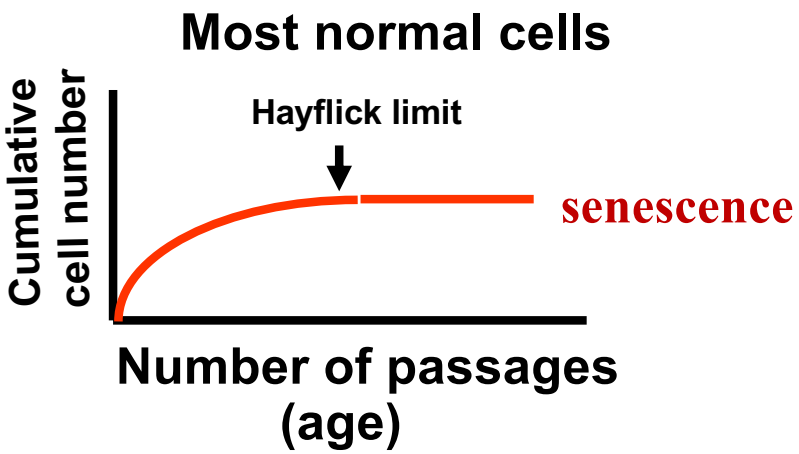
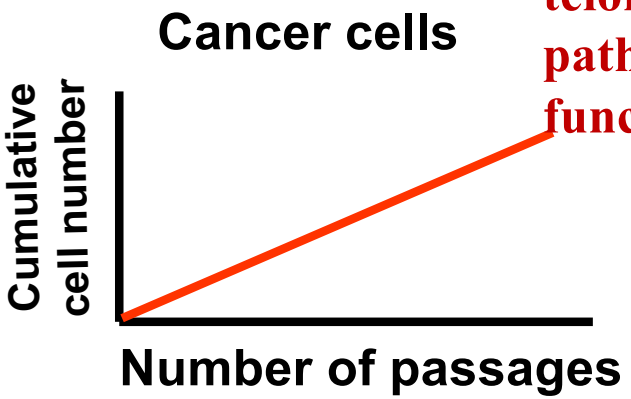
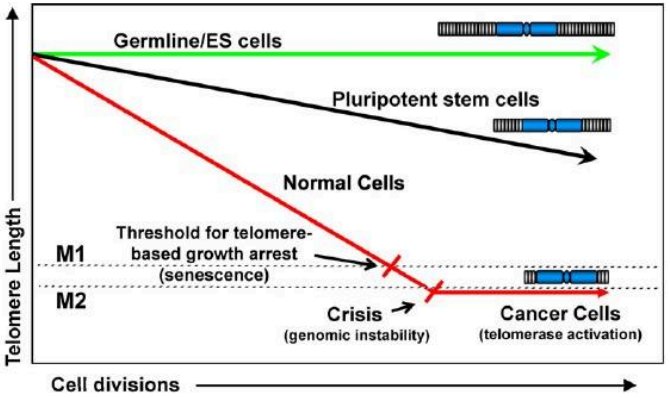
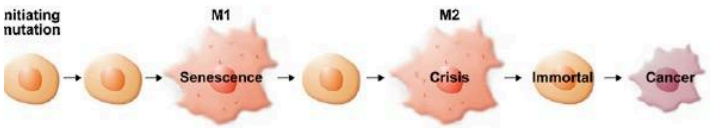
Most normal somatic cells can only replicate a finite number of times

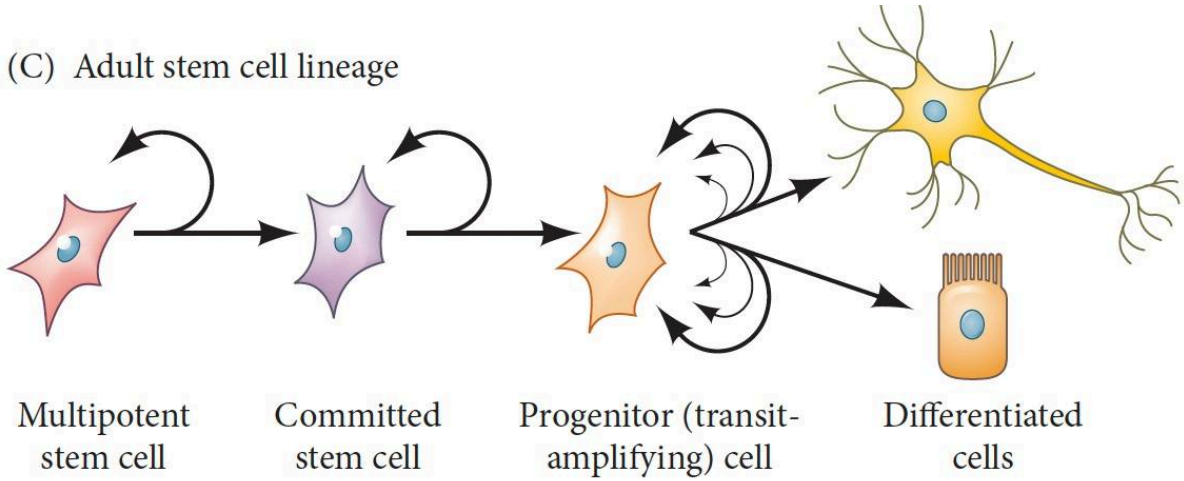




ALL cancers reactivate telomerase or an alternative pathway that serves the same function







Telomere shortening rate predicts species life span

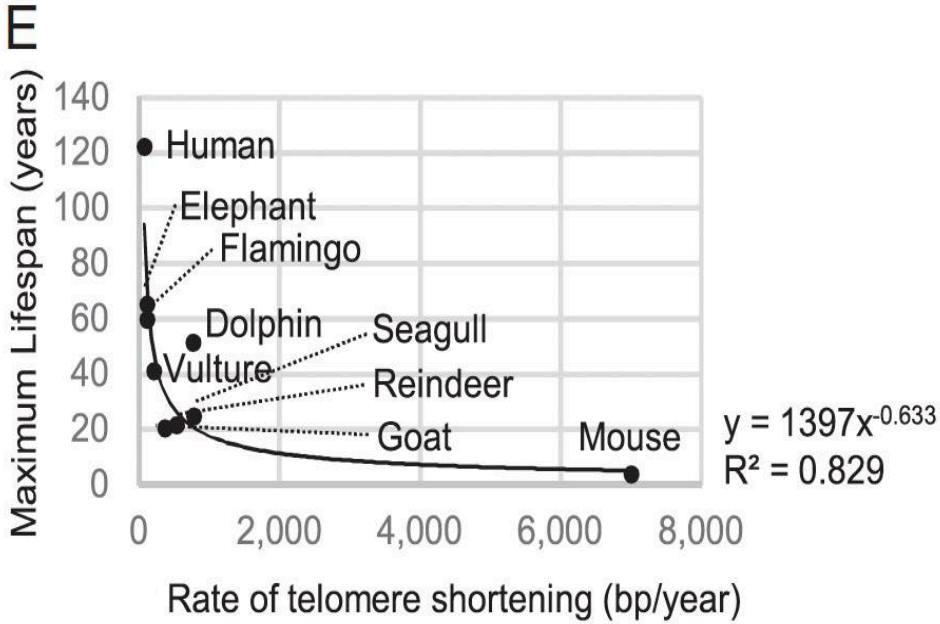
Kurt Whittemore[a], Elsa Vera[a], Eva Martínez-Nevado[b], Carola Sanpera[c,d], and Maria A. Blasco[a,1]

[a]Telomeres and Telomerase Group, Molecular Oncology Program, Spanish National Cancer Research Centre, 28029 Madrid, Spain; [b]Veterinary Department, Madrid-Zoo Aquarium, 28011 Madrid, Spain; [c]Departament de Biologia Evolutiva, Ecologia i Ciències Ambientals, Facultat de Biologia, Universitat de Barcelona, 08028 Barcelona, Spain; and [d]Institut de Recerca de la Biodiversitat, Universitat de Barcelona, 08028 Barcelona, Spain

Edited by Margarita Salas, Consejo Superior de Investigaciones Cientificas, Madrid, Spain, and approved June 11, 2019 (received for review February 13, 2019)

Telomere shortening to a critical length can trigger aging and shorter life spans in mice and humans by a mechanism that involves induction of a persistent DNA damage response at chromosome ends and loss of cellular viability. However, whether telomere length is a universal determinant of species longevity is not known. To determine whether telomere shortening can be a single parameter to predict species longevities, here we measured in parallel the telomere length of a wide variety of species (birds and mammals) with very different life spans and body sizes, including mouse (*Mus musculus*), goat (*Capra hircus*), Audouin's gull (*Larus audouinii*), reindeer (*Rangifer tarandus*), griffon vulture (*Gyps fulvus*), bottlenose dolphin (*Tursiops truncatus*), American flamingo (*Phoenicopterus ruber*), and Sumatran elephant (*Elephas maximus sumatranus*). We found that the telomere shortening rate, but not the initial telomere length alone, is a powerful predictor of species life span. These results support the notion that critical telomere shortening and the consequent onset of telomeric DNA damage and cellular senescence are a general determinant of species life span.

previously shown a rate of telomere shortening of around 7,000 bp per y, which is 100-fold faster than that reported in humans (4).



LETTER

doi:10.1038/nature09603

Telomerase reactivation reverses tissue degeneration in aged telomerase-deficient mice

Mariela Jaskelioff[1], Florian L. Muller[1], Ji-Hye Paik[1], Emily Thomas[1], Shan Jiang[1], Andrew C. Adams[2], Ergun Sahin[1], Maria Kost-Alimova[1], Alexei Protopopov[1], Juan Cadiñanos[1], James W. Horner[1], Eleftheria Maratos-Flier[2] & Ronald A. DePinho[1]

An ageing world population has fuelled interest in regenerative remedies that may stem declining organ function and maintain fitness. Unanswered is whether elimination of intrinsic instigators driving age-associated degeneration can reverse, as opposed to simply arrest, various afflictions of the aged. Such instigators include progressively damaged genomes. Telomerase-deficient mice have served as a model system to study the adverse cellular and organismal consequences of wide-spread endogenous DNA damage signalling activation *in vivo*[1]. Telomere loss and uncapping provokes progressive tissue atrophy, stem cell depletion, organ system failure and impaired tissue injury responses[1]. Here, we sought to determine whether entrenched multi-system degeneration in adult mice with severe telomere dysfunction can be halted or possibly reversed by reactivation of endogenous telomerase activity. To this end, we engineered a knock-in allele encoding a 4-hydroxytamoxifen (4-OHT)-inducible telomerase reverse transcriptase-oestrogen receptor (TERT-ER) under transcriptional control of the endogenous TERT promoter. Homozygous TERT-ER mice have short dysfunctional telomeres and sustain increased DNA damage signalling and classical degenerative phenotypes upon successive generational matings and advancing age. Telomerase reactivation in such late generation TERT-ER mice extends telomeres, reduces DNA damage signalling and associated cellular checkpoint responses, allows resumption of proliferation in quiescent cultures, and eliminates degenerative phenotypes across multiple organs including testes, spleens and intestines. Notably,

onset of tissue atrophy and organ system failure in degenerative diseases such as ataxia-telangiectasia, Werner syndrome, dyskeratosis congenita and liver cirrhosis, among others[1,3]. In cell-based models of ataxia-telangiectasia and Werner syndrome, enforced TERT can restore normal cellular proliferative potential[8]. These findings build on seminal cell culture studies showing that enforced TERT expression can endow primary human cells with unlimited replicative potential[9]. Importantly, TERT overexpression in epithelial tissues of cancer-resistant mice leads to extended median lifespan[10]. In addition, intercrossing wild-type and late generation $mTerc^{-/-}$ mice with severe degenerative phenotypes results in healthy offspring[11], indicating that viable late generation $mTerc^{-/-}$ germ cells can be restored to normal telomere function on introduction of a wild-type *mTerc* allele at the time of fertilization. However, to our knowledge, there are no genetic or pharmacological studies showing somatic reversal of age-related degenerative phenotypes driven by endogenous genotoxic stresses in adult mammals. Here, in telomerase-deficient mice experiencing severe tissue degeneration, we investigated whether endogenous telomerase-mediated restoration of telomere function throughout the organism would quell DNA damage signalling and either arrest, or possibly reverse, cellular checkpoint responses and associated tissue atrophy and dysfunction. Notably, the mice enlisted into this study are adults exhibiting significant progeroid phenotypes.

Construction and functional validation of the germline TERT-ER knock-in allele are detailed in Supplementary Fig. 1. In the absence of 4-OHT, ER fusion proteins remain in an inactive misfolded state[12] and thus we first sought to verify whether mice homozygous for TERT-ER

Genetic variation in human telomerase is associated with telomere length in Ashkenazi centenarians

Gil Atzmon[a,b,1,2], Miook Cho[a,1], Richard M. Cawthon[c], Temuri Budagov[b], Micol Katz[b], Xiaoman Yang[b], Glenn Siegel[b], Aviv Bergman[d], Derek M. Huffman[a,b], Clyde B. Schechter[e], Woodring E. Wright[f], Jerry W. Shay[f], Nir Barzilai[a,b], Diddahally R. Govindaraju[g], and Yousin Suh[a,b,2]

[a]Departments of Medicine and Genetics, Albert Einstein College of Medicine, Bronx, NY 10461; [b]Institute for Aging Research, Diabetes Research and Training Center, Albert Einstein College of Medicine, Bronx, NY 10461; [c]Department of Human Genetics, University of Utah, Salt Lake City, UT 84112; [d]Department of Systems and Computational Biology, Albert Einstein College of Medicine, Bronx, NY 10461; [e]Department of Family and Social Medicine, Albert Einstein College of Medicine, Bronx, NY 10461; [f]Department of Cell Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390; and [g]Department of Neurology, Boston University School of Medicine, Boston, MA 02118

Edited by Stephen Curtis Stearns, Yale University, New Haven, CT, and accepted by the Editorial Board October 7, 2009 (received for review July 20, 2009)

Telomere length in humans is emerging as a biomarker of aging because its shortening is associated with aging-related diseases and early mortality. However, genetic mechanisms responsible for these associations are not known. Here, in a cohort of Ashkenazi Jewish centenarians, their offspring, and offspring-matched controls, we studied the inheritance and maintenance of telomere length and variations in two major genes associated with telomerase enzyme activity, *hTERT* and *hTERC*. We demonstrated that centenarians and their offspring maintain longer telomeres compared with controls with advancing age and that longer telomeres are associated with protection from age-related diseases, better cognitive function, and lipid profiles of healthy aging. Sequence analysis of *hTERT* and *hTERC* showed overrepresentation of synonymous and intronic mutations among centenarians relative to controls. Moreover, we identified a common *hTERT* haplotype that is associated with both exceptional longevity and longer telomere length. Thus, variations in human telomerase gene that are associated with better maintenance of telomere length may confer healthy aging and exceptional longevity in humans.

quantitative traits (16). Heritability estimates for telomere length vary from 35 to 80% (9, 13, 17). Although several candidate genes have been identified as potential modulators of telomere length in humans (17, 18), none of these genes seem to play a direct role in maintenance of telomere length (19). Recently, one of the most obvious candidate genes of telomere maintenance, telomerase, has been shown to play a direct role in the maintenance of telomere length in humans (20). Telomerase is a specialized ribonucleoprotein enzyme complex that adds telomere repeats to the ends of chromosomes and has two essential components: a catalytic component encoded by the human telomerase reverse transcriptase (hTERT) and a human telomerase RNA component (hTERC). The latter component provides the template for nucleotide addition by hTERT. Heterozygote mutations in the *hTERT* and *hTERC* genes lead to short telomeres and are the major risk factors for rare hematopoietic disorders of bone marrow failure, including aplastic anemia and dyskeratosis congenital. These results indicate that the levels of functional telomerase are critical for telomere maintenance (21).

Telomerase gene therapy in adult and old mice delays aging and increases longevity without increasing cancer

Bruno Bernardes de Jesus[1], *Elsa Vera*[1], *Kerstin Schneeberger*[1], *Agueda M. Tejera*[1], *Eduard Ayuso*[2,3], *Fatima Bosch*[2,3], *Maria A. Blasco*[1*]

Keywords: AAV9; aging; gene therapy; health span; TERT

DOI 10.1002/emmm.201200245

Received February 22, 2012
Revised March 29, 2012
Accepted March 30, 2012

→See accompanying article
http://dx.doi.org/10.1002/emmm.201200246

A major goal in aging research is to improve health during aging. In the case of mice, genetic manipulations that shorten or lengthen telomeres result, respectively, in decreased or increased longevity. Based on this, we have tested the effects of a telomerase gene therapy in adult (1 year of age) and old (2 years of age) mice. Treatment of 1- and 2-year old mice with an adeno associated virus (AAV) of wide tropism expressing mouse TERT had remarkable beneficial effects on health and fitness, including insulin sensitivity, osteoporosis, neuromuscular coordination and several molecular biomarkers of aging. Importantly, telomerase-treated mice did not develop more cancer than their control littermates, suggesting that the known tumorigenic activity of telomerase is severely decreased when expressed in adult or old organisms using AAV vectors. Finally, telomerase-treated mice, both at 1-year and at 2-year of age, had an increase in median lifespan of 24 and 13%, respectively. These beneficial effects were not observed with a catalytically inactive TERT, demonstrating that they require telomerase activity. Together, these results constitute a proof-of-principle of a role of TERT in delaying physiological aging and extending longevity in normal mice through a telomerase-based treatment, and demonstrate the feasibility of anti-aging gene therapy.

telomerase is necessary but not sufficient for cancer

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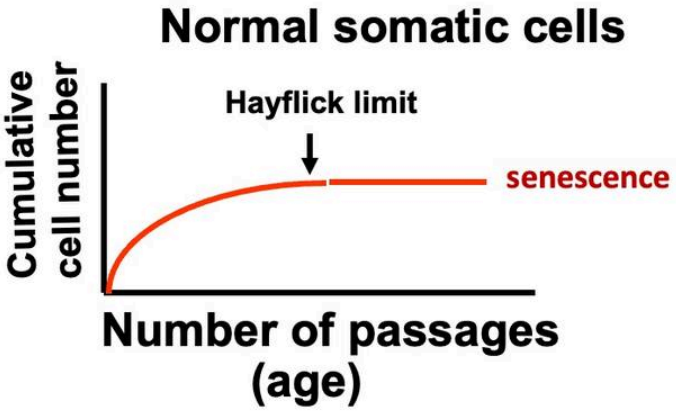
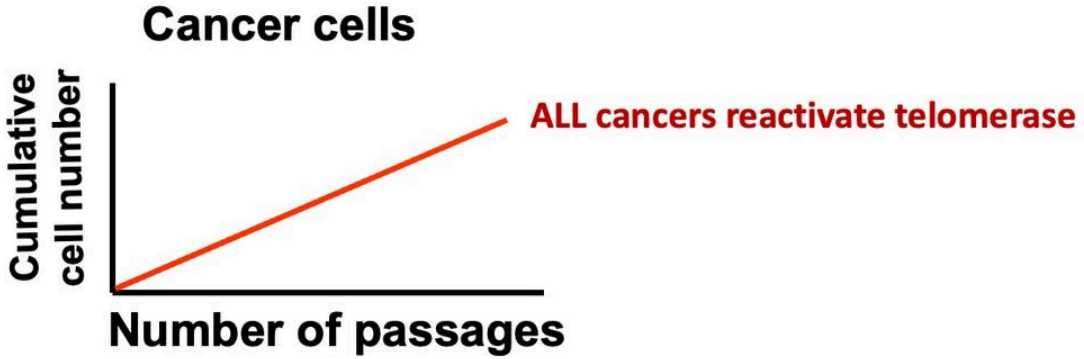
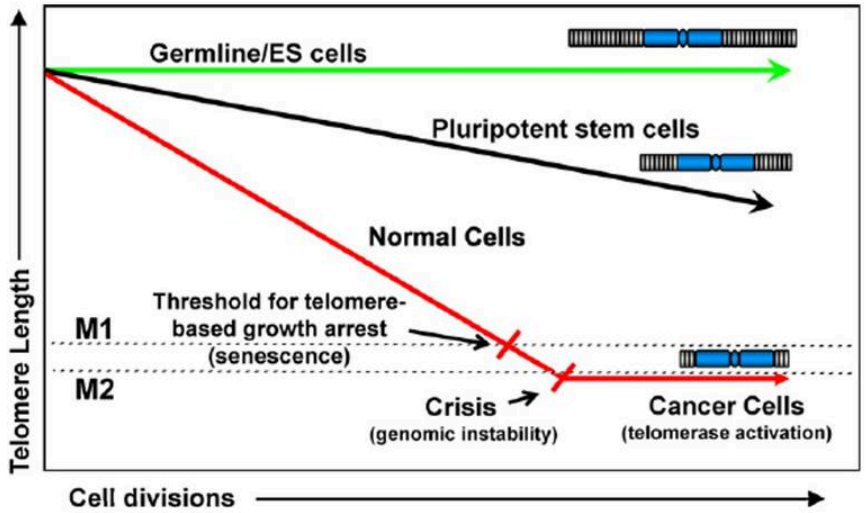
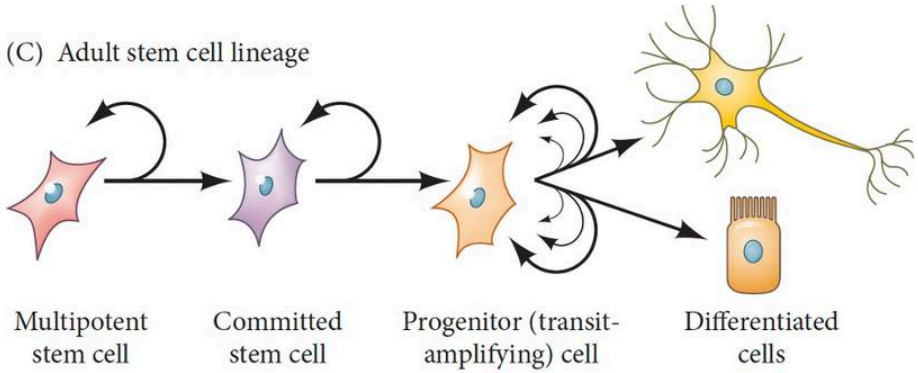
Being able to divide only a finite number of times provides a hard stop on lifespan, but also works to prevent cancer





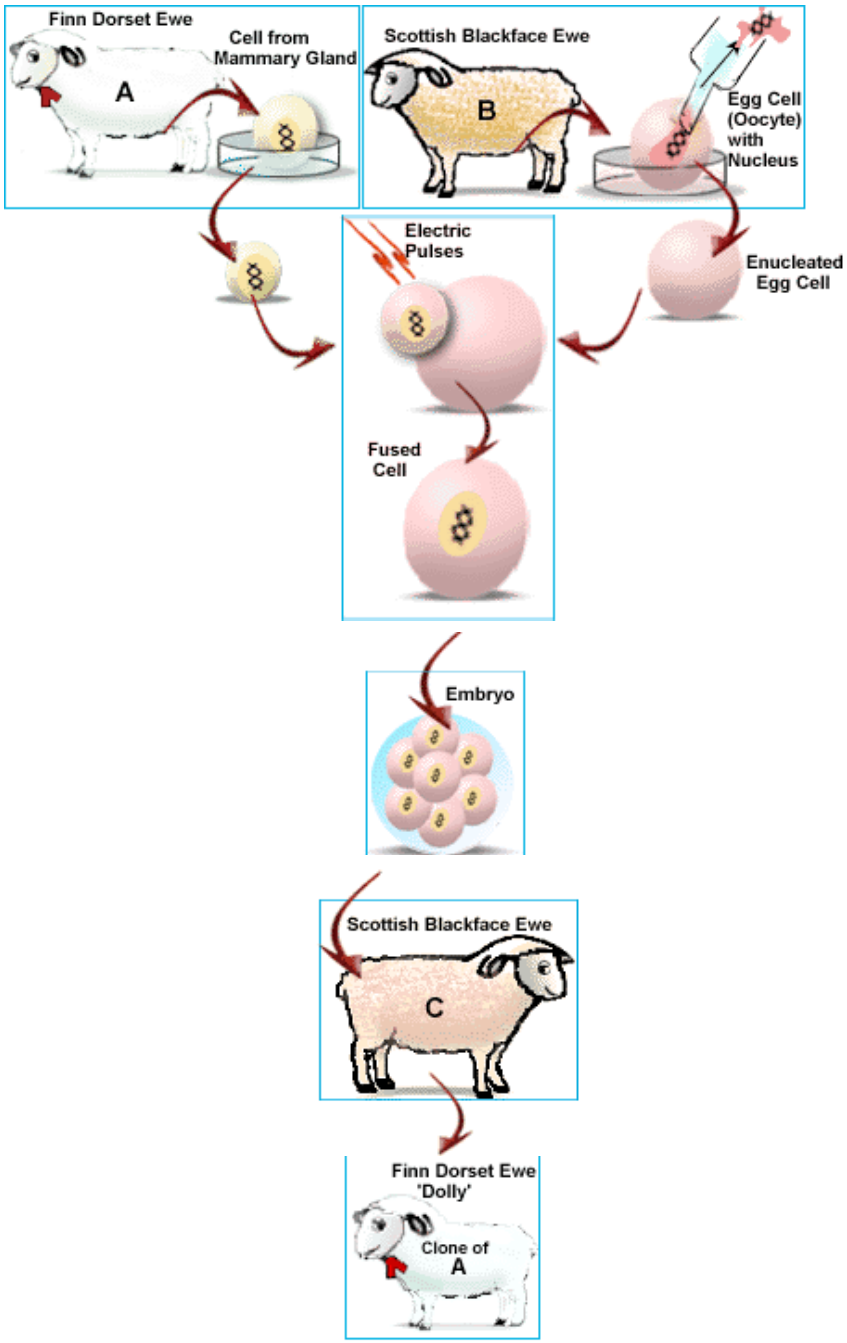




In normal reproduction

- Sperm and oocytes retain telomere length due to the activity of telomerase

- The offspring will have the same length telomeres as the parents



Nucleus removed From egg cell

Cell with DNA fused Into enucleated egg cell

Implantation into The surrogate mother

Birth of clone of Sheep A (Dolly)

Although the clone of sheep A (Dolly) could have been created using only sheep A, sheep B and C were used in the cloning process in order to ensure that Dolly was truly a clone and the not the result of unexpected mating.

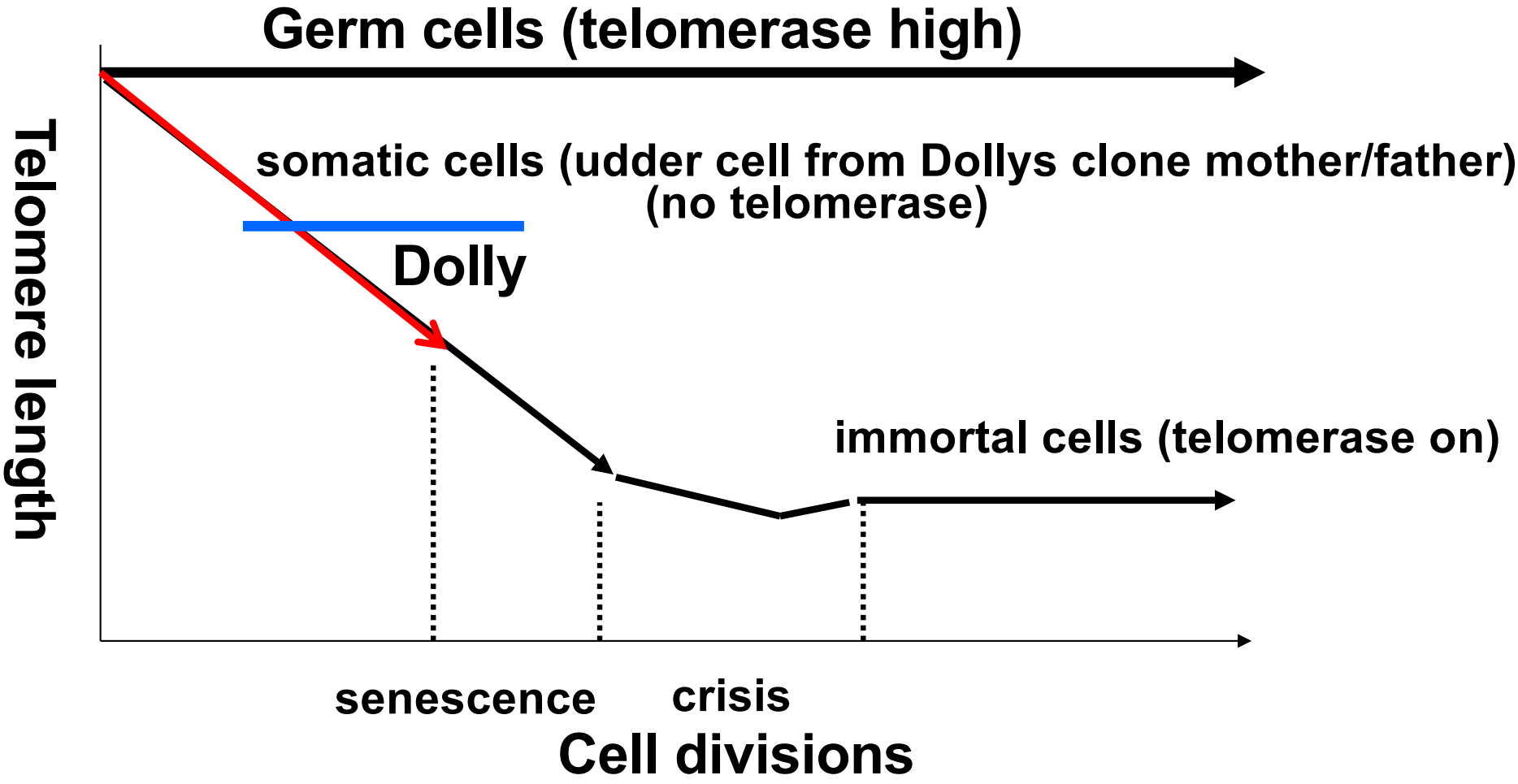
In cloned animals

- Oocytes are enucleated

- Donor cells are somatic cells. No telomerase activity is present.

- Shorter telomere length in these somatic cells compared to sperm/oocyte

What is Dolly's age?



Telomere length of cells in Dolly?

- Comparable to that of a six year older control (sheep live to be about 12 normally) **Nature 399:316-317**

News focus

Death of Dolly marks cloning milestone

Dolly the cloned sheep marked both an icon of scientific possibility and a potential ethical nightmare. Researchers in related fields of stem cell research need to learn the lessons and the right vocabulary if they are to make progress in their fields. Nigel Williams reports.

Dolly the sheep, the world's first mammal to be cloned from an adult cell was put to sleep last month. She was only six and a half years old – barely 40 in human terms. Already being treated for arthritis, Dolly was found to be suffering from a progressive lung disease.

The premature death of Dolly supports the view of some scientists in Japan and the US who maintain that all cloned animals are born with health problems. Harry Griffin, spokesperson for the Roslin Institute, near Edinburgh, where Dolly was created, was cautious on the significance of the ewe's death. 'Sheep can live to 11 or 12 years,' he said. 'Lung infections are common in older sheep, particularly those housed inside. A full postmortem is being conducted and we will report any significant findings.' After the postmortem examination, Dolly will be stuffed and put on display at the National Museum of Scotland.

Dolly was born on July 5 1996, from three mothers: one ewe to provide the DNA, another to provide the egg into which the DNA was injected, and a third to carry the resulting cloned embryo to term. Dolly's genetic mother (the DNA was taken from an udder cell) was six when she was cloned. This may mean that the real age of clones is their age since birth, plus the age of the genetic donor.

The revelation to the world of Dolly's existence, in 1997, was the scientific sensation of the decade. Scientific orthodoxy declared that cloning mammals was impossible: here was the proof. A frenzy of speculation followed about what cloning could achieve. But it is now known that cloning is difficult, expensive and dangerous for the animals involved. Claims of cloned humans remain unproven.

Speculation about its potential came quickly back to earth with the announcement that Dolly had

Goodbye Dolly: The creation of a cloned sheep caused a media sensation but her death demands a rethink of attitudes and presentation of cloning and related stem cell research. (Picture: Science Photo Library.)

nature COMMUNICATIONS

ARTICLE

Received 6 Apr 2016 | Accepted 27 Jun 2016 | Published 26 Jul 2016

DOI: 10.1038/ncomms12359 OPEN

Healthy ageing of cloned sheep

K.D. Sinclair[1], S.A. Corr[1], C.G. Gutierrez[1,2], P.A. Fisher[1], J.-H. Lee[1,†], A.J. Rathbone[1], I. Choi[1,†], K.H.S. Campbell[1,✠] & D.S. Gardner[1]

Figure 1 | Four 8-year old Finn-Dorset clones born in July 2007 and derived from the mammary-gland cell line that gave rise to Dolly.

Genex Cooperative Inc News

VIEW BY MONTH:

Visit News Archive

A Legend Passes

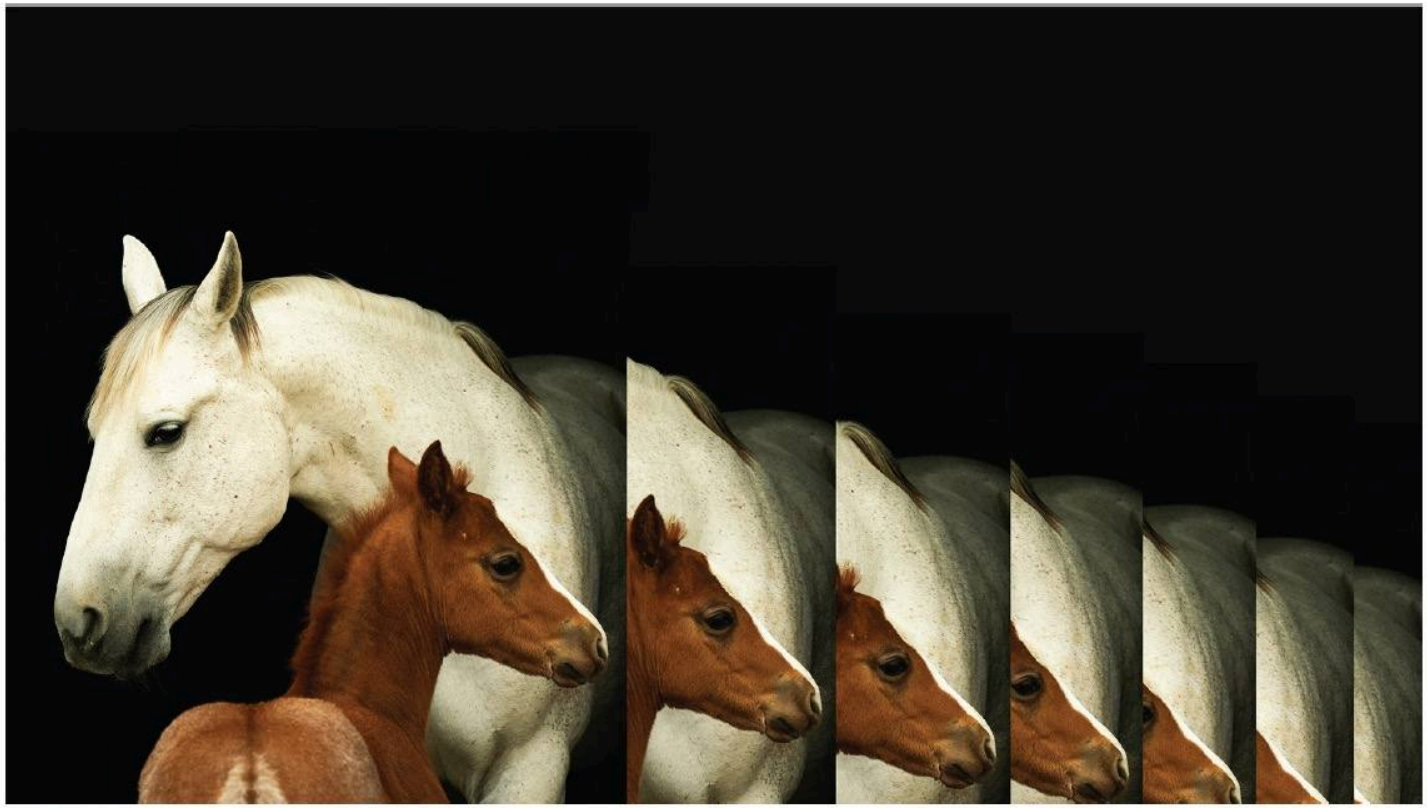
SHAWANO, Wis. – 1AN01044 S A V **FINAL ANSWER** 0035, at 14 years of age, has passed away. Born on February 22, 2000, he sold in the 2001 Martin and Angie Schaff Complete Retirement Dispersal. Genex acquired FINAL ANSWER in 2002. Since then, he has become the highest selling beef sire in the history of Genex.

Since 2009, FINAL ANSWER has been on the top 10 list for Angus registrations every year, ranking as the number one sire for registrations at the end of fiscal year 2012. He currently has 28,712 progeny registered with the American Angus Association along with countless commercial offspring. FINAL ANSWER achieved a great feat for any beef sire, by producing his 500,000th unit of semen on July 25, 2013.

He has attained many notable accomplishments, due in part to his commercial acceptability and extensive use worldwide. He leaves behind moderate, efficient replacement females and superior sons, such as 1AN01146 RIGHT ANSWER, 1AN01222 PRIORITY and 1AN01141 PIONEER. In addition, his legacy continues in his clone, 1AN01259 FINAL ANSWER II, a sire that can be used with the same expectations as FINAL ANSWER.

“I have had the opportunity to work with some of the greatest maternal sires of the breed,” states Willie Altenburg, Genex Associate Vice President of Beef Genetics. “Among that group of iconic sires is Final Answer, he will go down in history as one of the greatest calving ease and maternal sires of his era.”

About Genex
Genex Cooperative, Inc., headquartered in Shawano, Wisconsin, is the trusted provider of world-class animal genetics, progressive reproductive solutions, value-added products and innovative services to members and customers across the U.S. This is accomplished through 950 dedicated employees working in three product and service segments: cattle genetics and reproduction, livestock marketing, and milking and farmstead equipment. Genex is a subsidiary of Cooperative Resources International. Learn more at http://genex.crinet.com.



IDEAS

INSIDE THE BIG BUSINESS OF CLONING ANIMALS

Faster horses, superior cattle, immortal pets

By Bianca Bosker

Photographs by Brian Finke

A digression: Sex seems complicated. Why bother with sexual reproduction at all?

Why is the creation of new combinations/diversity so important?

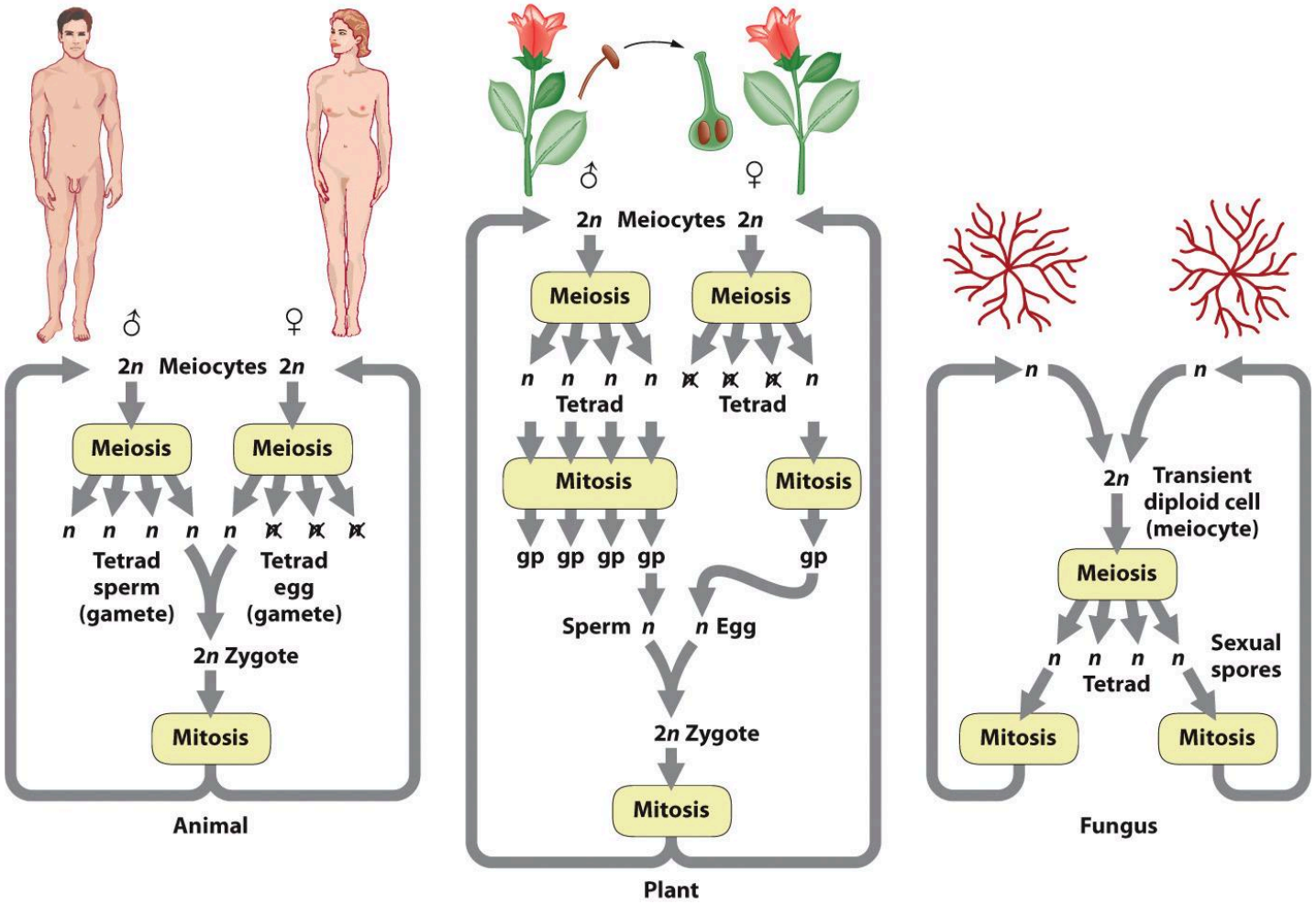


Figure 2-6
Introduction to Genetic Analysis, Twelfth Edition

No sex please, we're lizards

Telegraph.co.uk

By Roger Highfield

Last Updated: 2:02am GMT 21/12/2006

A Komodo dragon (Varanus komodoensis) has astonished the scientific world by produ
clutch of eight viable eggs without any assistance from a male.

Flora, the Komodo dragon who resides at Chester Zoo

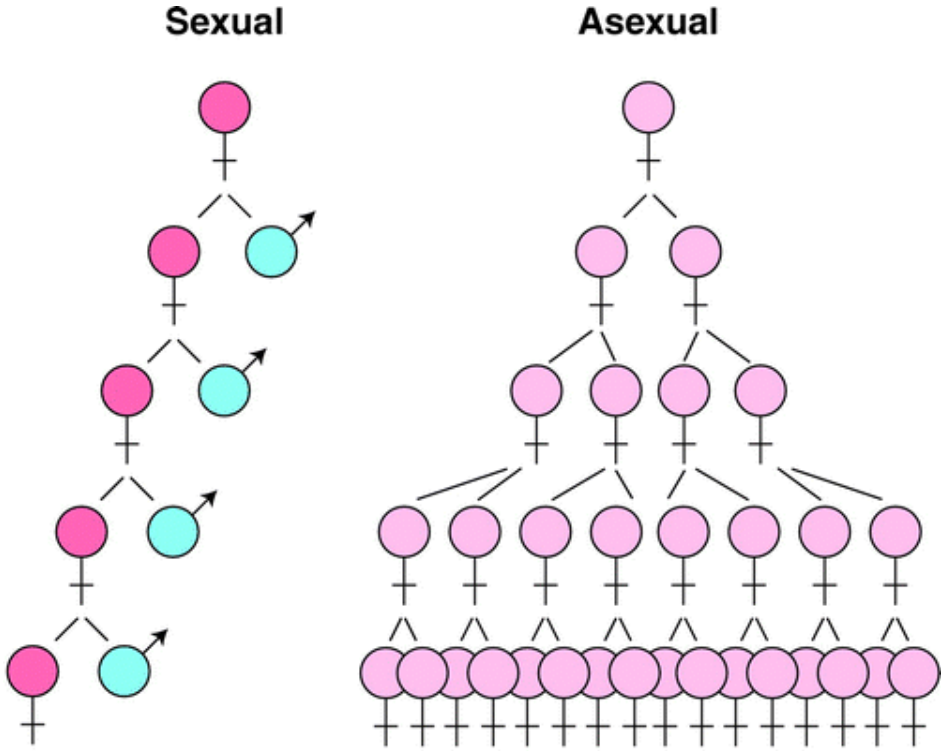
Fittingly, the baby dragons could hatch in time for Christmas in what would effectively be a virgin birth.

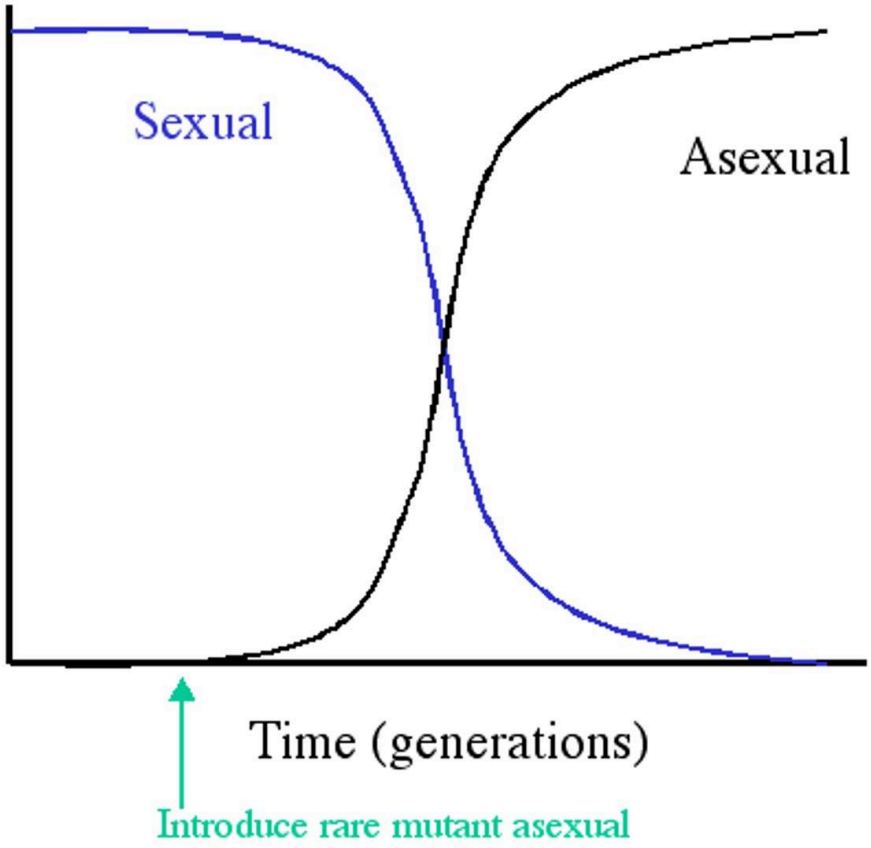
Parthenogenesis, the production of offspring without fertilization by a male, is carried out by King Edward potatoes, bees and greenfly but is rare in vertebrate species.

Now Phillip Watts of Liverpool University and colleagues have used genetic fingerprinting to reveal that parthenogenetic offspring have been produced by Flora the Komodo in Chester Zoo. Flora and her sister Nessie are now the only two sexually mature dragons in Europe.

The problem with males:
Asexuals should spread within a population of sexuals

Each female produces two progeny





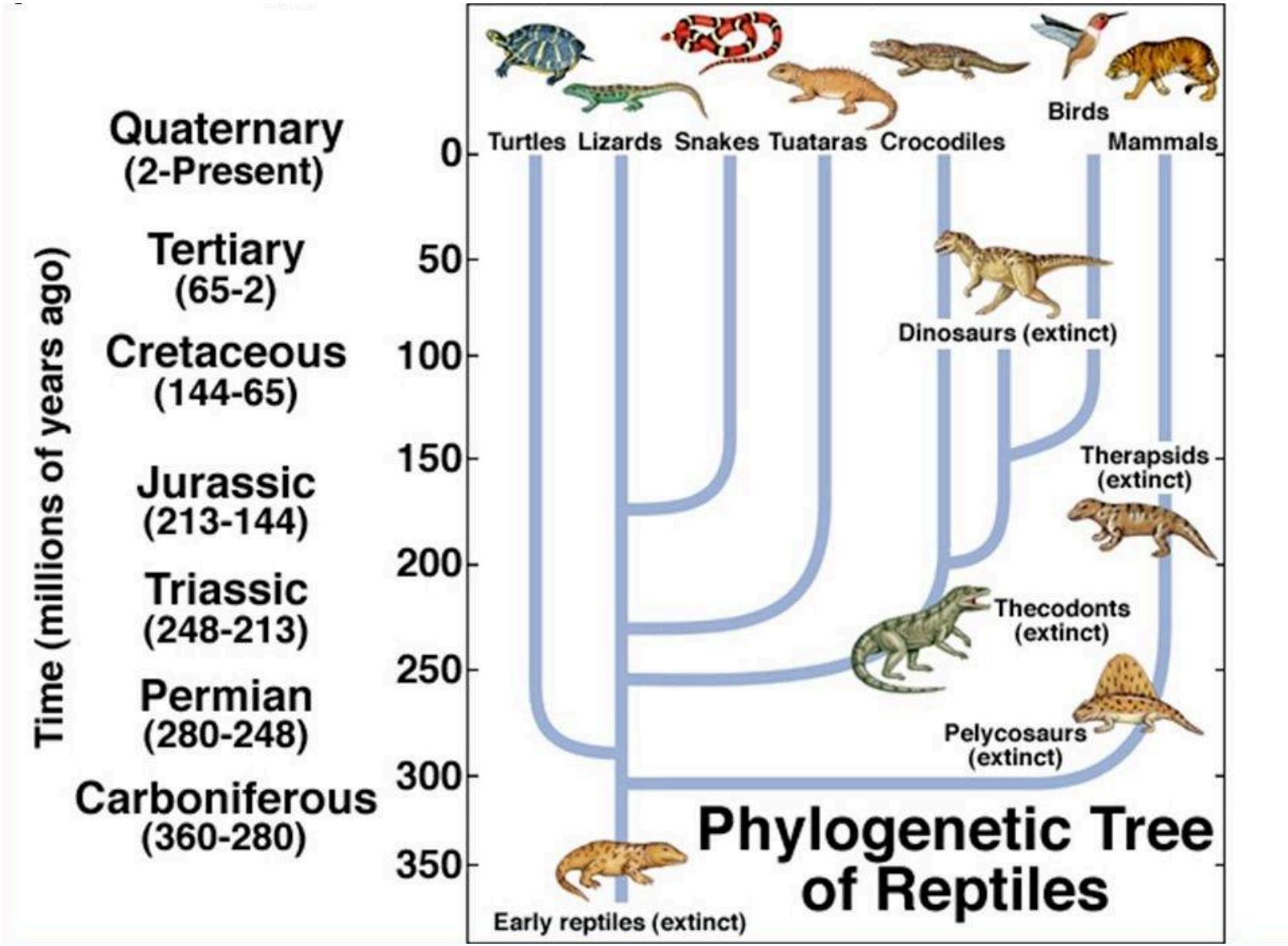
Milinski M. 2006.
Annu. Rev. Ecol. Evol. Syst. 37:159–86

Self-cloning marbled crayfish are now prohibited in Michigan

Paige Filice, Michigan State University Extension - June 11, 2020

> **Recent addition to Michigan's prohibited species list makes marbled crayfish illegal to possess live.**

Parthenogenetic species (no sex) always sit at the tip of phylogenetic trees. As though they exist only transiently and then go extinct



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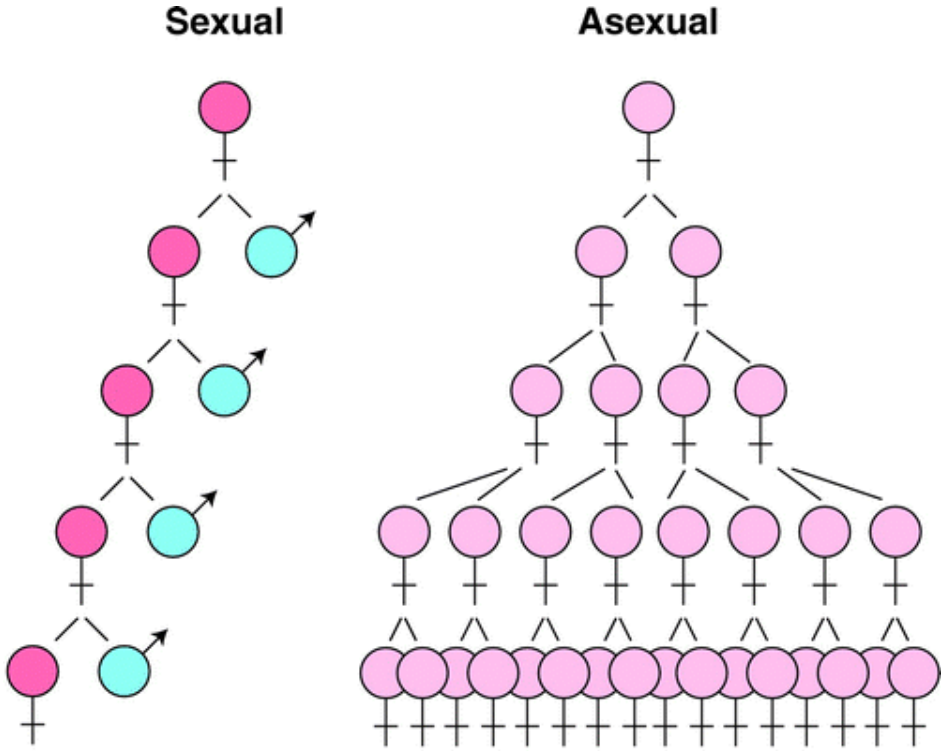

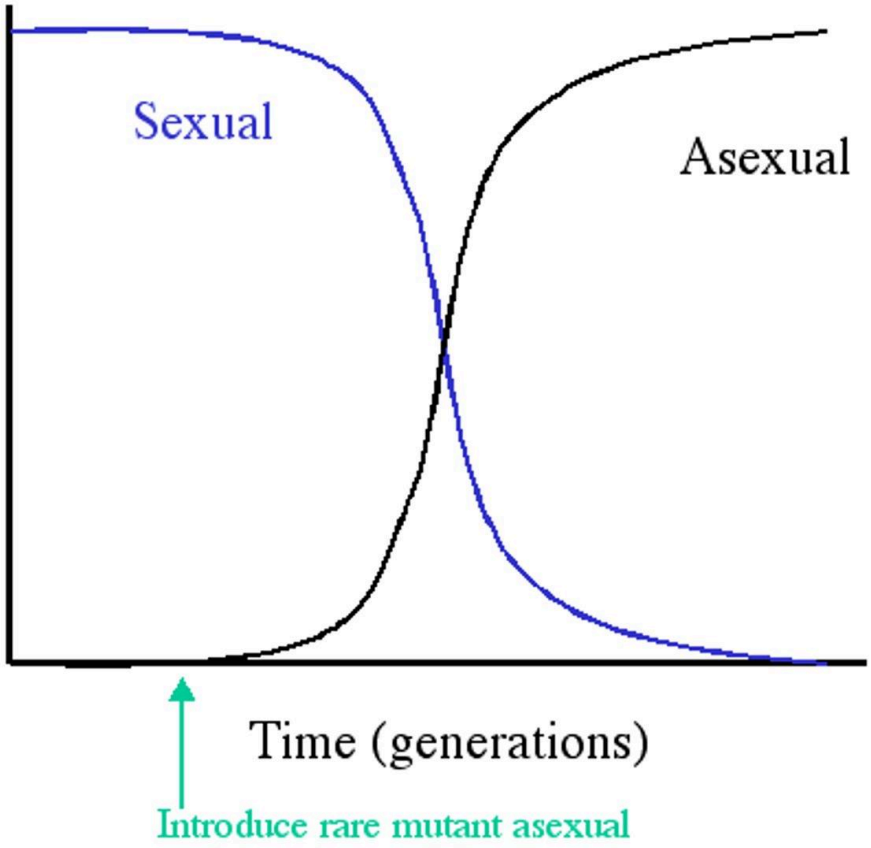

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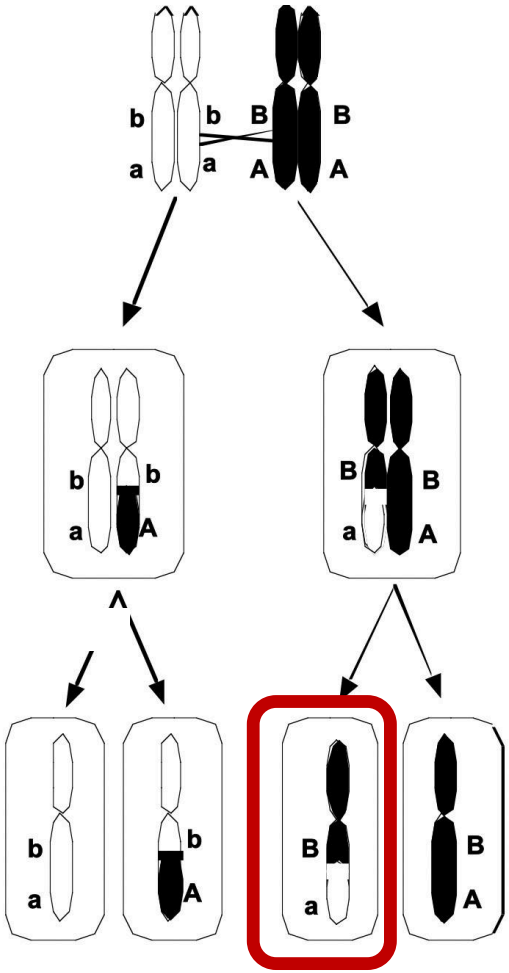
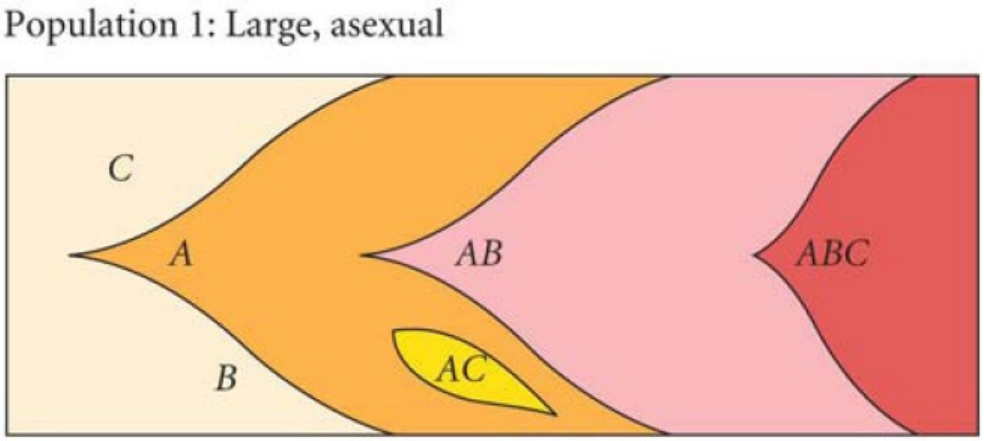
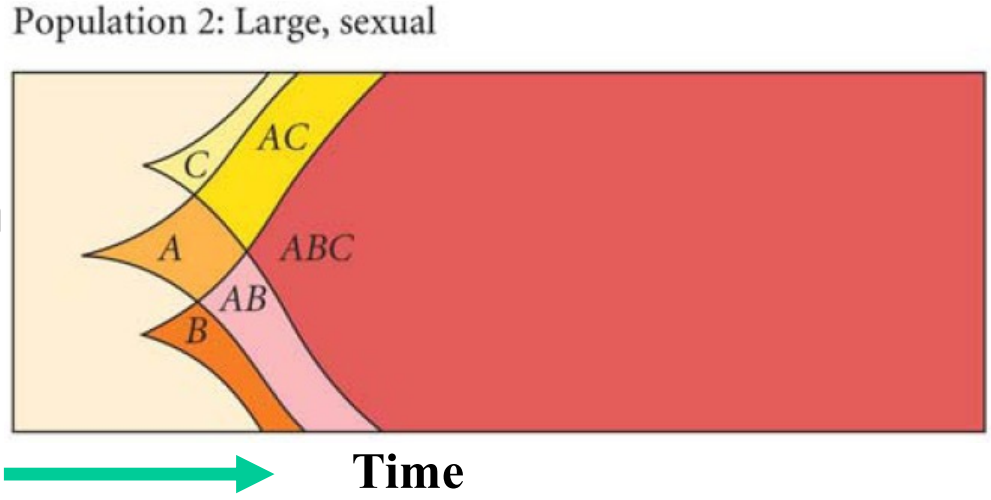
Sex and recombination bring together rare, advantageous gene combinations in the same individual



No sex and recombination



Sex and Recombination



The Red Queen Hypothesis: evolution never stops because competing species are also evolving

“Now, here, you see, it takes all the running you can do to keep in the same place. If you want to get to somewhere else, you must run twice as fast as that”

https://www.youtube.com/watch?v=y6rqugj_mVk

Brief description of red queen dynamics in the context of virus-host interactions

Infectious disease and the benefits of sex

If a pathogen can successfully attack one member of a clonal population, it can attack all.

Sex creates diversity that always (most of the time) allows some individuals to be resistant to attack

MICHIGAN STATE UNIVERSITY — MSU Extension

Self-cloning marbled crayfish are now prohibited in Michigan

Paige Filice, Michigan State University Extension - June 11, 2020

> Recent addition to Michigan's prohibited species list makes marbled crayfish illegal to possess live.

Muller's ratchet

In the absence of recombination genomes that acquire deleterious mutations cannot lose them through recombination

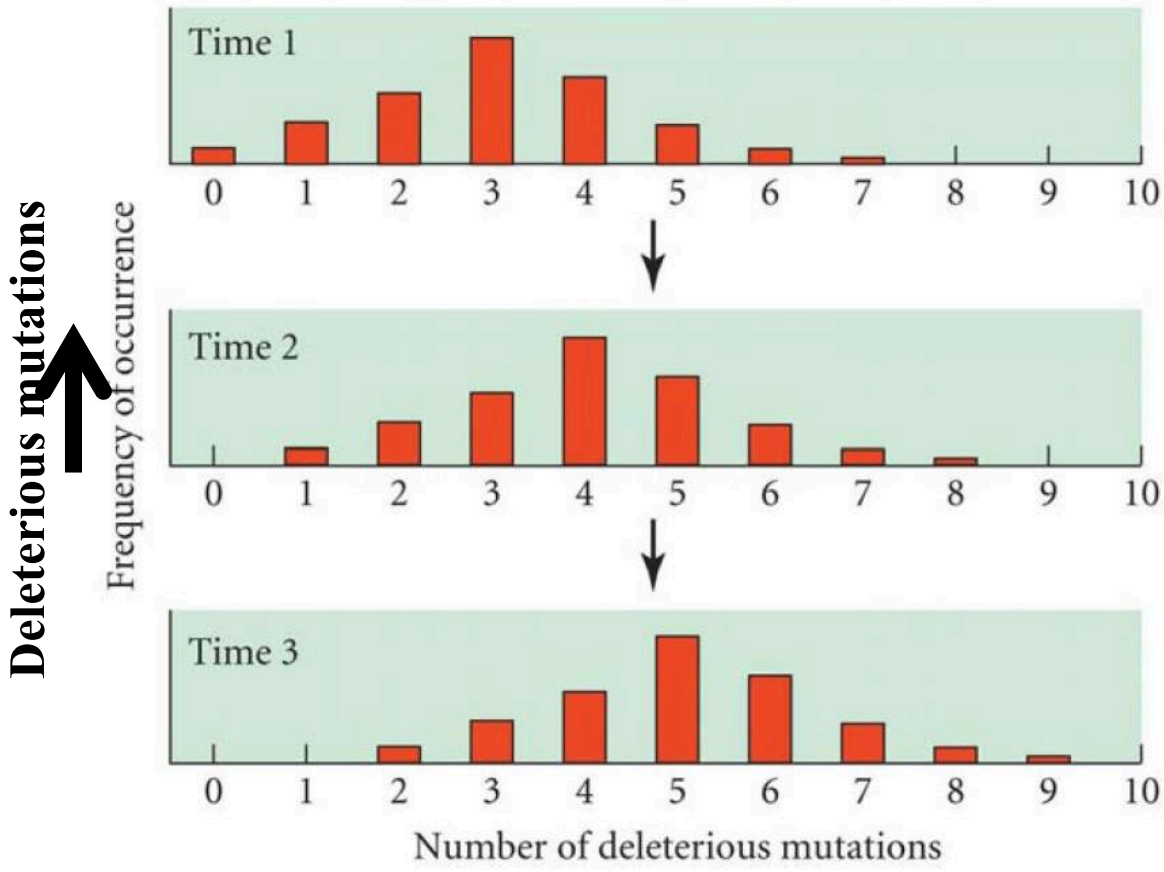
When a cell acquires a deleterious mutation (in gene A) it is much more likely that a second deleterious mutation (in gene B) will appear before a reversion mutation occurs in gene A.

In short, there are many more ways to break a gene than there are to fix a broken gene.

Thus, all other things being equal, genomes within a population should accumulate deleterious mutations over time.

How do prokaryotes avoid this problem?

ALL asexuals will suffer the effects of "Muller's Ratchet"

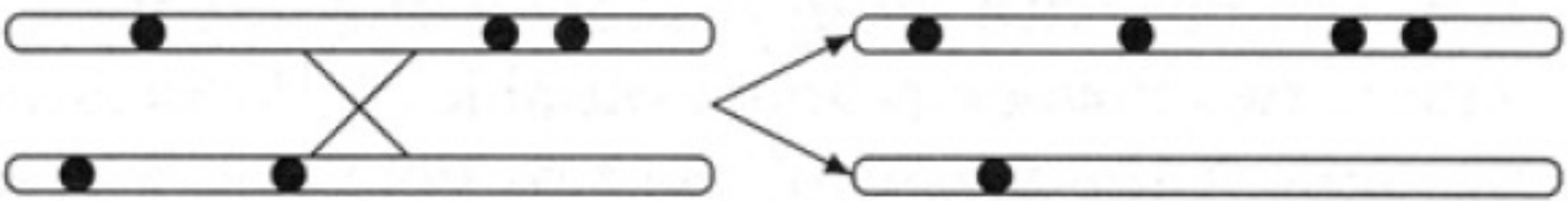


Deleterious mutations accumulate in asexual populations

● = a deleterious mutation

Chromosomes better (and worse) than any in the current population can be generated by crossing over in meiosis.

Sex promotes both improvement and purging!



Some reasons for sex

1. The red queen hypothesis

Evolution cannot stop when an optimal phenotype arises (because its never optimal for long)

The pressure to evolve always exists since those you compete with (other species) are also always evolving

2. Populations can undergo a “mutational meltdown” due to Muller’s ratchet

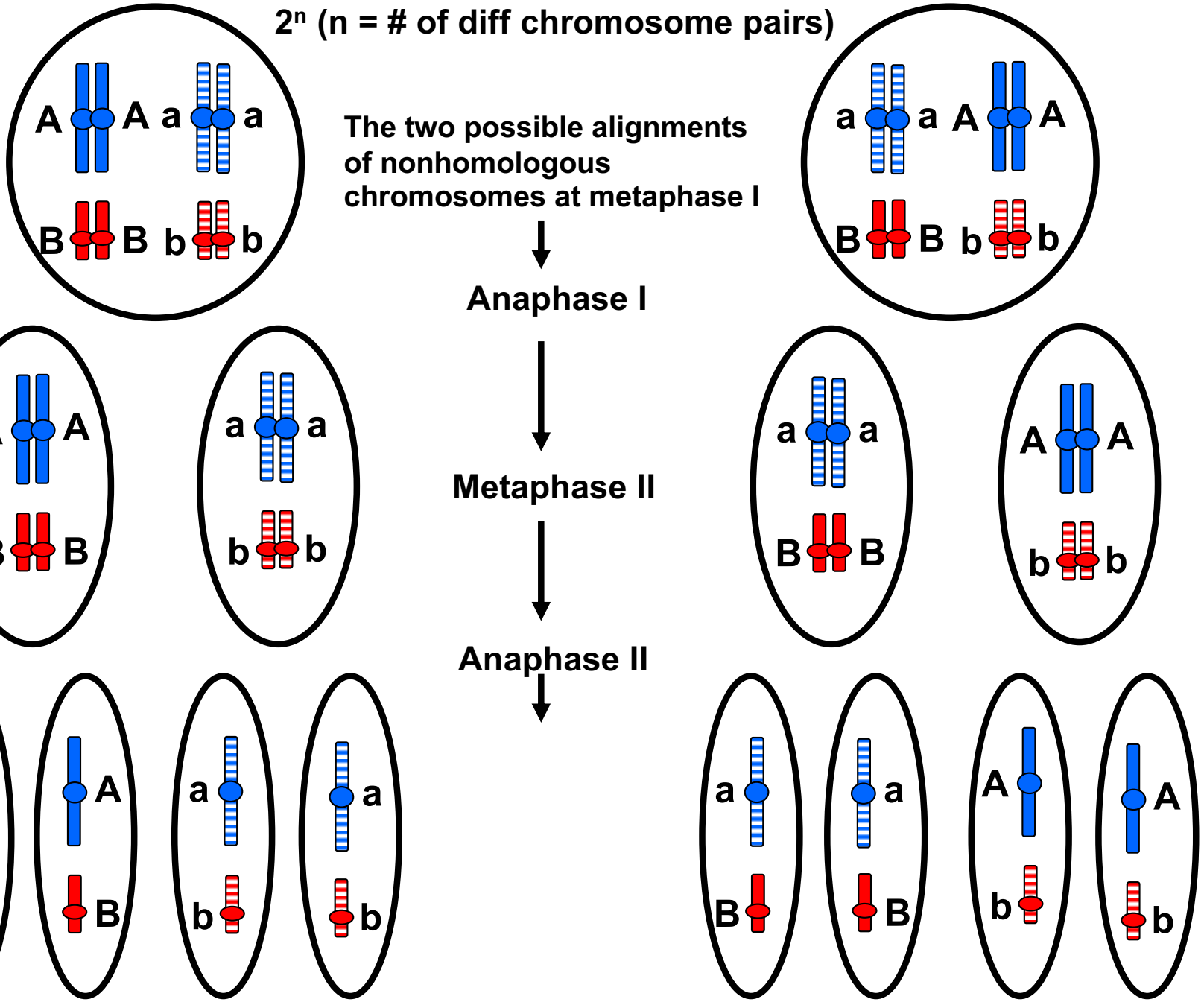
3. Meiosis can both create and purge beneficial/deleterious combinations of genes

Mendelian Genetics

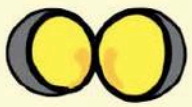
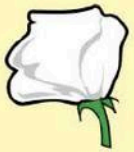
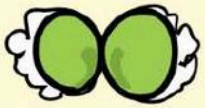
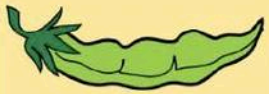
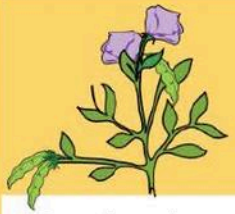
- Gregor Mendel (1822-1884),
  - Augustinian monk,
    - » Botanist,
      - *Pisum sativa,*
        - Garden pea,
          - » 1st "Model Organism".

Meiosis without recombination. Independent assortment of homologs to different Poles creates gamete diversity

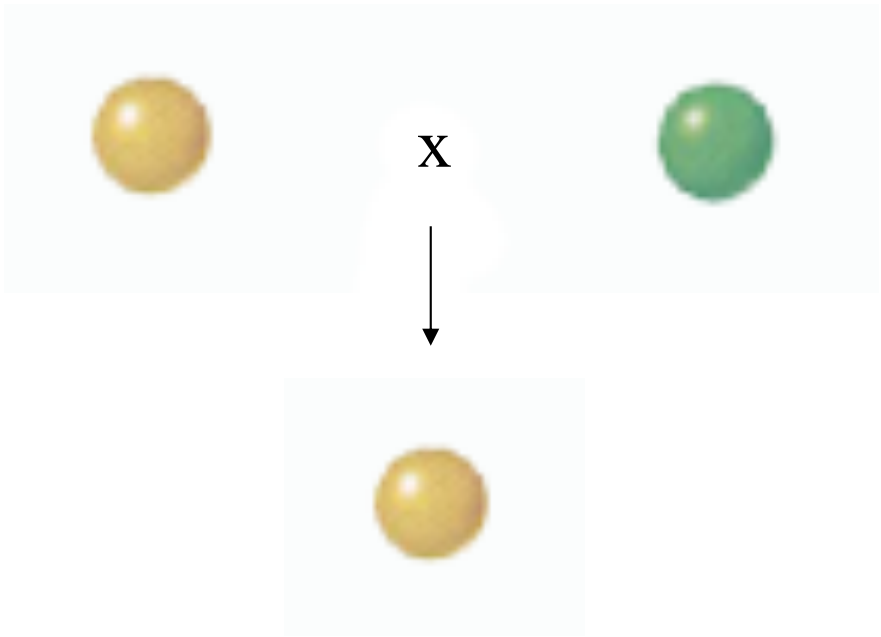
2^n (n = # of diff chromosome pairs)



Alternate form (phenotypes)

Seed		Flower	Pod		Stem	
Form	Cotyledons	Color	Form	Color	Place	Size
						
Grey & Round	Yellow	White	Full	Yellow	Axial pods, Flowers along	Long (6-7ft)
						
White & Wrinkled	Green	Violet	Constricted	Green	Terminal pods, Flowers top	Short (<1ft)
1	2	3	4	5	6	7

Dominant vs. Recessive Traits



The trait that appears in the F1 generation is the **DOMINANT** trait.

The trait that disappears in the F1 generation is termed **RECESSIVE**.

Genotype and phenotype

Genotype for the Seed Color Gene

Phenotype

YY
Homozygous dominant

Yellow

Dominant allele + **Recessive allele**

Yy
Heterozygous

Yellow

yy
Homozygous recessive

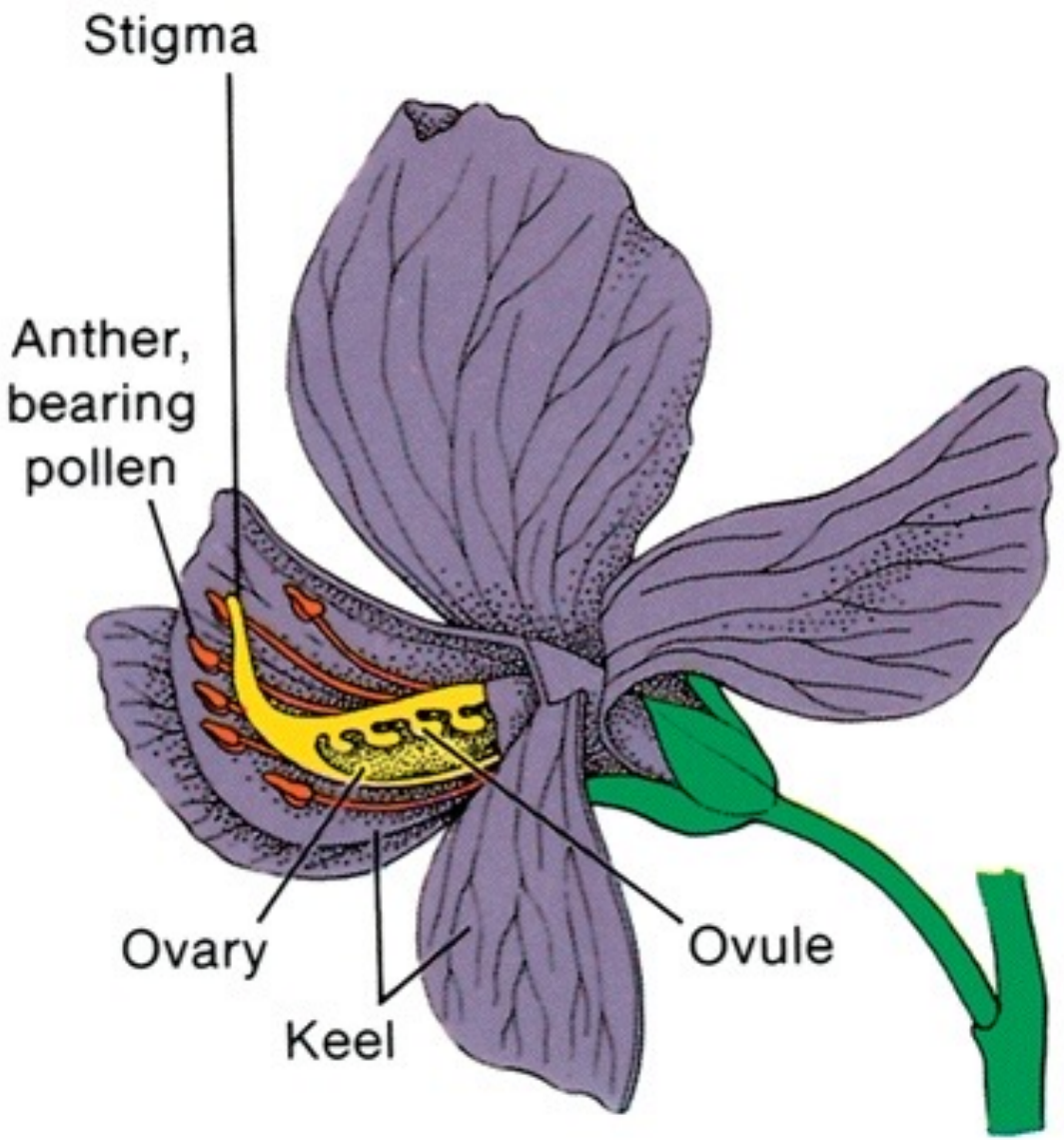
Green

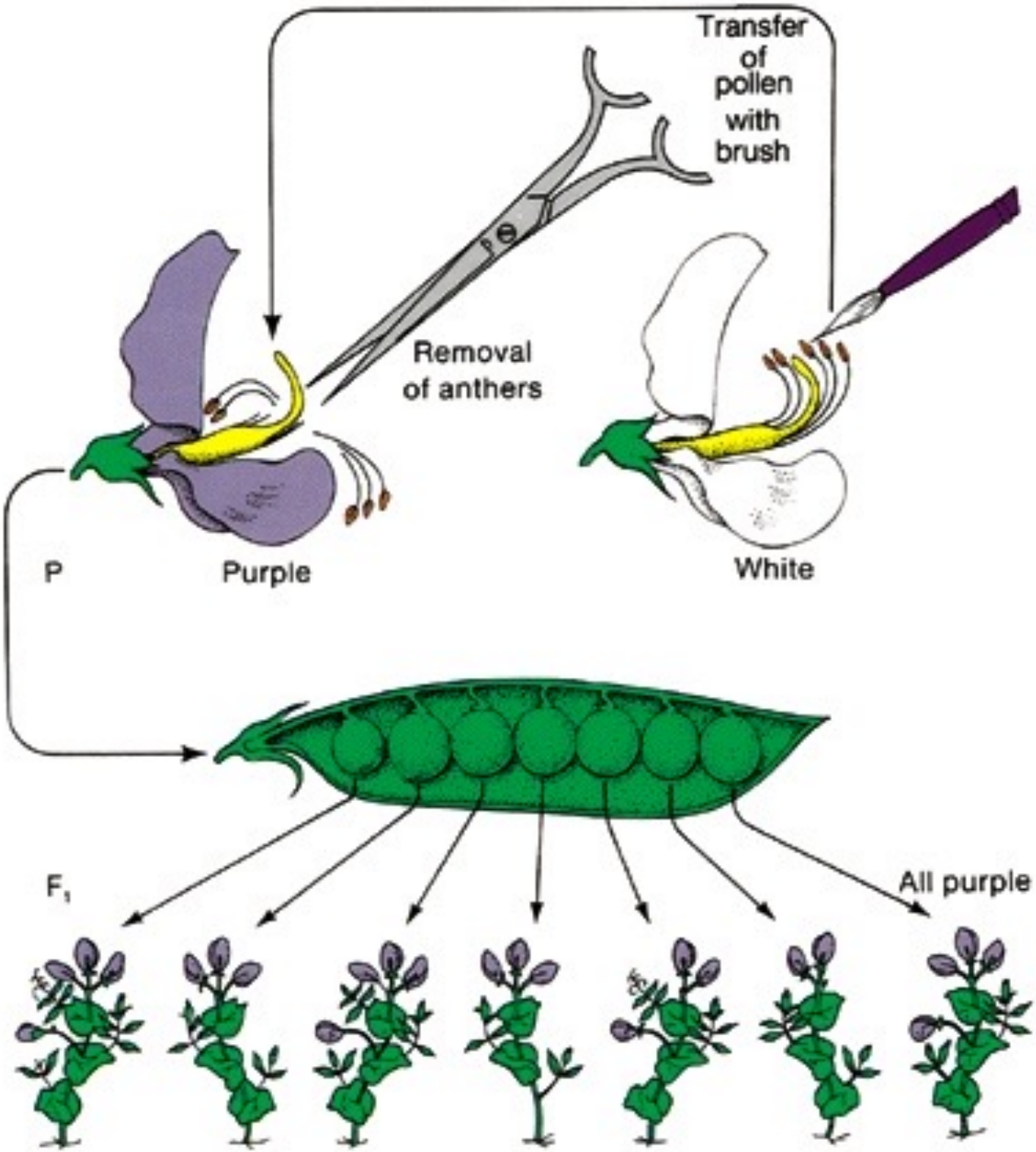
What are the mutations that underlie Mendels traits?

Table 1. The genes responsible for polymorphism for the traits that Mendel investigated in pea

Mendel's phenotypic polymorphism	Plant part affected	Classical symbol for mutation	Modern gene designation	Type of mutation
Tall versus dwarf	Stem	*le*	Gibberellin 3-oxidase (*GA3ox1*)	Single base change
Round versus wrinkled	Seed	*r*	Starch branching enzyme (*SBE1*)	Large insertion in last exon
Yellow versus green	Cotyledon	*i*	Mg dechelatase (*SGR*)	Large insertion in third intron
Pigment present versus absent	Testa and flower	*a*	bHLH transcription factor	Several alleles, usually producing a truncated protein
Green versus yellow	Pod	*gp*	Chlorophyll synthase (*ChlG*)	Large upstream deletion affecting gene expression
Parchment present versus absent	Pod	*p*	CLE41 transcription factor	Single base change producing premature stop codon
or	Pod	*v*	MYB26 transcription factor	Large upstream insertion
Normal versus fasciated	Stem and inflorescence	*fa*	CIK2/3 transcription factor	Small deletion producing premature stop codon

Many plants are hermaphrodites. They carry both male and female sex organs, and can self-fertilize




Transfer of pollen with brush
Removal of anthers
P
Purple
White
F_1
All purple

Monohybrid Cross

- **Mating between individuals that differ in only one trait,**
  - **yellow pea x green pea,**
  - **violet flower x white flower**
  - **tall x dwarf**
  - **round seed x wrinkled seed**
  - **full pod x constricted pod**
  - **etc.**

Monohybrid crosses

Generation

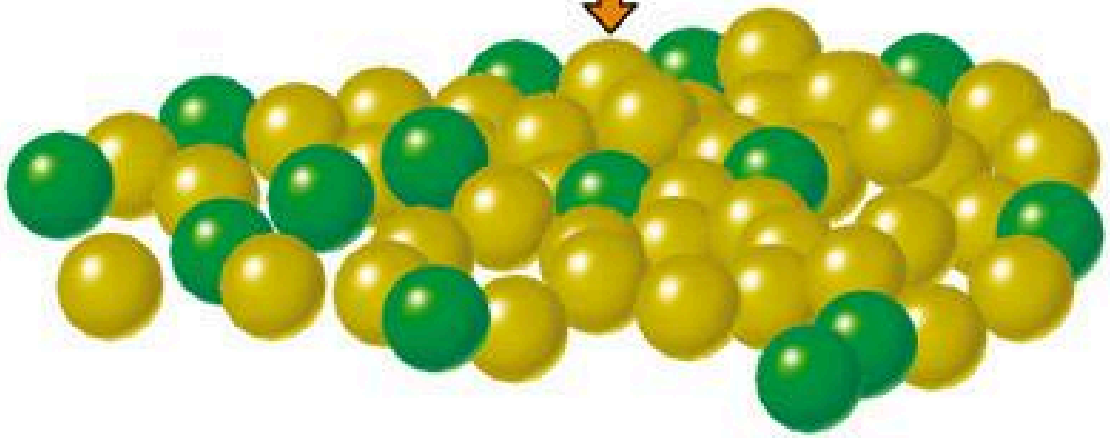
Parental (P) (pure-breeding)

First filial (F_1)

All yellow

Self-fertilization

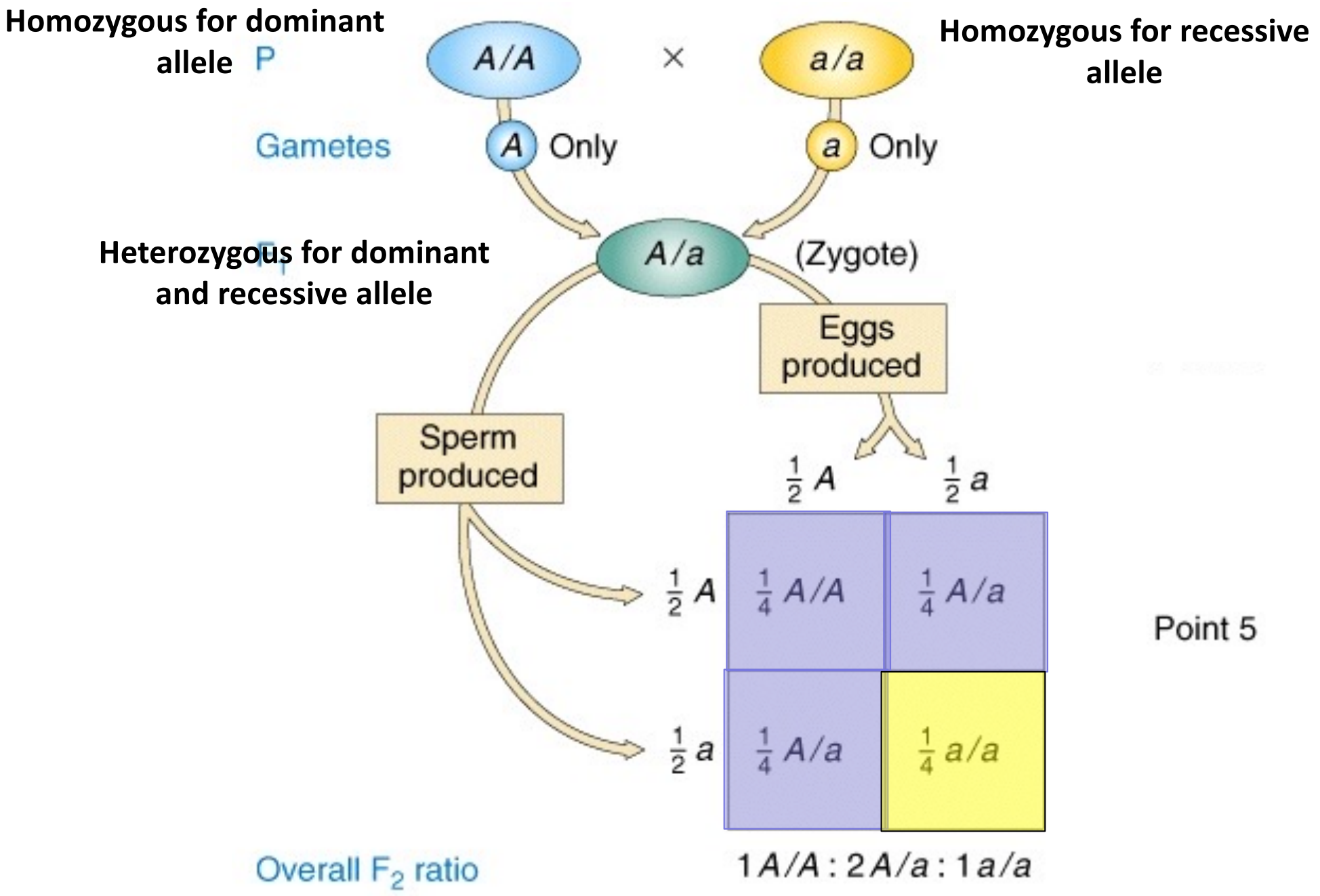
Second filial (F_2)

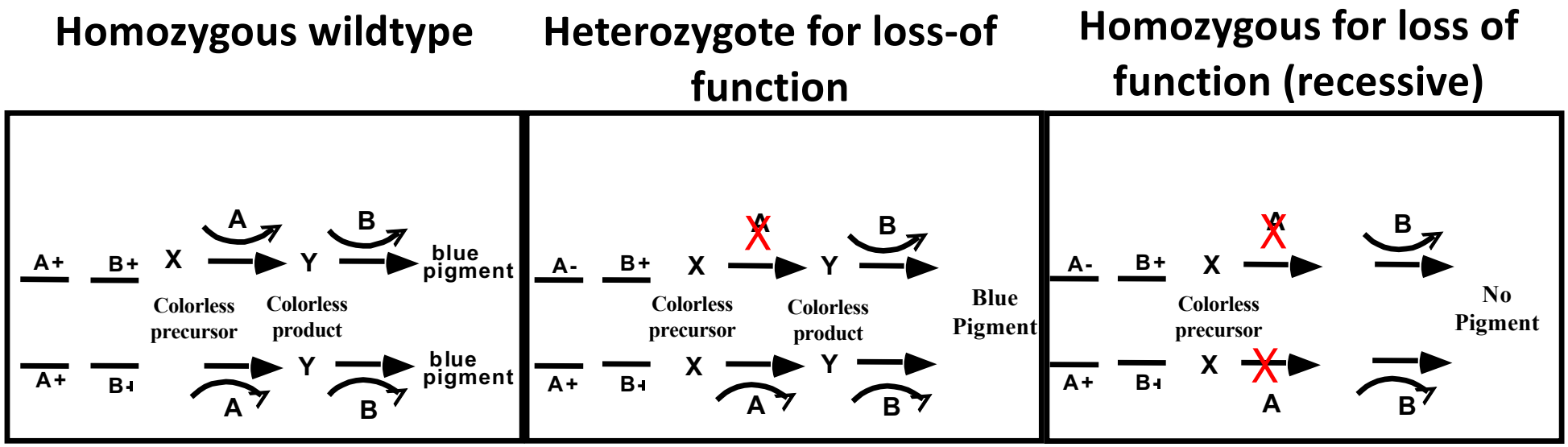


6022 yellow : 2001 green

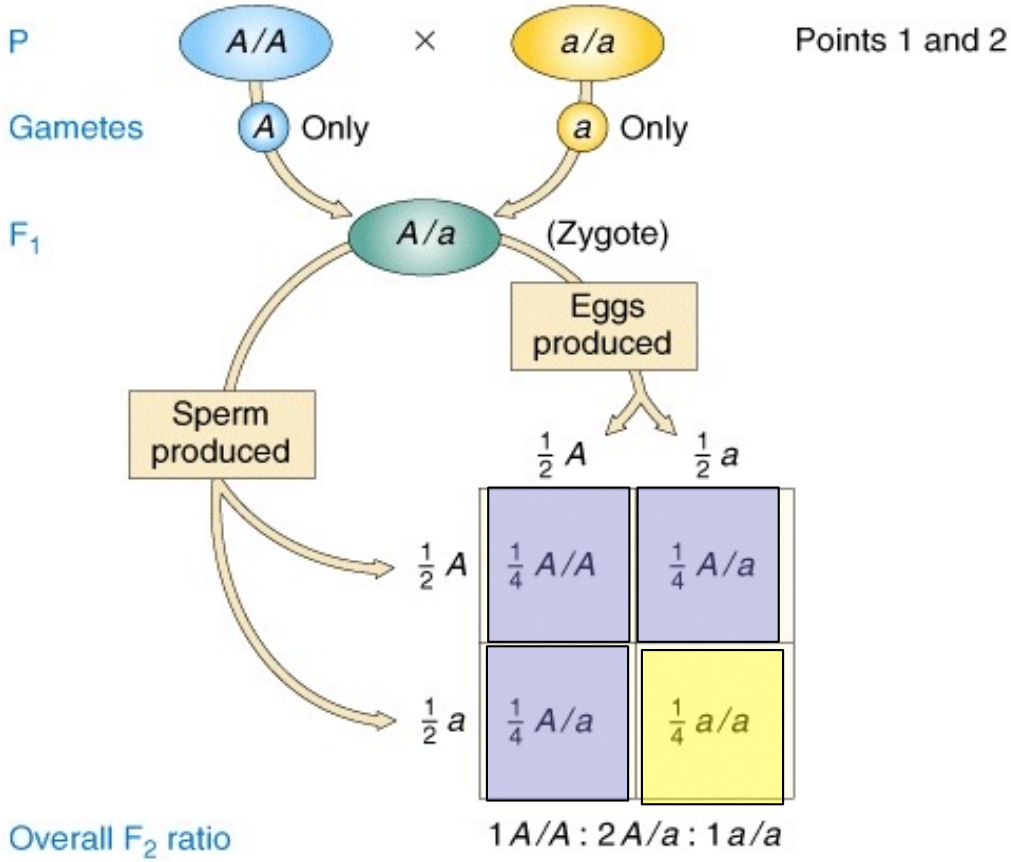
3 : 1

Independent segregation of A/a locus alleles during meiosis

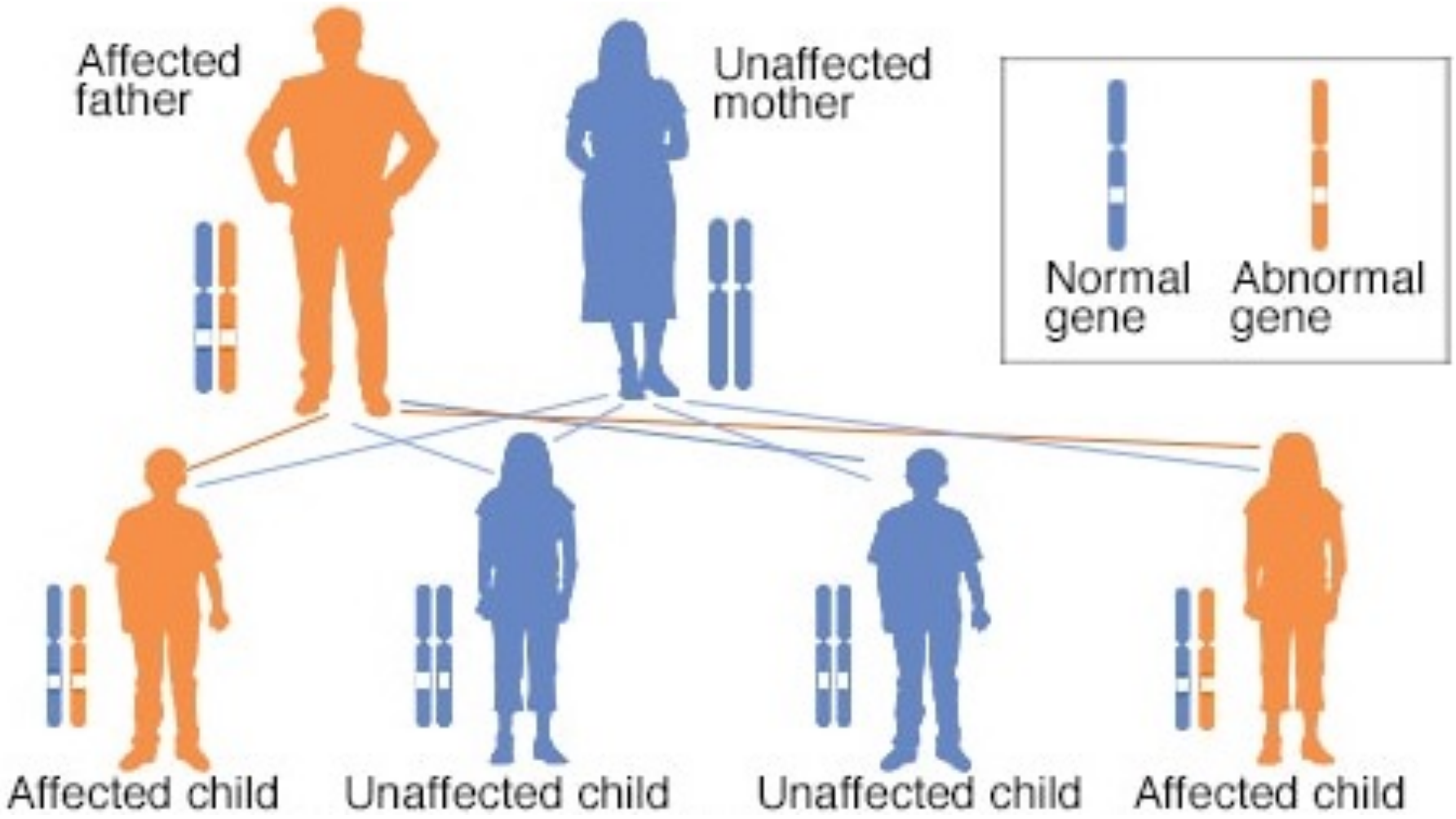




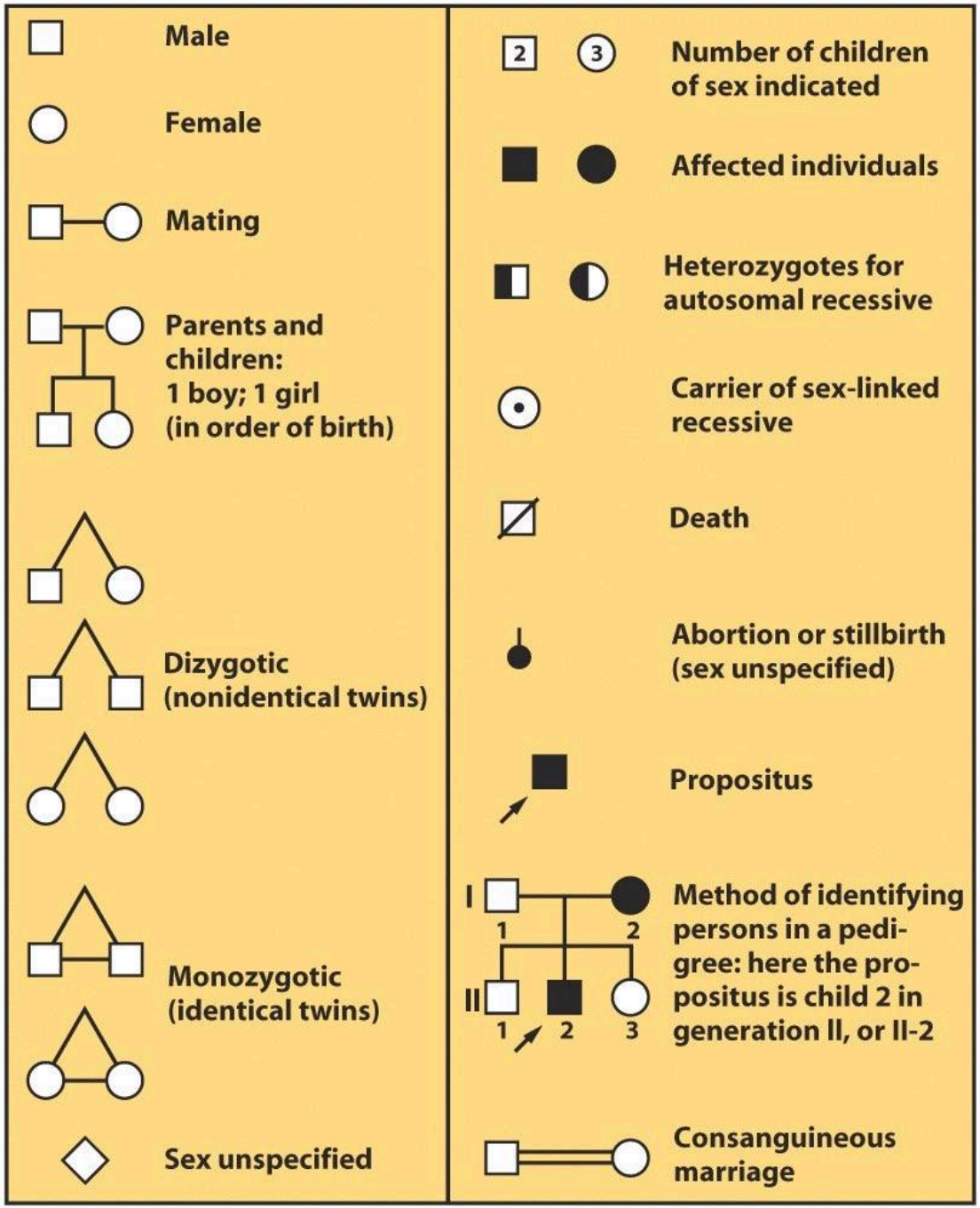
Complete dominance

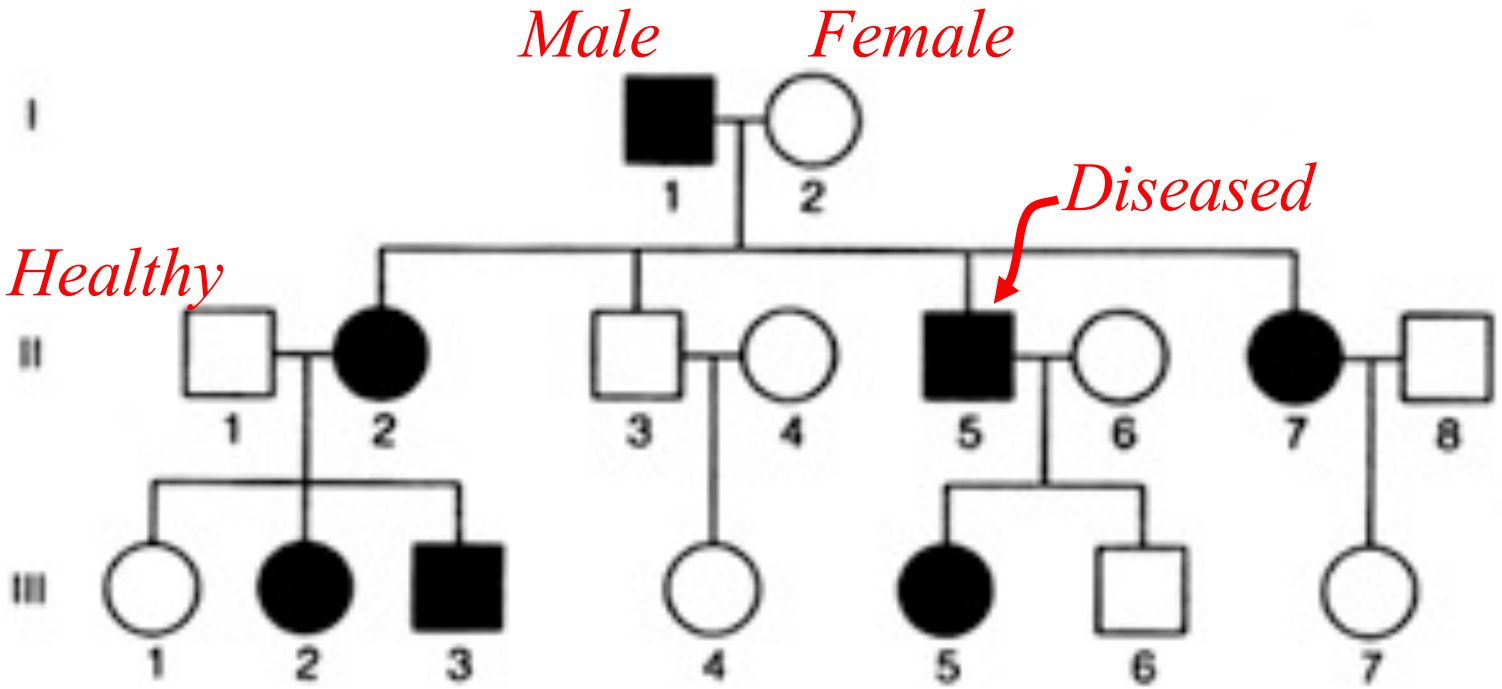


Dominant alleles are not always Wildtype. They can also encode versions of a protein that dominantly cause disease in the presence of a Wildtype allele

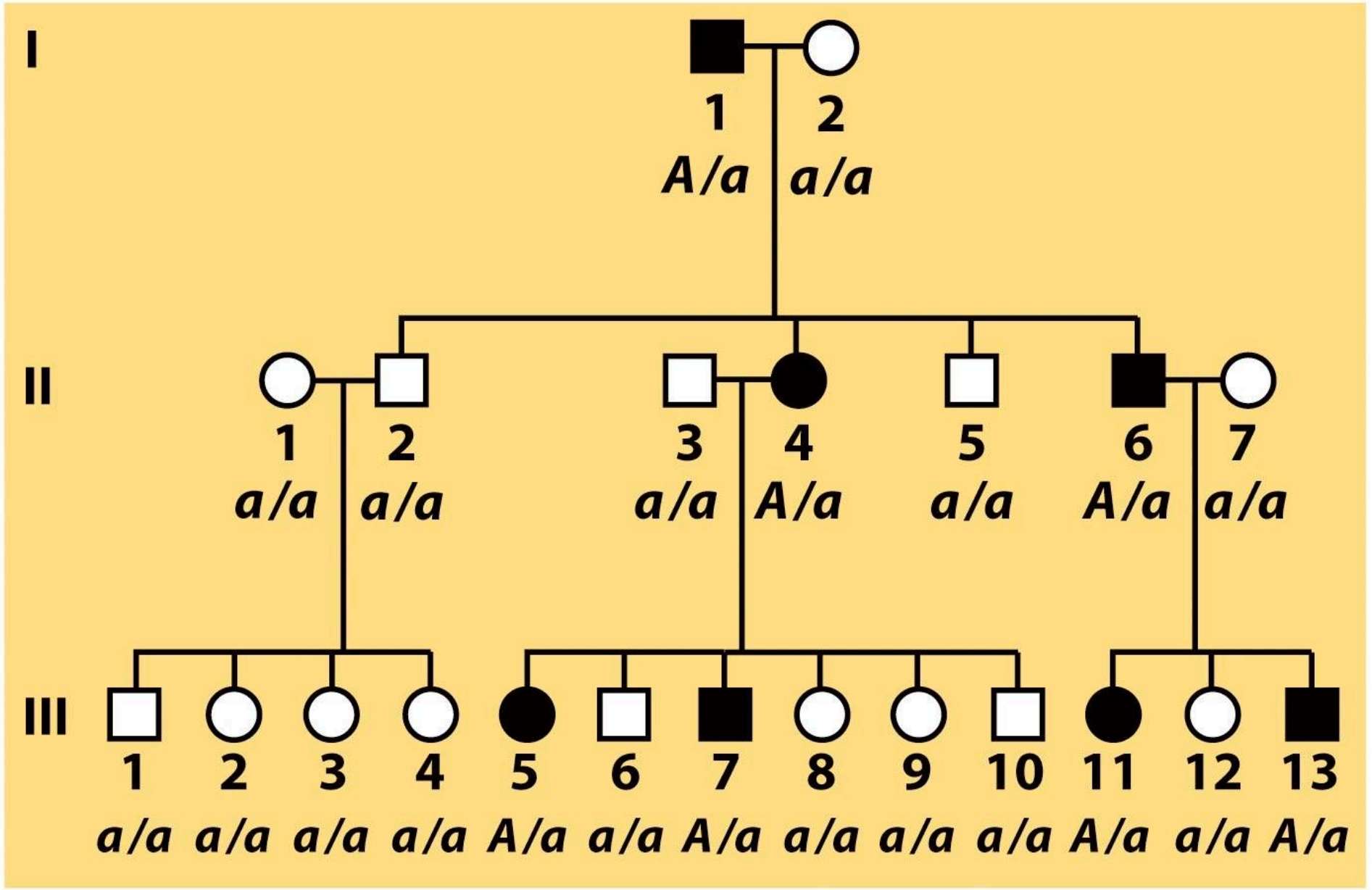


Look at human pedigree genetics in book

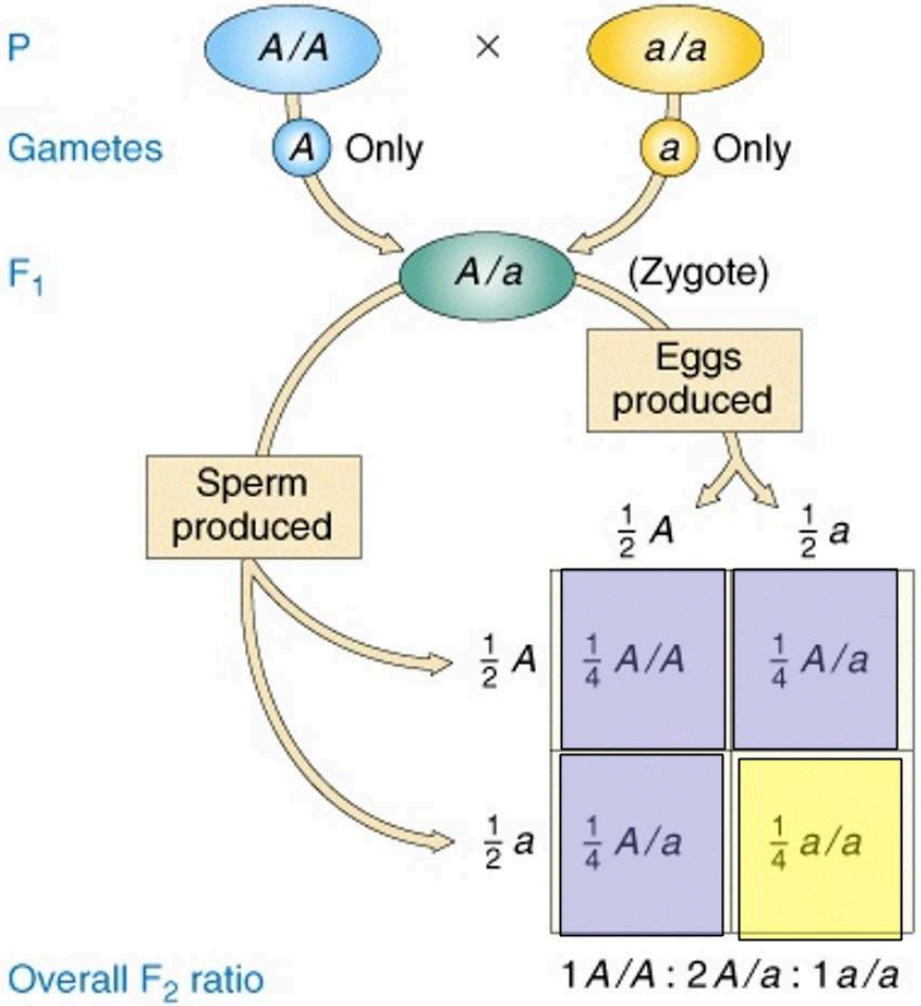


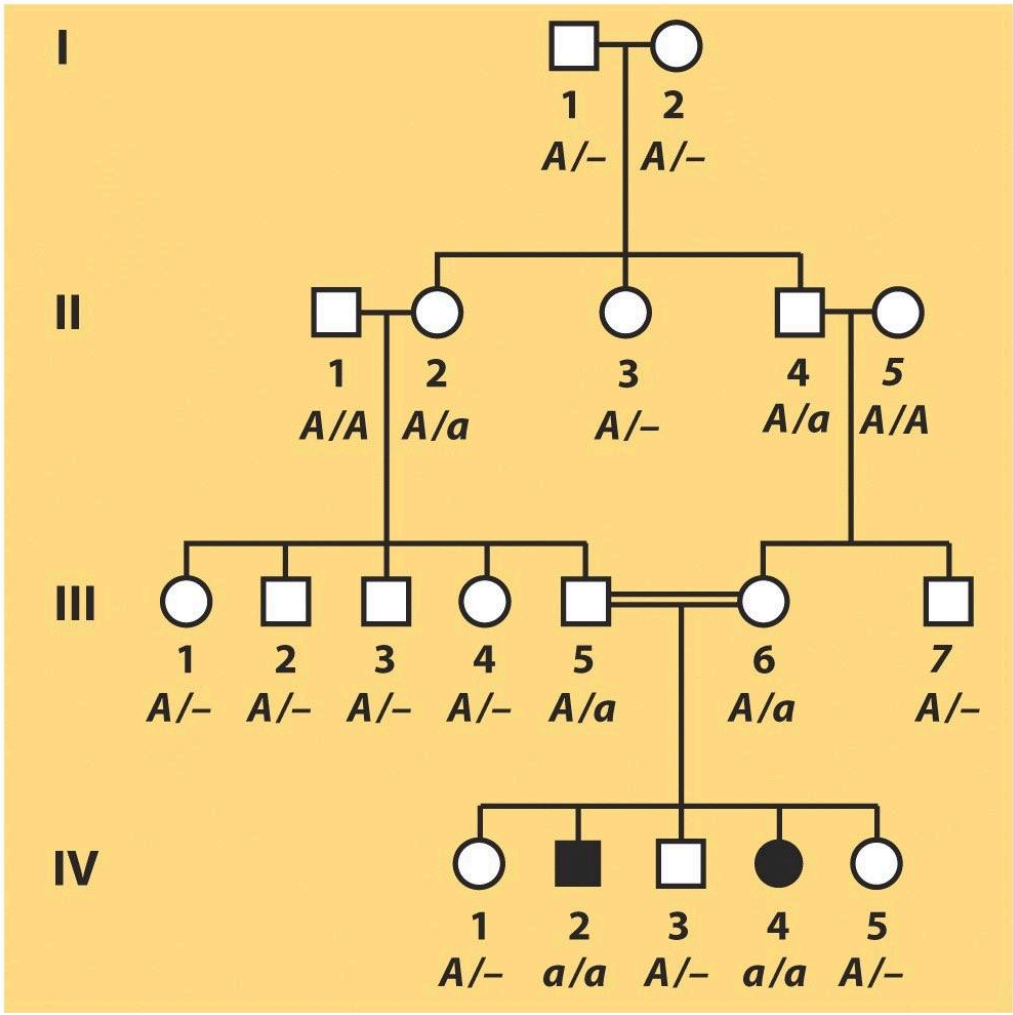

Male
Female
Diseased
Healthy
I
II
III
1
2
1
2
3
4
5
6
7
8
1
2
3
4
5
6
7

Dominant phenotype associated with A

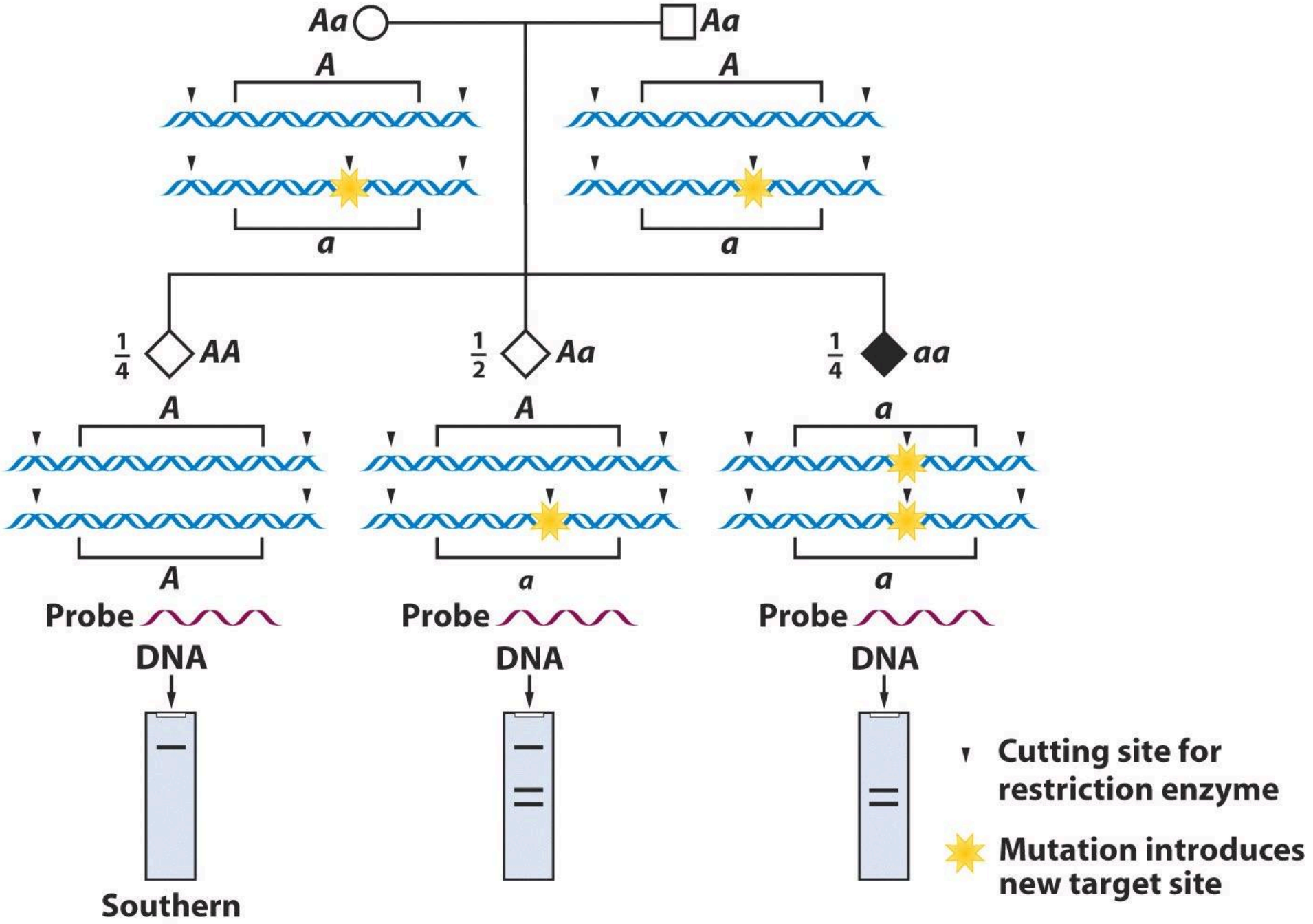


Recessive autosomal trait

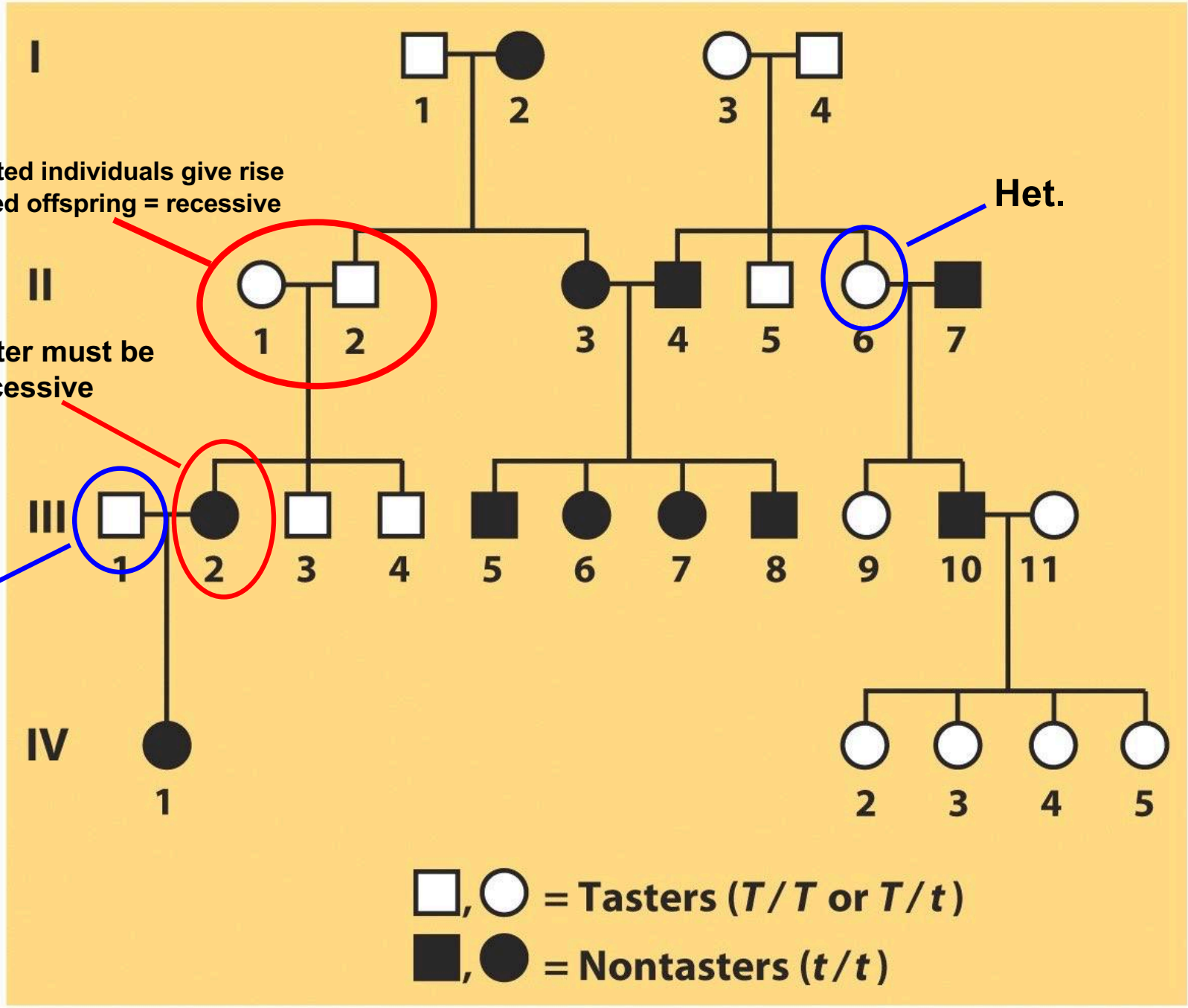




Molecular mapping: codominant markers



A highly polymorphic recessive trait



Two unaffected individuals give rise To an affected offspring = recessive trait

Het.

nontaster must be recessive

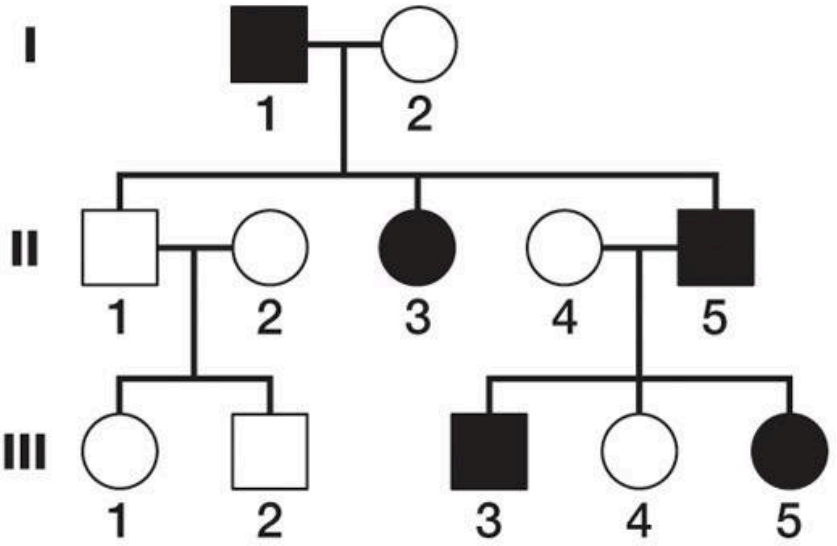
Het.

Foreshadowing a few lectures down the road.....

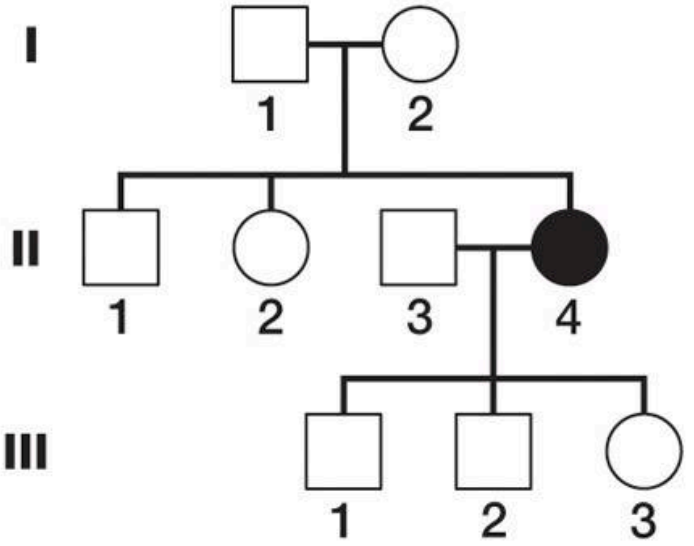
Homozygous loss-of- function of the RB gene in individual cells predisposes those cells to tumorigenesis (a recessive phenotype).

Why does inheritance of the disease state look like that of a dominant allele?

Familial retinoblastoma



Sporadic retinoblastoma



Manx cats: origin on the Isle of Man

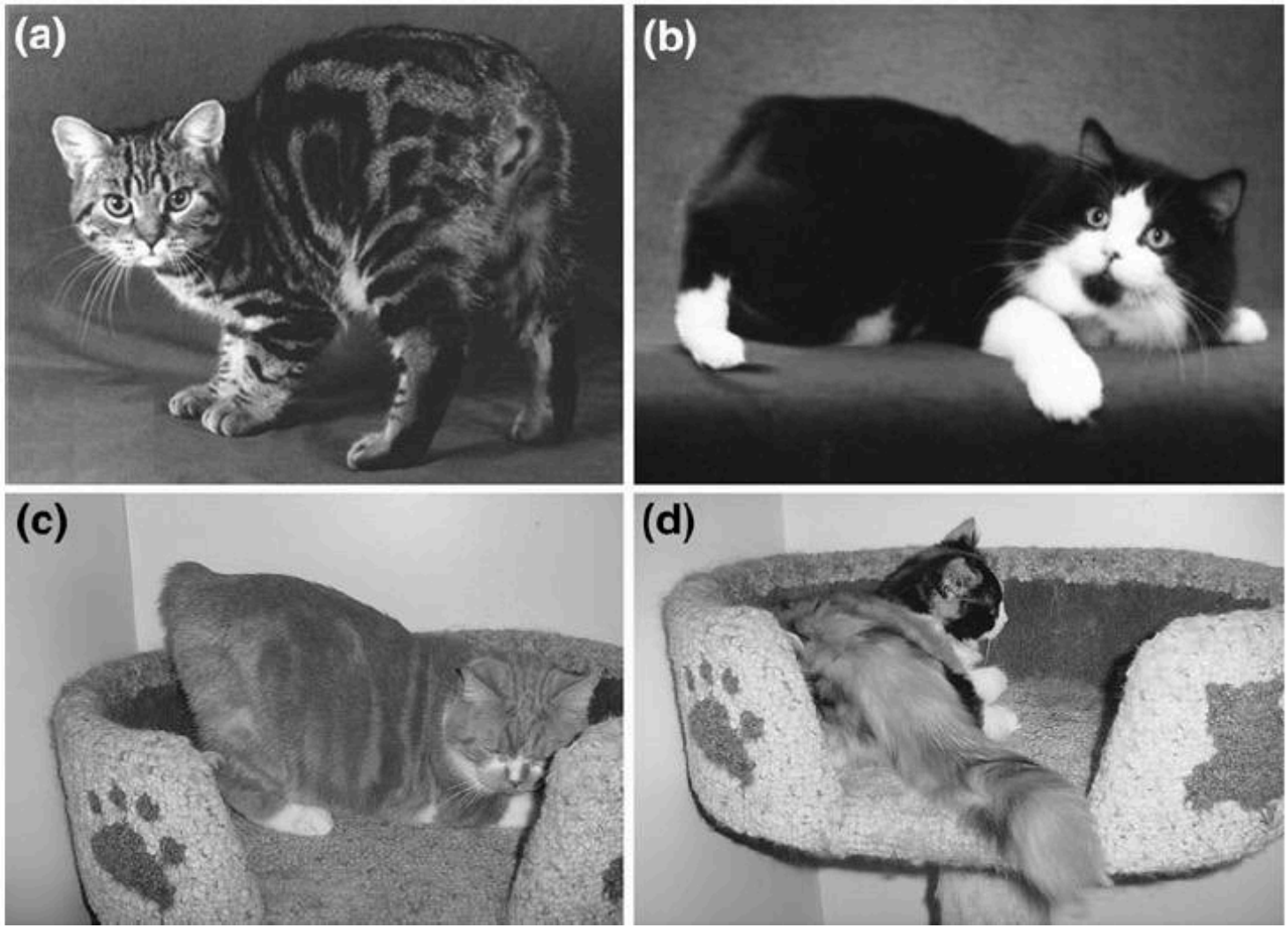


Fig. 1 Variable tail length phenotypes of the Manx cat. Manx cats exhibit varied tail lengths, including absence of the tail or rumpy (**a**), a minimal tail or rumpy-riser (**b**), a short tail or stumpy (**c**), and a full tail or longie (**d**). Cats pictured in a and b are Pedigree A2, V:3 and Pedigree A1, IV:4, respectively in Fig. 3

Manx cat genetics

x

Average litter: 2 tailless kittens : 2 tailed kittens

Manx cat genetics

x

Average litter: 2 tailless kittens : 2 tailed kittens

How do we explain the ratio of phenotypes in the F1 generation?

X

Average litter: 2 tailless kittens to 1 tailed kitten

- **Is the tailless allele recessive or dominant?**
- **Is the tailless cat homozygous or heterozygous?**
- **How can we explain the 2:1 offspring ratio**

Recessive lethality (associated with a dominant allele)

Manx is homozygous lethal

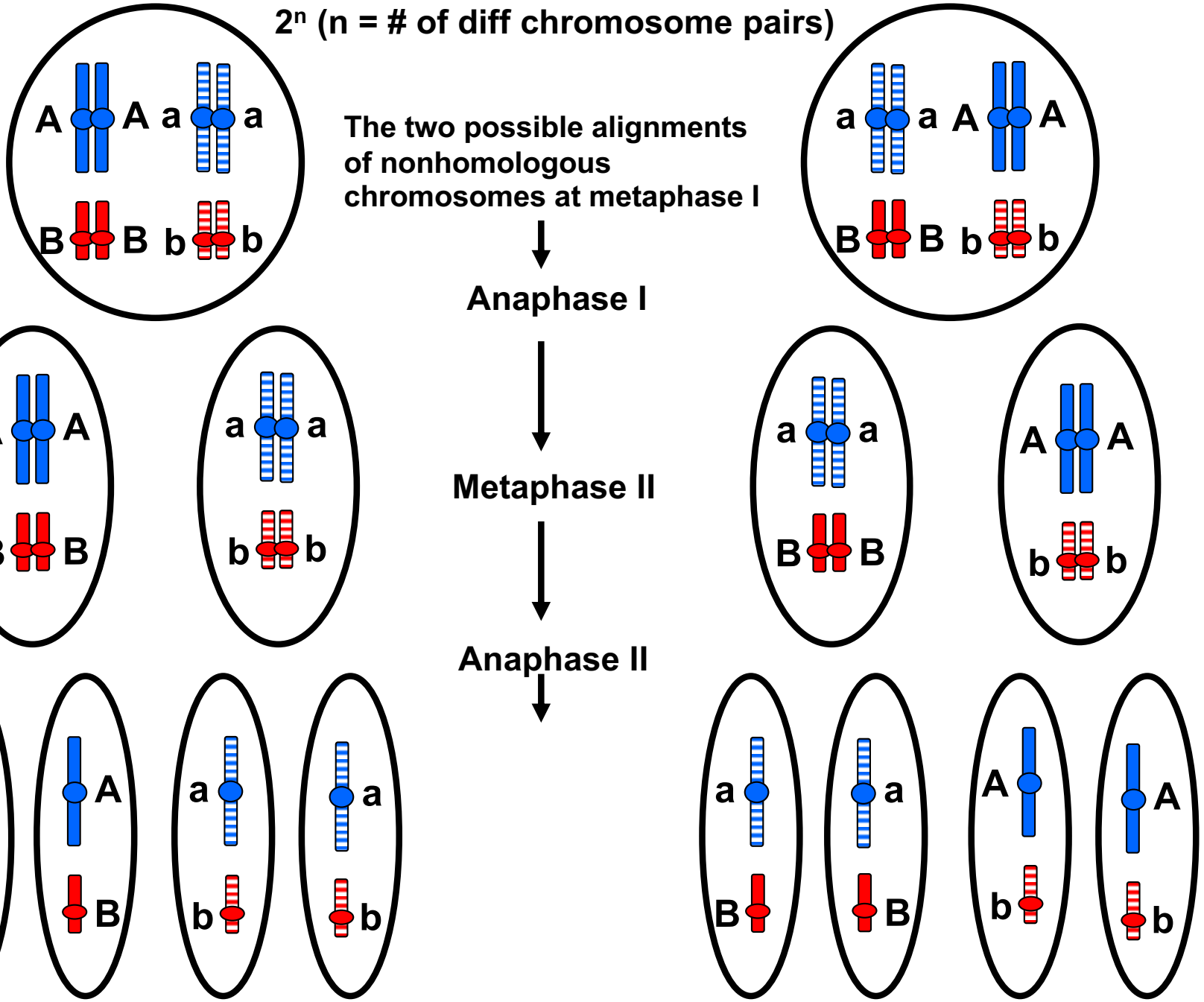
X

tailless Manx X tailless Manx		Tailless Male	
		M	**m**
Tailless Female	**M**	~~MM~~	Mm Tailless
	m	Mm Tailless	mm Tailed

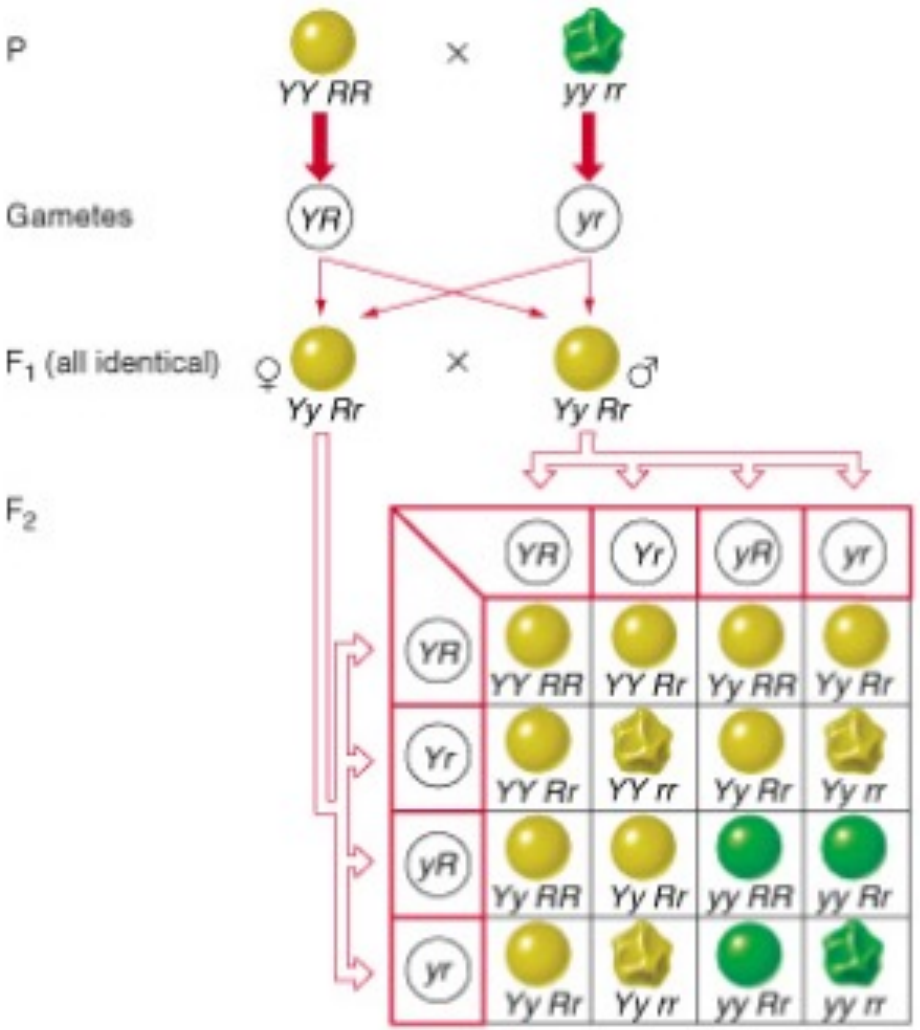
2 tailless : 1 tailed

Meiosis without recombination. Independent assortment of homologs to different Poles creates gamete diversity

2^n (n = # of diff chromosome pairs)



Dihybrid crosses



Type	Genotype	Phenotype	Number	Phenotypic ratio
Parental	*Y—R—*	yellow, round	315	9/16
Recombinant	*yy R—*	green, round	108	3/16
Recombinant	*Y—rr*	yellow, wrinkled	101	3/16
Parental	*yy rr*	green, wrinkled	32	1/16

Ratio of yellow (dominant) to green (recessive) = 12:4 or 3:1

Ratio of round (dominant) to wrinkled (recessive) = 12:4 or 3:1

Can also use two probability rules to predict Mendel's results.

(probability: the # of times expect an event / # times event could happen.)

- The Product rule (a.k.a. the AND rule): The probability of two independent outcomes occurring simultaneously is the product of their individual probabilities.

- The Sum rule (a.k.a. the OR rule): The probability of two mutually exclusive outcomes occurring is the sum of their individual probabilities.

We can draw it, or we can use the product rule to save time and space!

The probability of getting round, yellow peas is the probability of getting round peas AND the probability of getting yellow peas.
(3/4)(3/4) = 9/16

The probability of getting round, green peas is the probability of getting round peas AND the probability of getting green peas.
(3/4)(1/4) = 3/16

The probability of getting wrinkled, yellow peas is the probability of getting wrinkled peas AND the probability of getting yellow peas.
(1/4)(3/4) = 3/16

The probability of getting wrinkled, green peas is the probability of getting wrinkled peas AND the probability of getting green peas.
(1/4)(1/4) = 1/16

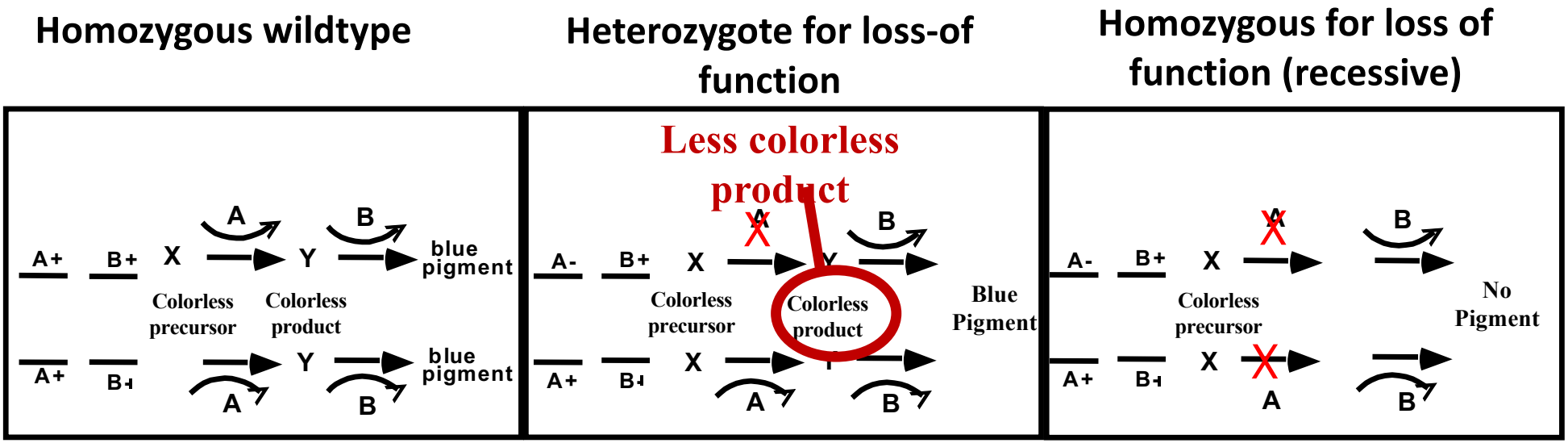
Extensions to simple mendelian analysis

Penetrance and expressivity

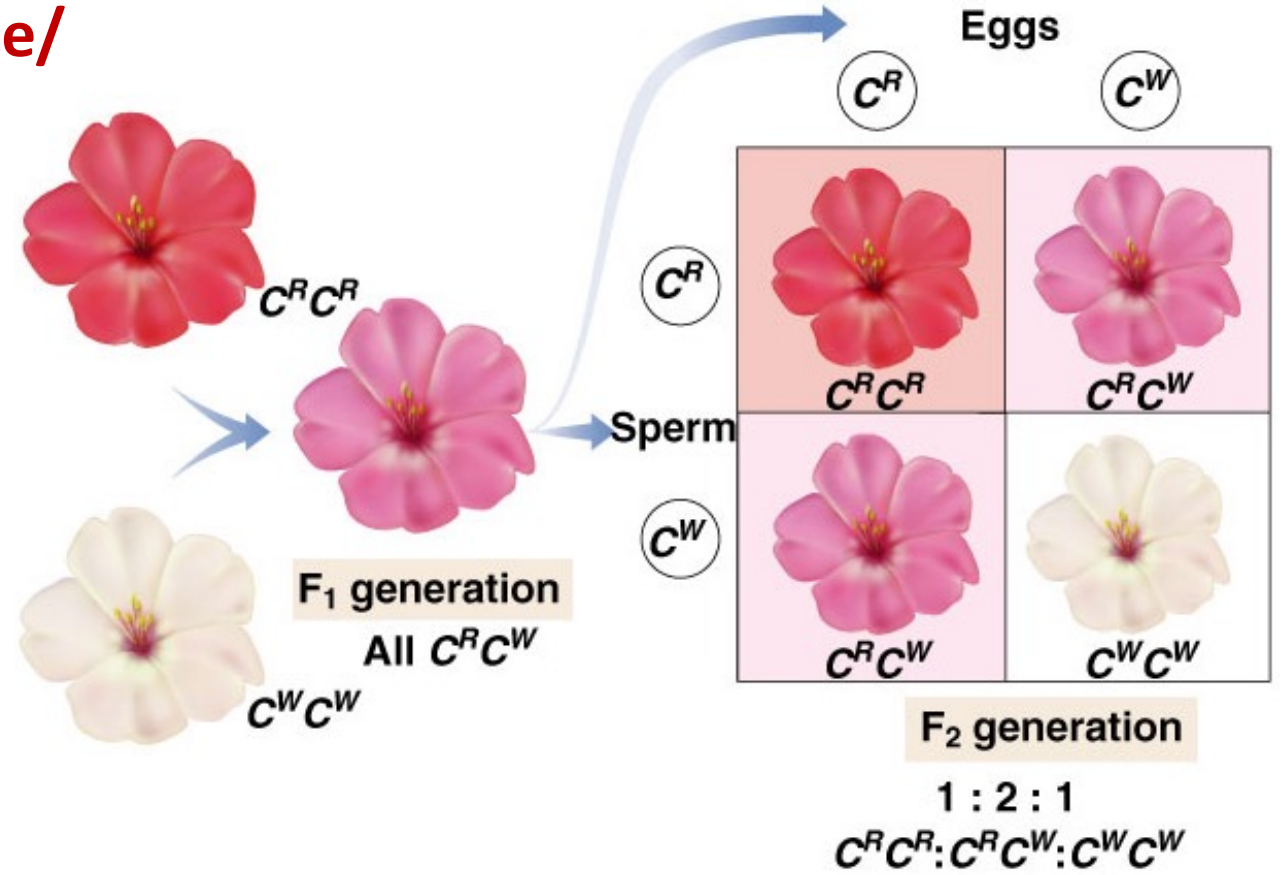
---Penetrance: The percentage of individuals with a given genotype expressing the expected phenotype. This depends on the whole genotype of the individual causing specific allelic interactions, and on the environment.

---Expressivity: Determines the extent to which a given genotype is expressed phenotypically in an individual.

1. **Incomplete dominance**
2. **Codominance**
3. **Multiple alleles**
4. **Recessive epistasis**
5. **Dominant epistasis**
6. **Recessive lethality**
7. **Gene interactions in different pathways**
8. **Complementary gene action**
9. **Duplicate genes**
10. **Pleiotropy**



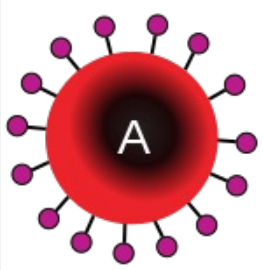
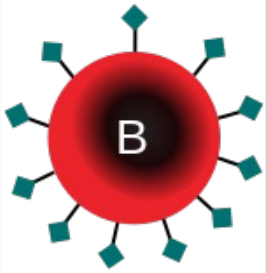
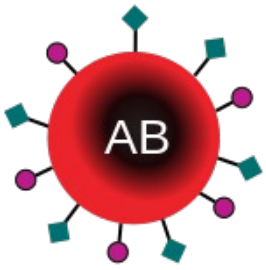
Incomplete dominance/ haploinsufficient



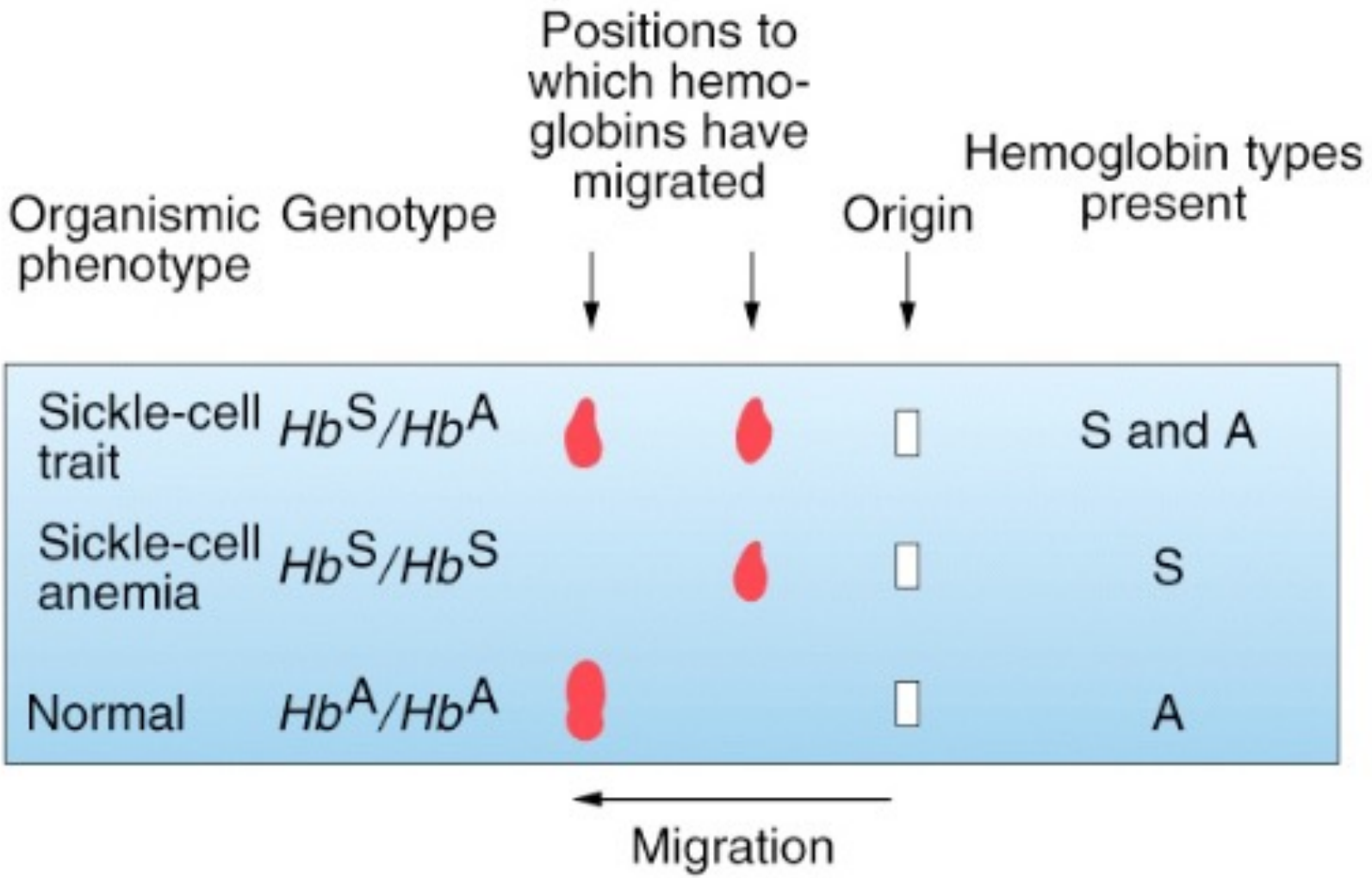
Codominance and multiple alleles: Blood group antigens

Three alleles:
I^A, I^B, or i

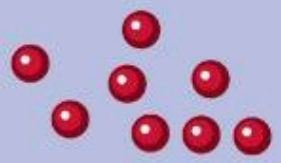
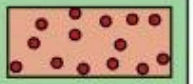
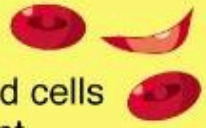
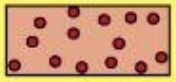
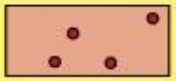
Expression of a A type sugar, a B type sugar, both, or no sugar on the I protein

	I^A,I^A or i,I^A	I^B,I^B or i,I^B	I^A,I^B	i,i
	Group A	Group B	Group AB	Group O
Red blood cell type				
Antibodies in plasma	 Anti-B	 Anti-A	None	  Anti-A and Anti-B
Antigens in red blood cell	 A antigen	 B antigen	 A and B antigens	None

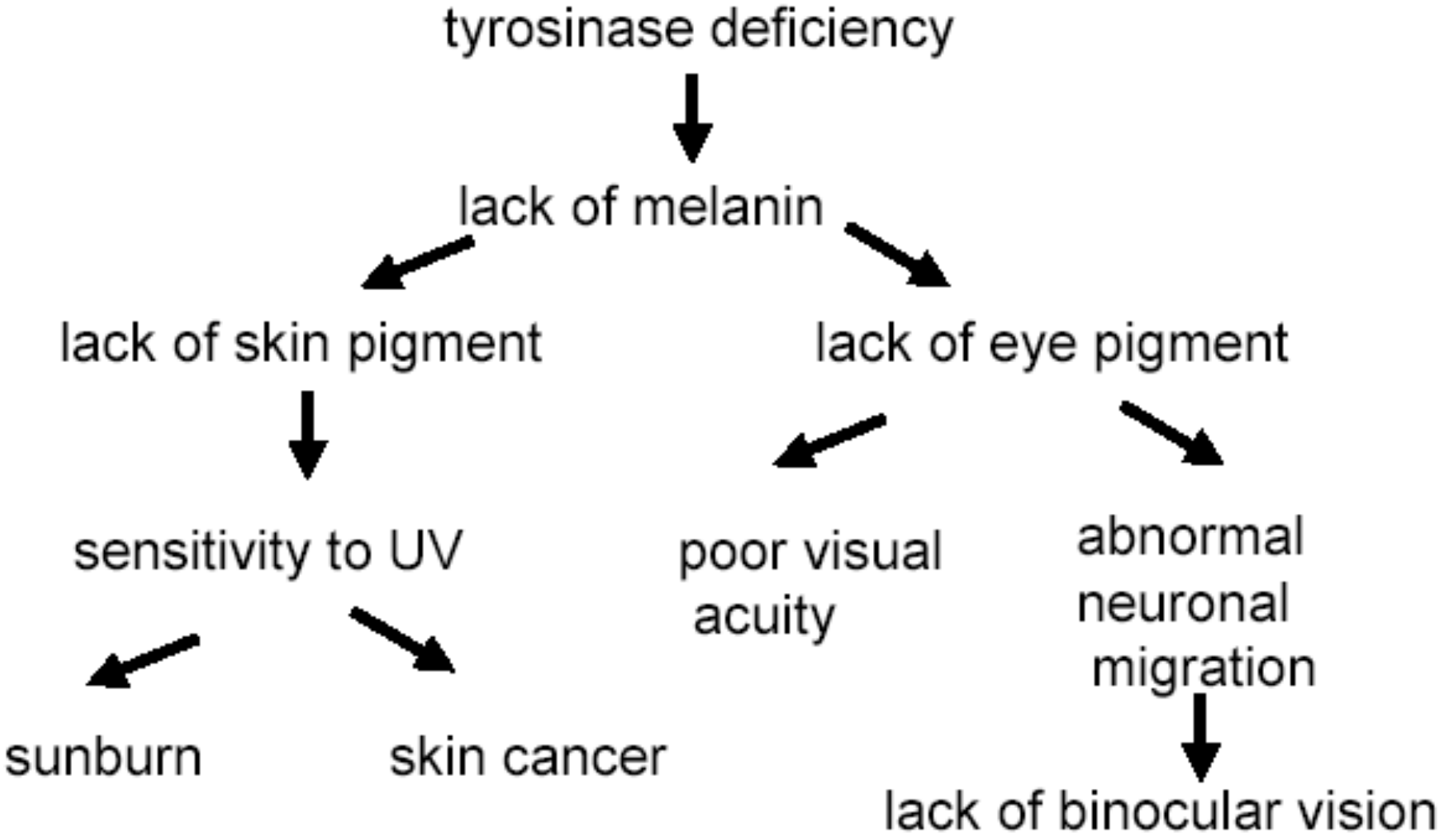
Dominance relationships are determined by the environment and the level of analysis. At the molecular level sickle cell and normal hemoglobin are codominant.



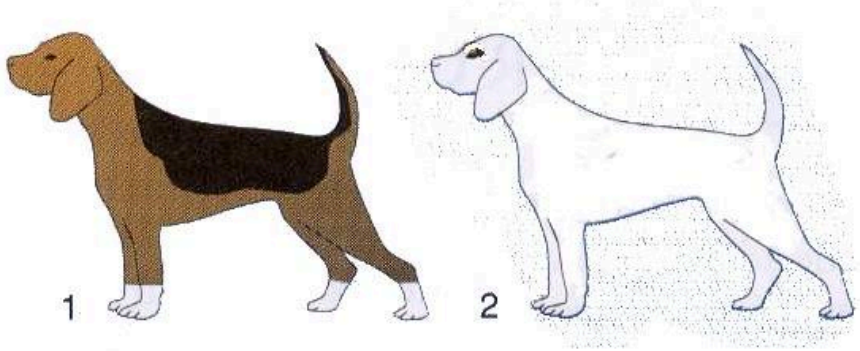
Pleiotropic mutations have effects on several different characters. In this case the dominance relationships depend on the phenotype examined.

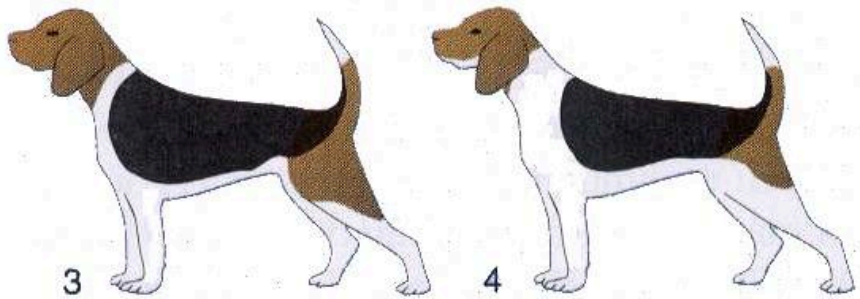
Phenotypes at Different Levels of Analysis	Normal *AA*	Carrier *AS*	Diseased *SS*	Dominance Relations at Each Level of Analysis
β–Globin polypeptide production				*A* and *S* are codominant
Red blood cell shape at sea level	 Normal	 Normal	 Sickled cells present	*A* is dominant *S* is recessive
Red blood cell concentration at sea level	 Normal cells	 Normal	 Lower	
Red blood cell shape at high altitudes	 Normal	 Sickled cells present	 Severe sickling	*A* and *S* show incomplete dominance
Red blood cell concentration at high altitudes	 Normal	 Lower	 Very low, anemia	
Susceptibility to malaria	 Normal susceptibility	 Resistant	 Resistant	*S* is dominant *A* is recessive

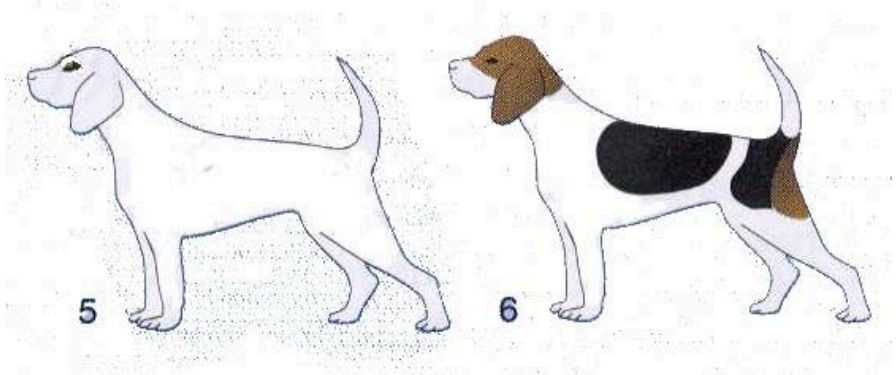
PLEIOTROPY


tyrosinase deficiency
lack of melanin
lack of skin pigment
lack of eye pigment
sensitivity to UV
poor visual acuity
abnormal neuronal migration
sunburn
skin cancer
lack of binocular vision

Penetrance





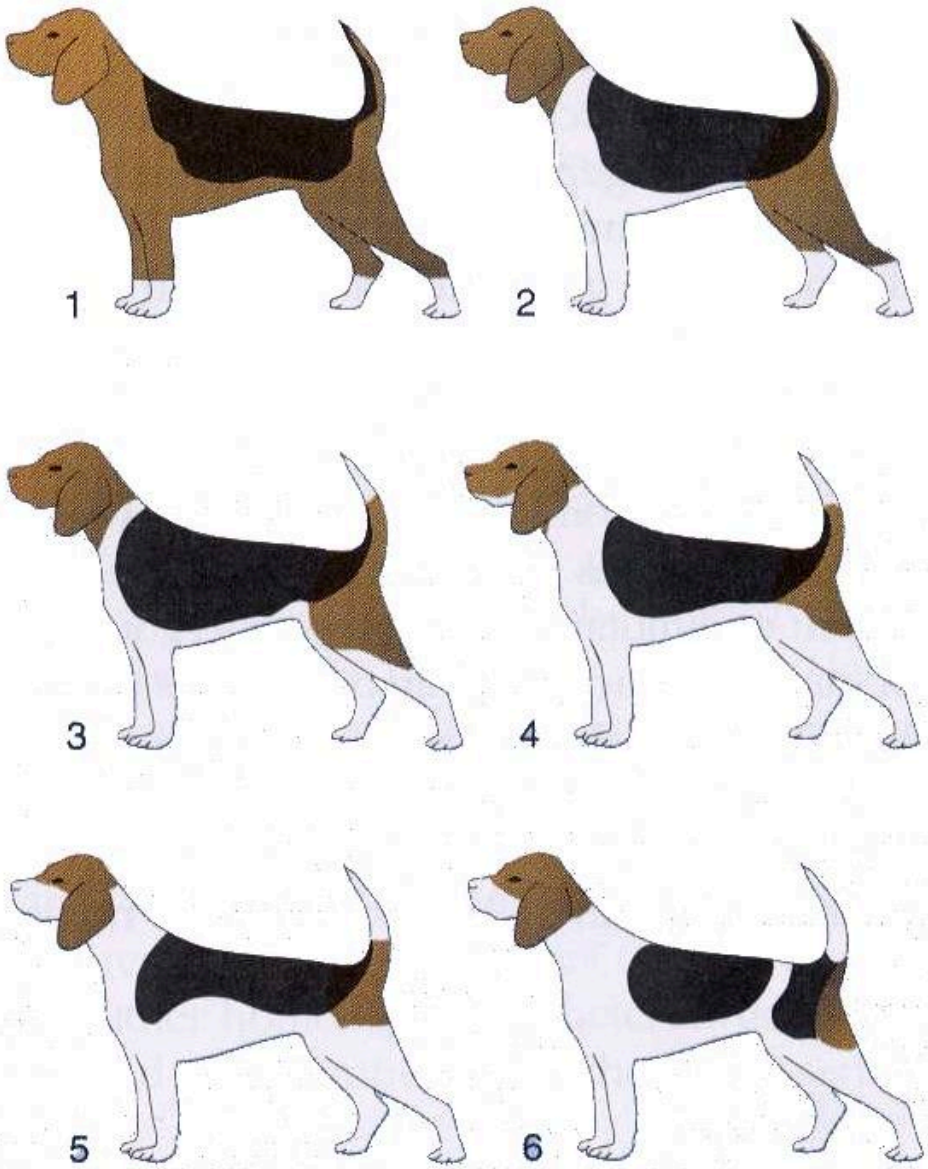


all the same genotype

…the frequency at which individuals with a given genotype manifest a specific phenotype.

- **4 of 6 dogs, or 66% of the population shows the phenotype, at some level,**
- **penetrance is usually referred to as a percentage.**

Expressivity



all the same genotype

…the degree or range within which a phenotype of a specific genotype is expressed

range of phenotypes

Phenotype strength may depend on the presence or absence of specific alleles at other genetic loci.

Himalayan rabbits carry a temperature-sensitive form of tyrosinase
Required for melanin synthesis

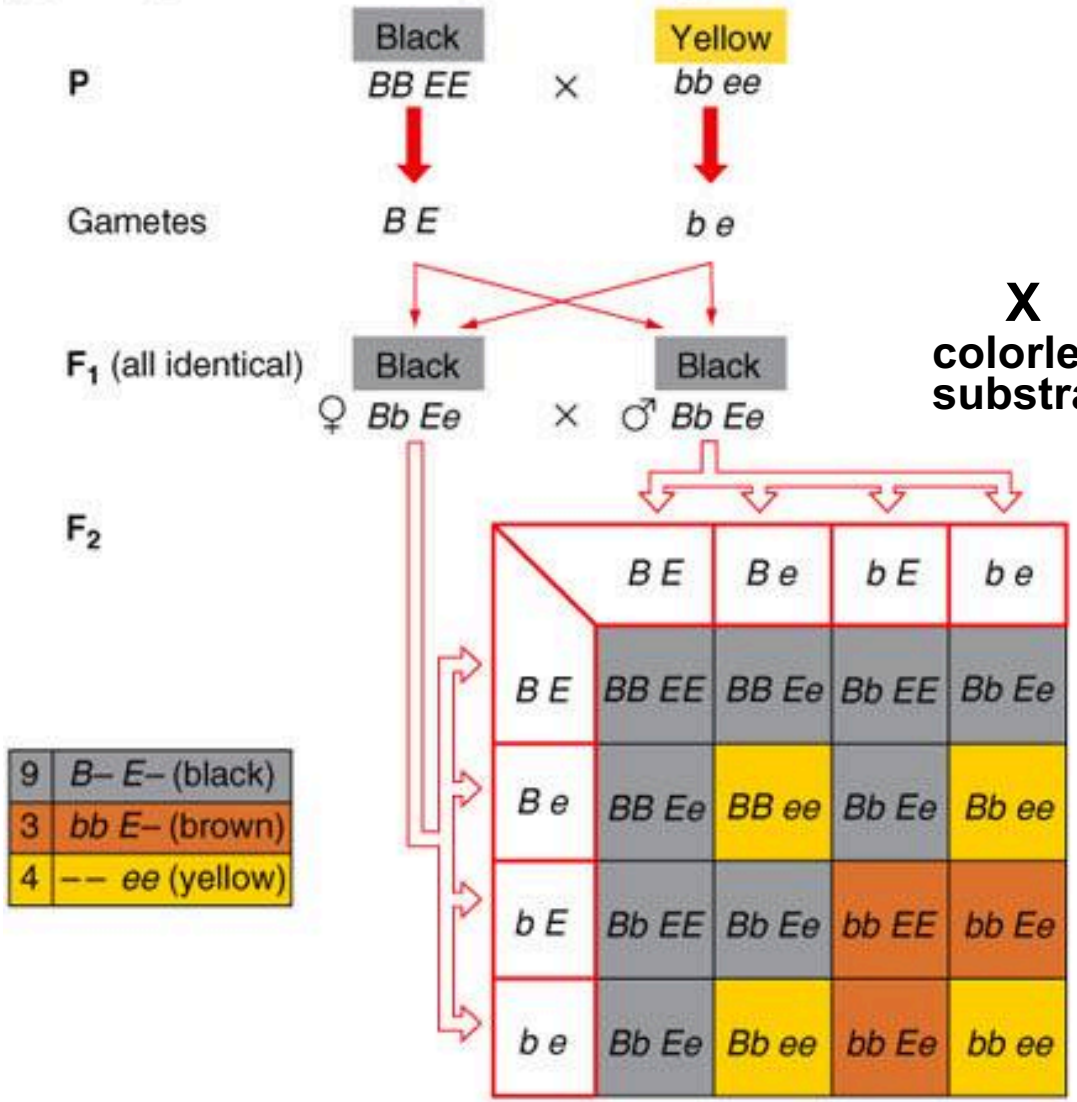
…Or phenotype may depend on the environment

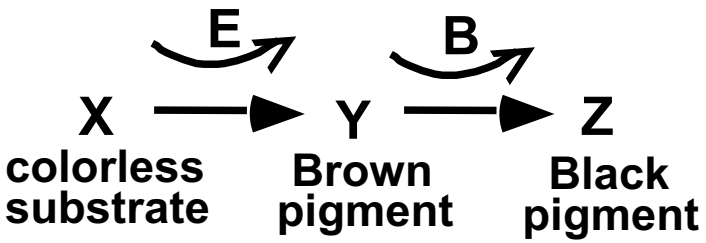
Epistasis and puppies

In epistasis the genotype at one locus masks the ability to determine the genotype at a second locus. Epistasis relationships are often found in biochemical pathways.

Recessive epistasis

Disruption of an early step in the pathway blocks the ability to determine the genotype with respect to genes involved in later steps





= 9: 3: 4

ee epistatic to bb

The functions of E and B

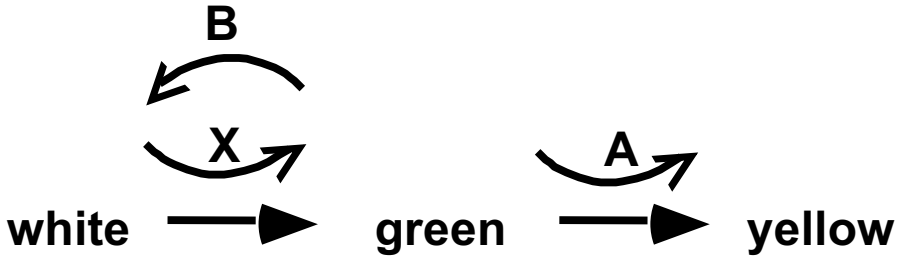
- E encodes melanocortin receptor 1 -- promotes production of eumelanin leaving dogs black or chocolate brown; null allele (e) means mc1r is not functional and dogs only produce phaeomelanin (yellow)
- B regulates distribution of melanin in hair shaft. B promotes dense packing of melanin (black) and b promotes less dense packing (chocolate brown).

Dominant epistasis produces ratios of 12:3:1 or 13:3

12:3:1---A dominant allele in one gene, B, masks the contribution of a second gene, A, (blocks color formation) regardless of the A allele. Thus in bb individuals the A- and aa genotypes can express themselves, resulting in a total of three different phenotypes.

Dominant epistasis: one possible mechanism

= 12 (white): 3(yellow): 1(green)

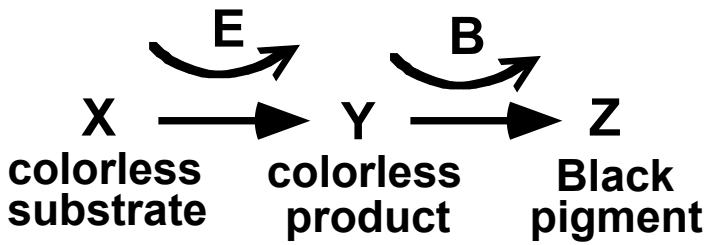


B acts to inhibit the processing of a white precursor into a green product.

In the absence of the B gene product the A product processes the green precursor into a yellow product.

Complementary gene action

Dominant alleles from two different genes must be present to produce a particular phenotype.



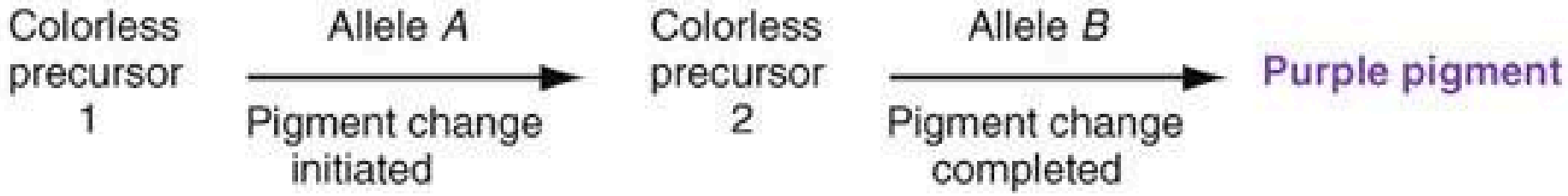
= 9: 7

	BE	Be	bE	be
BE	BBEE (Black)	BBEe (Black)	BbEE (Black)	BbEe (Black)
Be	BBeE (Black)	BBee (Golden)	BbeE (Black)	Bbee (Golden)
bE	bBEE (Black)	bBEe (Black)	bbEE (Golden)	bbEe (Golden)
be	bBeE (Black)	bBee (Golden)	bbeE (Golden)	bbee (Golden)

Notice that if we had a way to distinguish colorless product X from colorless product Y this would be an example of recessive epistasis.


How many genes contribute to a process
(flower color)

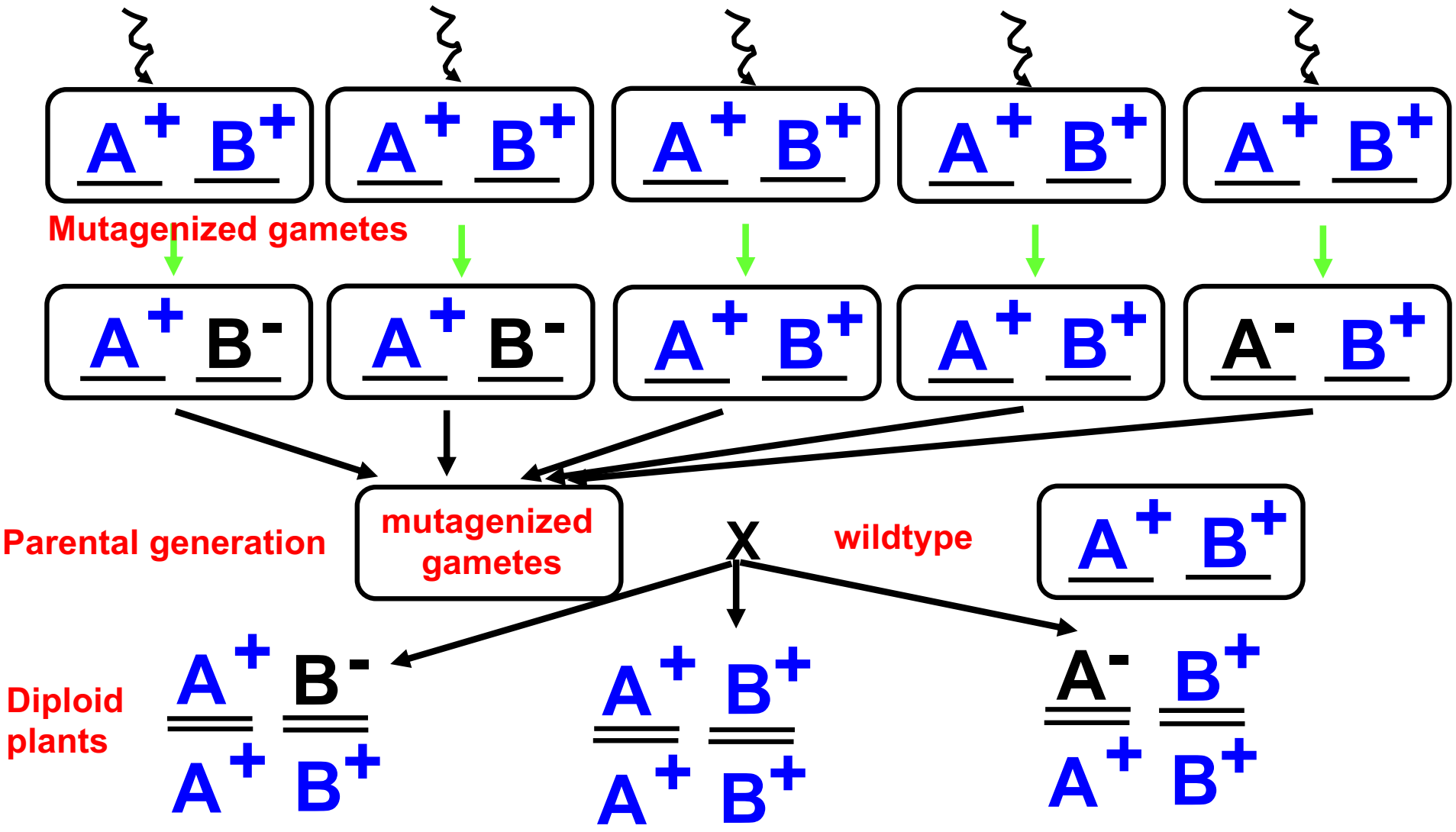
(c) A biochemical model for purple pigment production



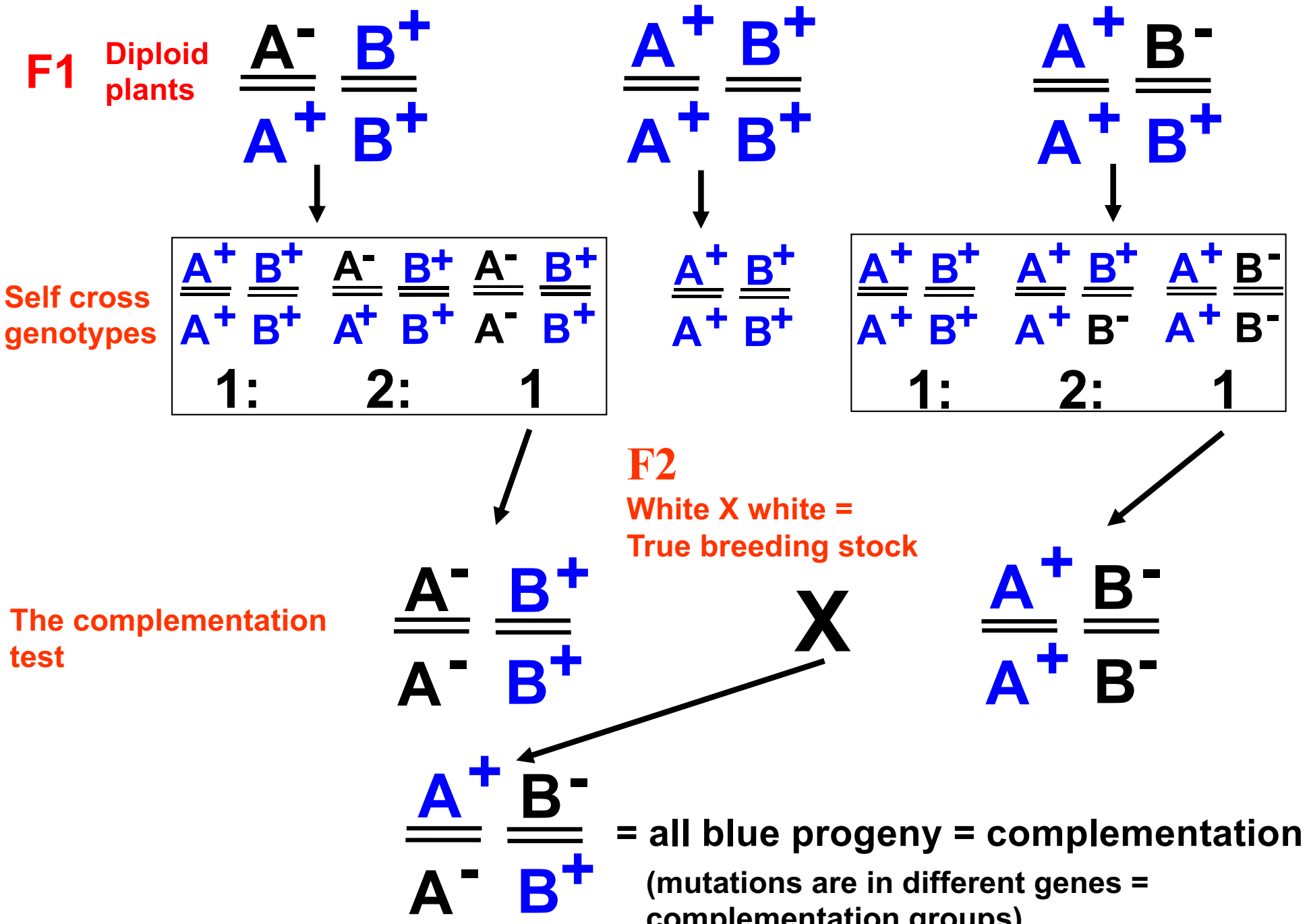
Complementation testing 1

How many genes are required to generate a particular phenotype such as flower color ?

1. Carry out a genetic screen for mutations that lack flower color.
2. Carry out complementation testing to determine which mutations effect the same gene.

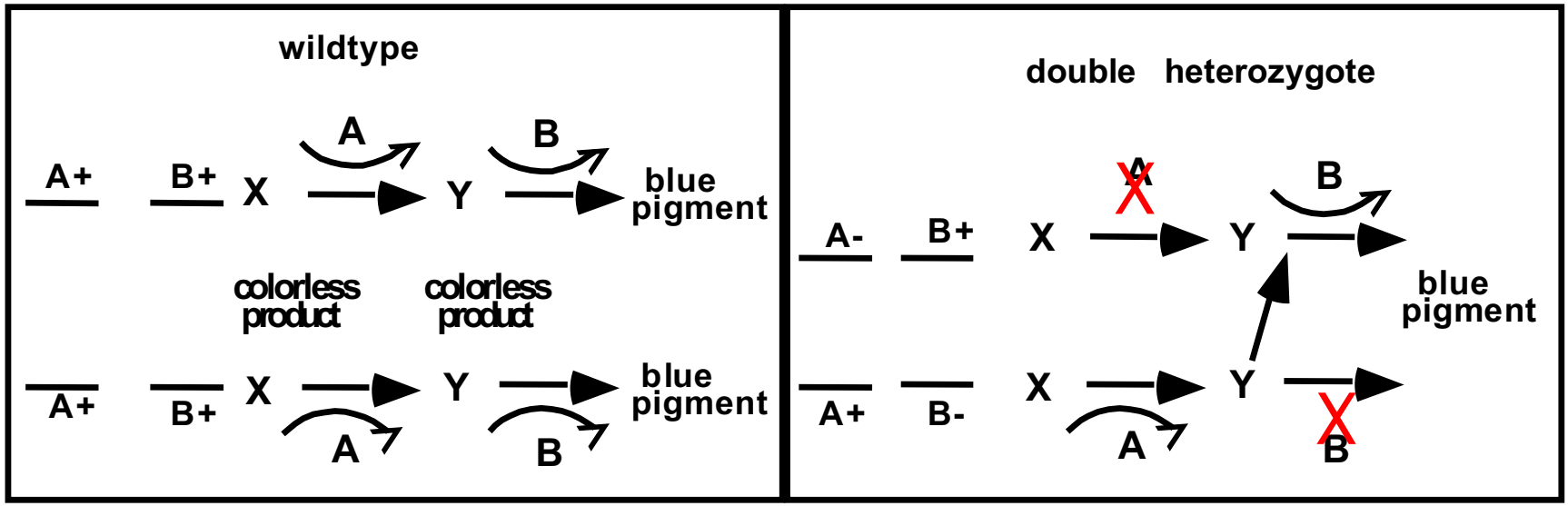


Complementation testing 2

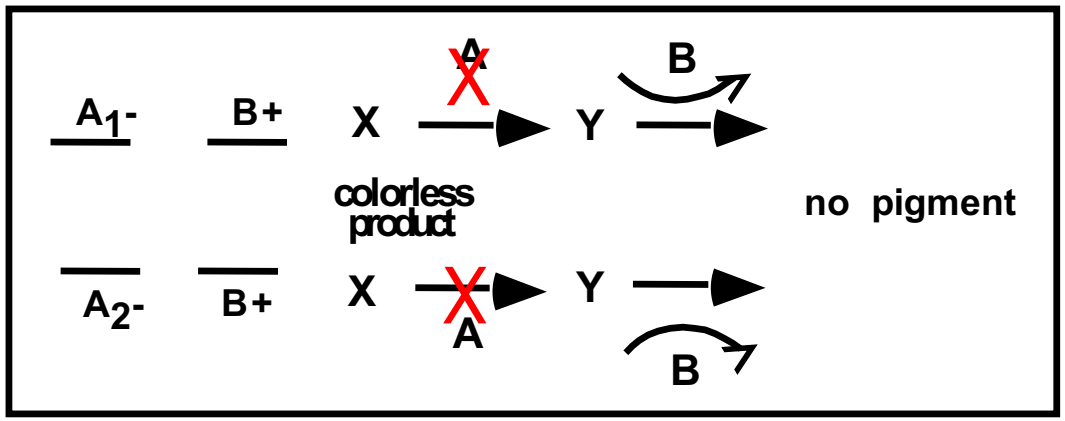


Complementation testing 3

$\frac{A-}{A-}$ $\frac{B+}{B+}$ X $\frac{A+}{A+}$ $\frac{B-}{B-}$ = all blue progeny = complementation



$\frac{A_1-}{A_1-}$ $\frac{B+}{B+}$ X $\frac{A_2-}{A_2-}$ $\frac{B+}{B+}$ = all white progeny = noncomplementation



How many different genes are required for a particular trait?
Genetic screens and complementation testing.

Phenotype

Genotype

Molecular mechanism

Matings between different white-flowered lines produce purple progeny

Mutations at different genes

Affected genes encode different proteins that are required for the same biochemical pathway

Complementation can occur during cell fusion.