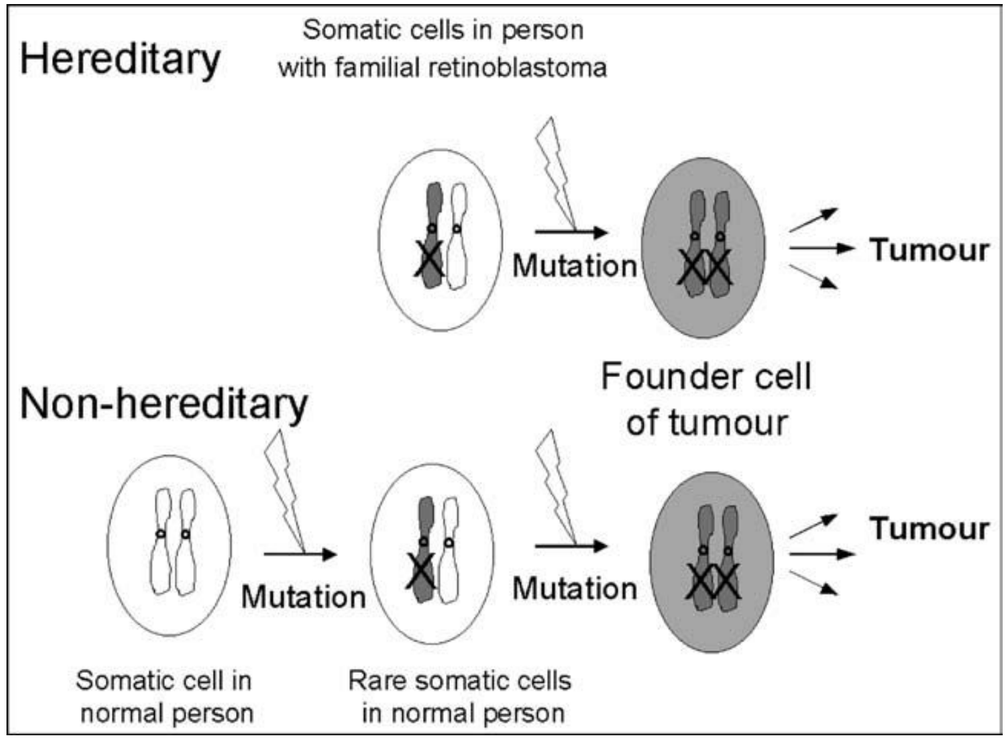
Genetics in the 1970's Continued

- DNA = Genetic material of inheritance ✔
- Proteins encoded by **transcription** and **translation** ✔
- Mutations induced by environment ✔
- **Cancer** showed familial patterns ✔
- **Germline** and **somatic** mutations **?**
- Cell cycle control and **DNA repair ?**
- Existence and function of **tumor suppressor** genes **?**



Knudson's Hypothesis

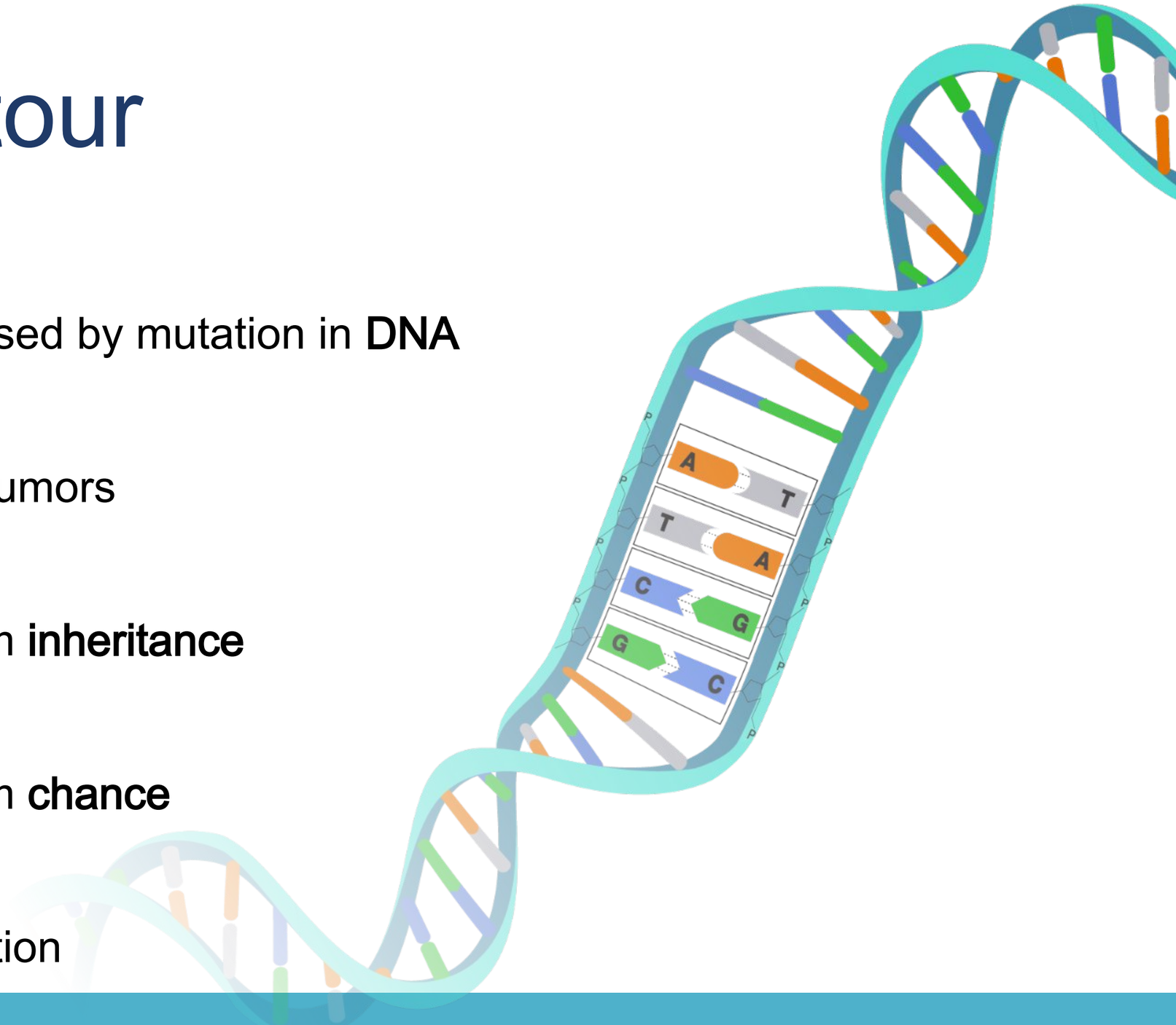
- Two-Hit Hypothesis (1971)
  - Two genetic "***hits***" required
  - One **inherited** or **spontaneous**
  - One **somatic** mutation
- **Hereditary cancer** = one inherited & one spontaneous somatic "*hits*"
- **Sporadic cancer** = two independent somatic "*hits*"



Knudson's "Two-Hit" Hypothesis: tumour formation in both hereditary and non-hereditary retinoblastomas (Modjtahedi, 2007)

Definition Detour

- **Cancer**
  - Genetic disease caused by mutation in **DNA**
- **Retinoblastoma**
  - Pediatric malignant tumors
- **Hereditary Cancer**
  - Cancer resulting from **inheritance**
- **Sporadic Cancer**
  - Cancer resulting from **chance**
- “***Hit***”
  - An **inactivation** mutation



Definition Detour Continued

- **Somatic**
  - Body cells
- **Germline**
  - Reproductive cells
- **Unilateral**
  - Affecting *one* allele
- **Bilateral**
  - Affecting *both* alleles
- **Poisson Distribution**
  - Probability of *rare events* occurring over time

Knudson’s Hypothesis Continued

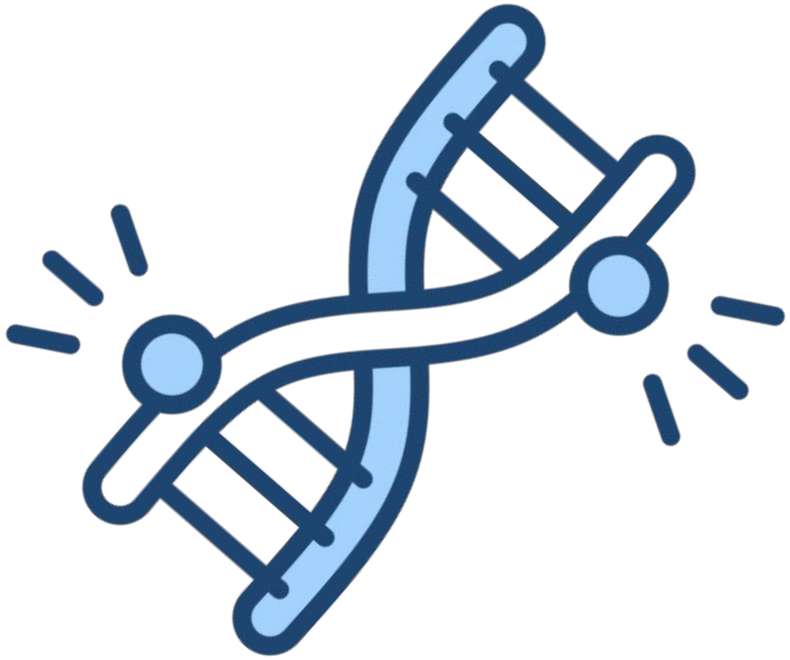
- **Retinoblastoma**: loss of tumor suppressor gene (**RB1**) function
- Two mutational “***hits***” → ***both*** alleles inactivated
  - **Hereditary (familial) *vs* nonhereditary (sporadic)**
- Tumor formation only *after* both alleles nonfunctional
- Cellular mechanism: "*recessive*" loss of function
- Familial pattern: "*dominant*" predisposition

The First Hit

- Inactivates one allele of retinoblastoma susceptibility gene
  - **Hereditary** (familial)
    - First hit inherited (germline)
    - Carried by *all* retinal precursor cells
  - **Nonhereditary** (sporadic)
    - Arises in *single* retinal cell
- One functional allele remains
- Cell phenotype normal ("no cancer")
- ***No tumor*** after first hit

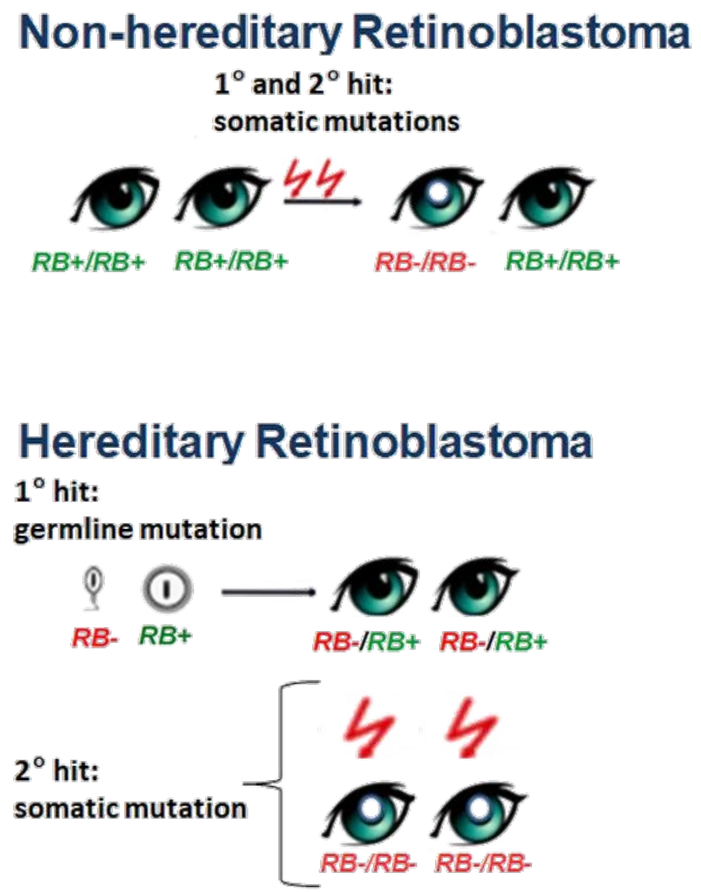
The Second Hit

- **Somatic mutation** of other allele
- Loss of *heterozygosity*
- *Both* alleles non-functional
- Growth suppression *lost*
- Clonal expansion
- Tumor initiation
- Each tumor = **independent** event



Tumor Multiplicity

- **Sporadic** carriers:
  - Typically **unilateral**
- **Germline** carriers:
  - Typically **bilateral**
  - Ca. ***3 tumors*** / carrier
  - Not all cells become tumors
  - Second hit *rare & random*
  - *Probabilistic* process ?



Formation of unilateral and bilateral retinoblastoma (Ariana et al.*, 2019)*

Poisson Statistics

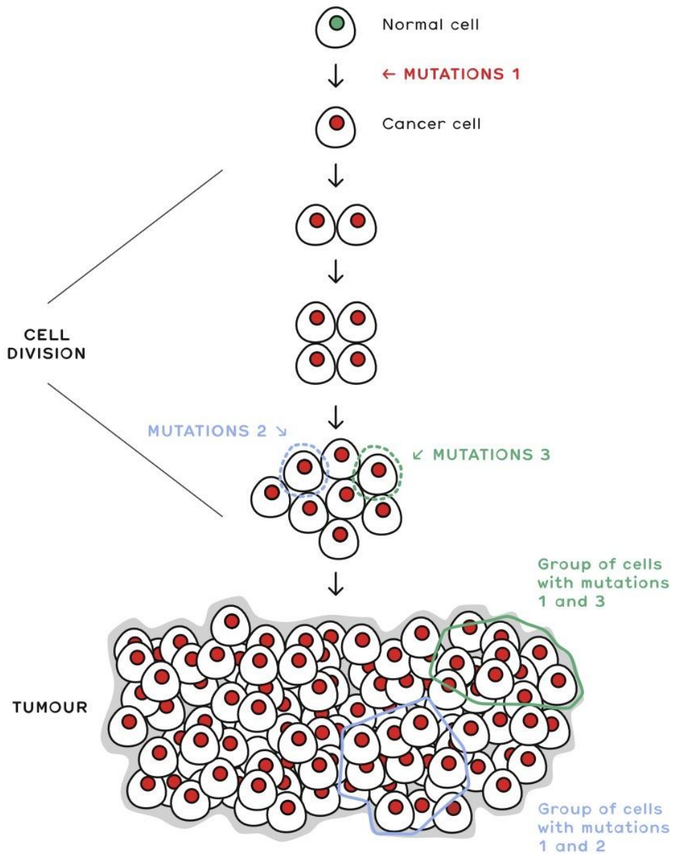
- **Two-Hit Model**
  - Models random independent events
  - **Mean (λ) ≈ 3 tumors/germline carrier**
  - Predicts variability
    - Most carriers ⟶ **0** tumors
    - Some ⟶ **1** tumor
    - Fewer ⟶ **2** tumors
    - Fewest → **3+** tumors

Experimental Procedure

- **48 Retinoblastoma cases**
- **Hospital records** 1944–1969
- **Pediatric patients**
- **Clinical data** collected
  - **Laterality** (Uni- vs bi-lateral)
  - **Age** at diagnosis
  - Family history
  - **# tumors** when possible

Analytical Strategy

- **Hereditary *vs* non-hereditary** cases
- **Tumor count** / individual
- **Statistical modeling**
  - **Poisson** distribution
  - **Rare** events
  - **Independent** mutations



Case Distributions

- **35 ~ 45% hereditary**
- **55 ~ 65% non-hereditary**
  - Hereditary → unilateral **+** bilateral
  - Non-hereditary → **unilateral only**
- **Bilateral tumors → inherited**
- **Unilateral tumors → sporadic**

TABLE 2. *Distribution of retinoblastoma cases by type and laterality (3, 5)*

	Bilateral	Unilateral	Total
Hereditary	25–30%	10–15%	35–45%
Nonhereditary	0	55–65%	55–65%
Total	25–30%	70–75%	100%

Age at diagnosis

- **Bilateral cases** [□ □ □, _____]
  - *Early* onset (50% **>9** months)
  - *Exponential* decline
- **Unilateral cases** [○ ○ ○, - - - - -]
  - *Late* onset (50% **>28** months)
  - ***Two**-mutation* pattern
- Consistent w/ **one-** *vs* **two-hit** model

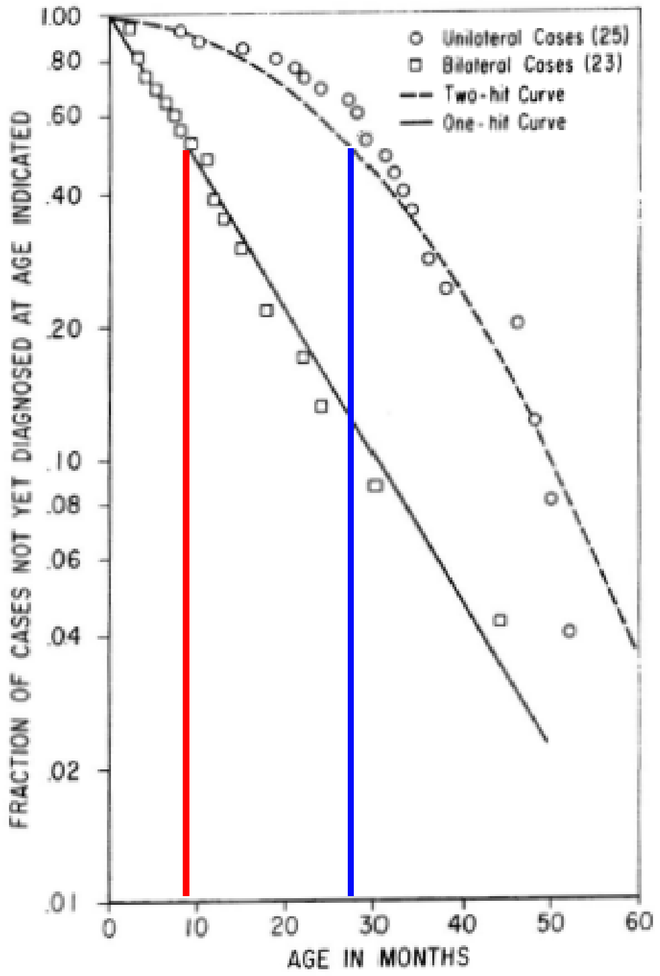
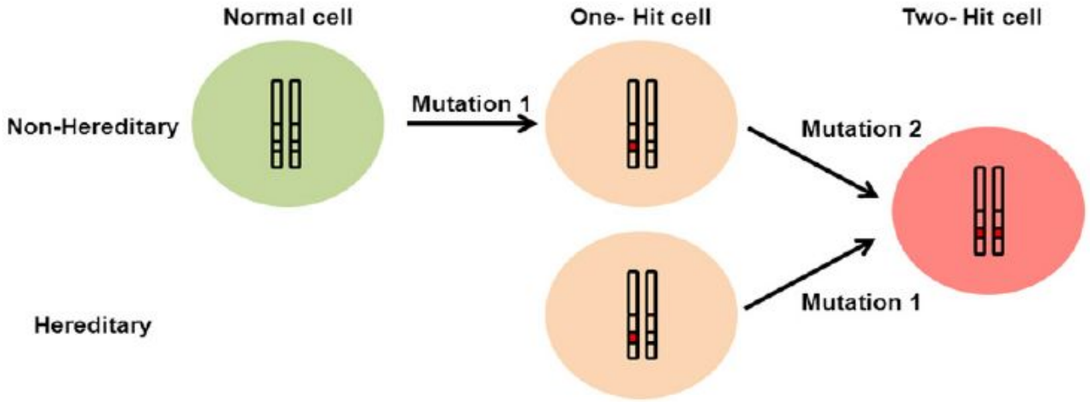


FIG. 1. Semilogarithmic plot of fraction of cases of retinoblastoma not yet diagnosed (S) vs. age in months (t). The one-hit curve was calculated from $\log S = -t/30$, the two-hit curve from $\log S = -4 \times 10^{-4} t^2$.

Conclusion

- ***Two* mutations required**
  - Germline **AND** somatic
  - **Both** somatic
- **Realistic mutation rates**
- ***Two-hit* hypothesis supported**



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