Genetics

2017.2.27

Introduction to Genetics

——Genetics, better life for all

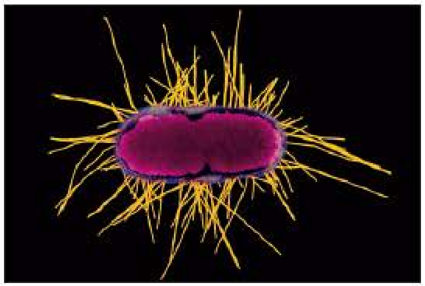
A family portrait. The extended family shown here includes members of four generations.

Genes——Heredity——Genetics

- **Heredity** is the way genes transmit biochemical, physical, and behavioral traits from parents to offspring.
- **Genetics** is the science of heredity.

The core of Genetics is

the Study of Biological Information


(a) Bacteria


(b) Clown fish


(c) Lion


(d) Oak tree


(e) Poppies


(f) Hummingbird


(g) Red-eyed tree frog


(h) Humans

The biological information in DNA generates an enormous diversity of living organisms

- What constitutes biological information?
- How the information becomes biological traits?
- How the information be propagated through time?
- How the information changes?
- ……

Then,

Genetics is the science of studying ....

Gene is the interface of heredity, development and evolution

```
S. cerevisiae     ---PGSAKKGATLFKTRCQQCHTIEEGGPNKV
A. thaliana       ----GDAKKGANLFKTRCAQCHTLKAGEGNKI
C. elegans        ---AGDYEKGKKVYKQRCLQCHVVDS-TATKT
D. melanogaster   ---AGDVEKGKKLFVQRCAQCHTVEAGGKHKV
M. musculus       ---MGDVEKGKKIFVQKCAQCHTVEKGGKHKT
H. sapiens        ---MGDVEKGKKIFIMKCSQCHTVEKGGKHKT
                      *   **  ..  .* *** .       *

S. cerevisiae     GPNLHGIFGRHSGQVKGYSYTDANINKNVKW
A. thaliana       GPELHGLFGRKTGSVAGYSYTDANKQKGIEW
C. elegans        GPTLHGVIGRTSGTVSGFDYSAANKNKGVVW
D. melanogaster   GPNLHGLIGRKTGQAAGFAYTDANKAKGITW
M. musculus       GPNLHGLFGRKTGQAAGFSYTDANKNKGITW
H. sapiens        GPNLHGLFGRKTGQAPGYSYTAANKNKGIIW
                  ** ***. ** .*   *. *. **  * .. *

S. cerevisiae     DEDSMSEYLTNPKKYIPGTKMAFAGLKKEKDR
A. thaliana       KDDTLFEYLENPKKYIPGTKMAFGGLKKPKDR
C. elegans        TKETLFEYLLNPKKYIPGTKMVFAGLKKADER
D. melanogaster   NEDTLFEYLENPKKYIPGTKMIFAGLKKPNER
M. musculus       GEDTLMEYLENPKKYIPGTKMIFAGIKKKGER
H. sapiens        GEDTLMEYLENPKKYIPGTKMIFVGIKKKEER
                    ...  *** *********** * *.**  .*

S. cerevisiae     NDLITYMTKAAK---
A. thaliana       NDLITFLEEETK---
C. elegans        ADLIKYIEVESA---
D. melanogaster   GDLIAYLKSATK---
M. musculus       ADLIAYLKKATN---
H. sapiens        ADLIAYLKKATN---
                   ***  ..   .
```

cytochrome C protein

* Indicates identical and . indicates similar

(a) (b)

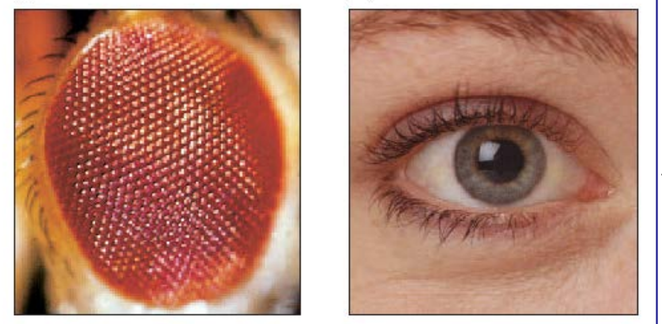
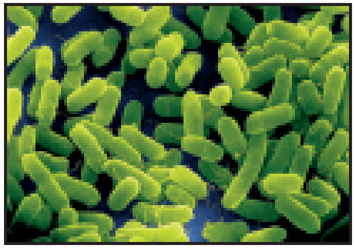
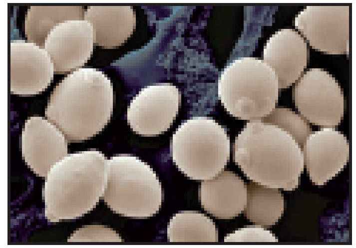
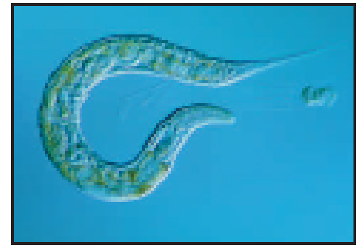


Figure 1.9 The eyes of insects and humans have a common ancestor. (a) A fly eye and **(b)** human eye.

***Pax*6**

Model Organisms in the Genetics Revolution

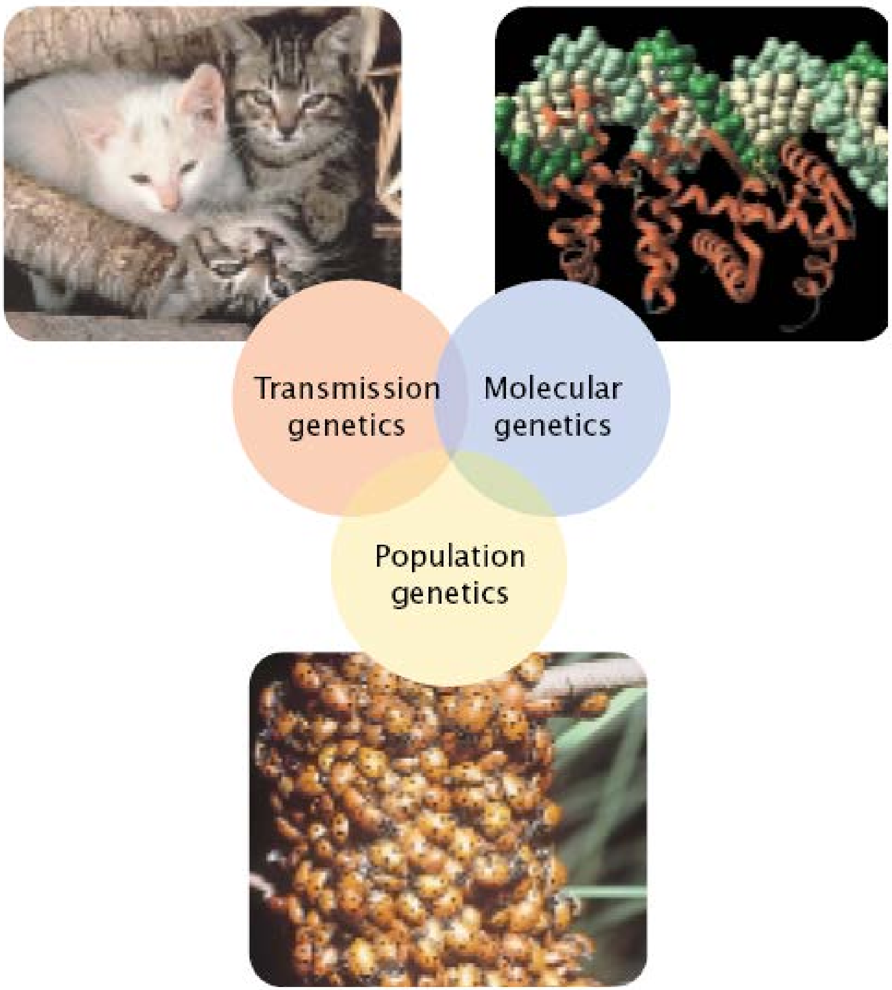

Organism	*E. coli*	*S. cerevisiae*	*C. elegans*	*A. thaliana*
Genome size	4.6 Mb	16 Mb	100 Mb	125 Mb
Number of protein-coding genes (approximate)	4300	5800	20,000	27,000



Organism	*D. melanogaster*	*D. rerio*	*M. musculus*
Genome size	130 Mb	1500 Mb	2700 Mb
Number of protein-coding genes (approximate)	13,000	36,000	25,000

Others……

Subdisciplines of Genetics



经典遗传学

↓

分子遗传学

↓

表观遗传学

个体水平

↓

细胞水平

↓

分子水平

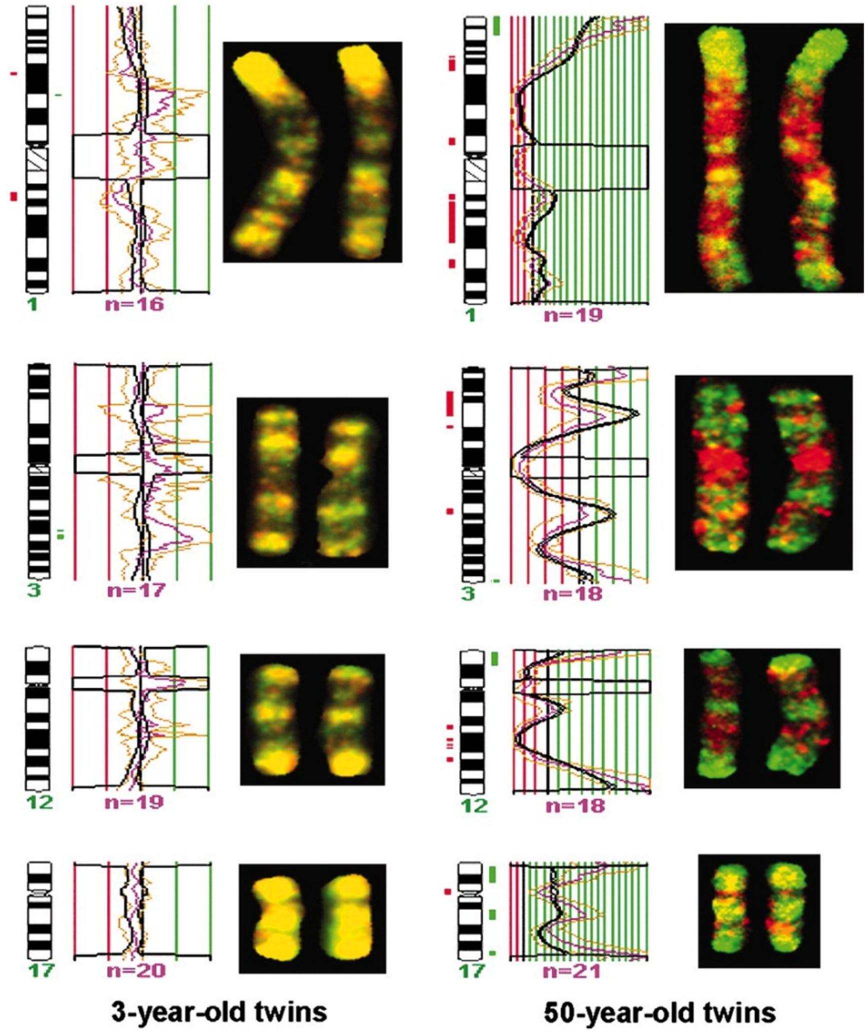
↓

表观水平

Example: **Epigenetics**

Mapping chromosomal regions with differential DNA methylation in MZ twins by using comparative genomic hybridization for methylated DNA

Fraga M F et al. *PNAS* 2005;102:10604-10609



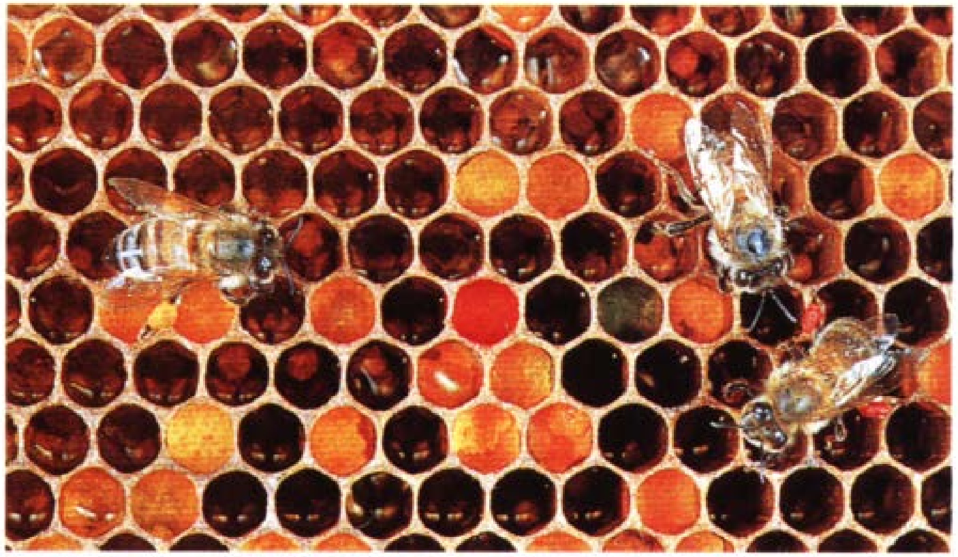
PNAS

Example: ***Behavior Genetics***

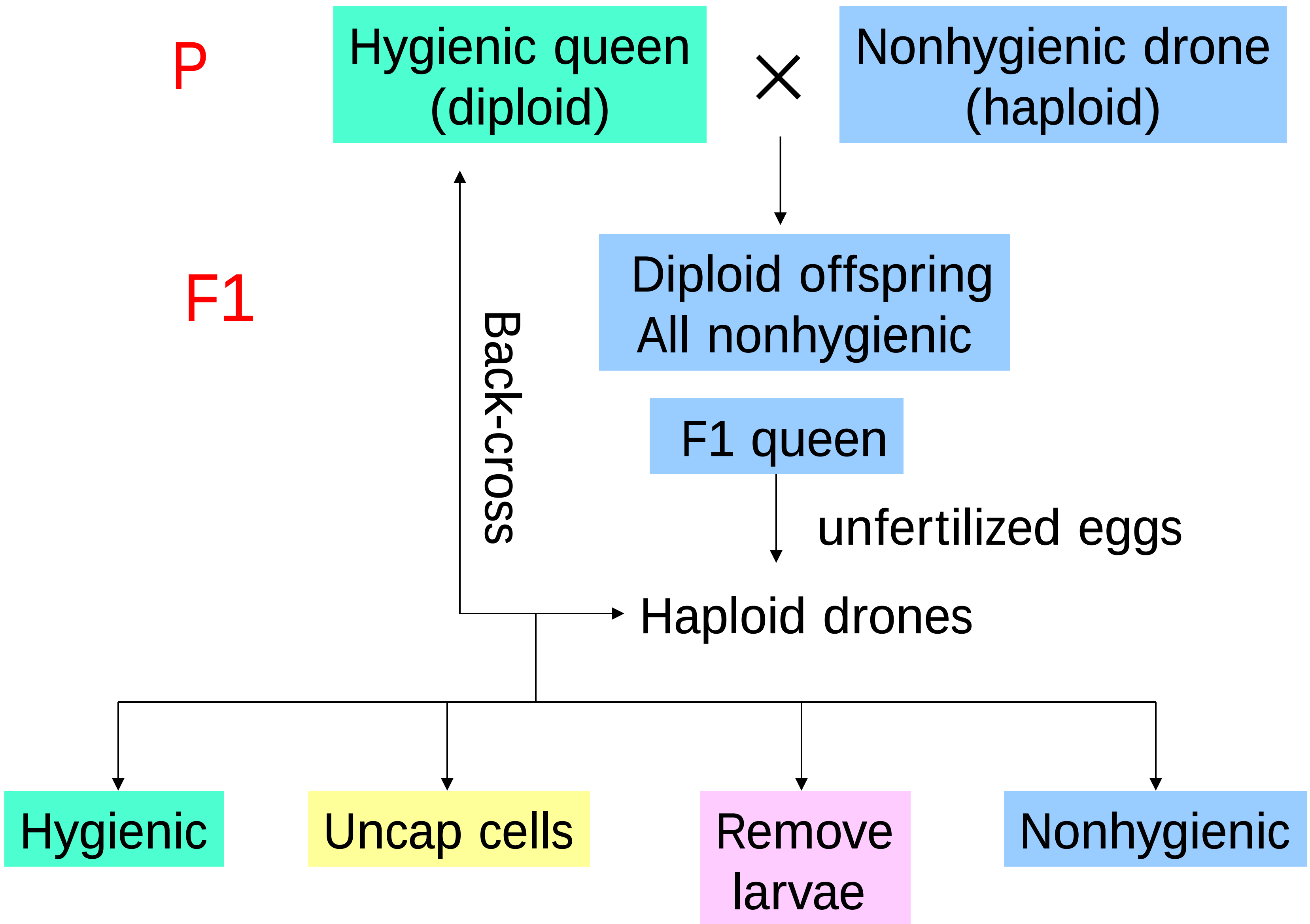
The social insects----ants, bees, wasps, termites exhibit a fascinating array of behavior

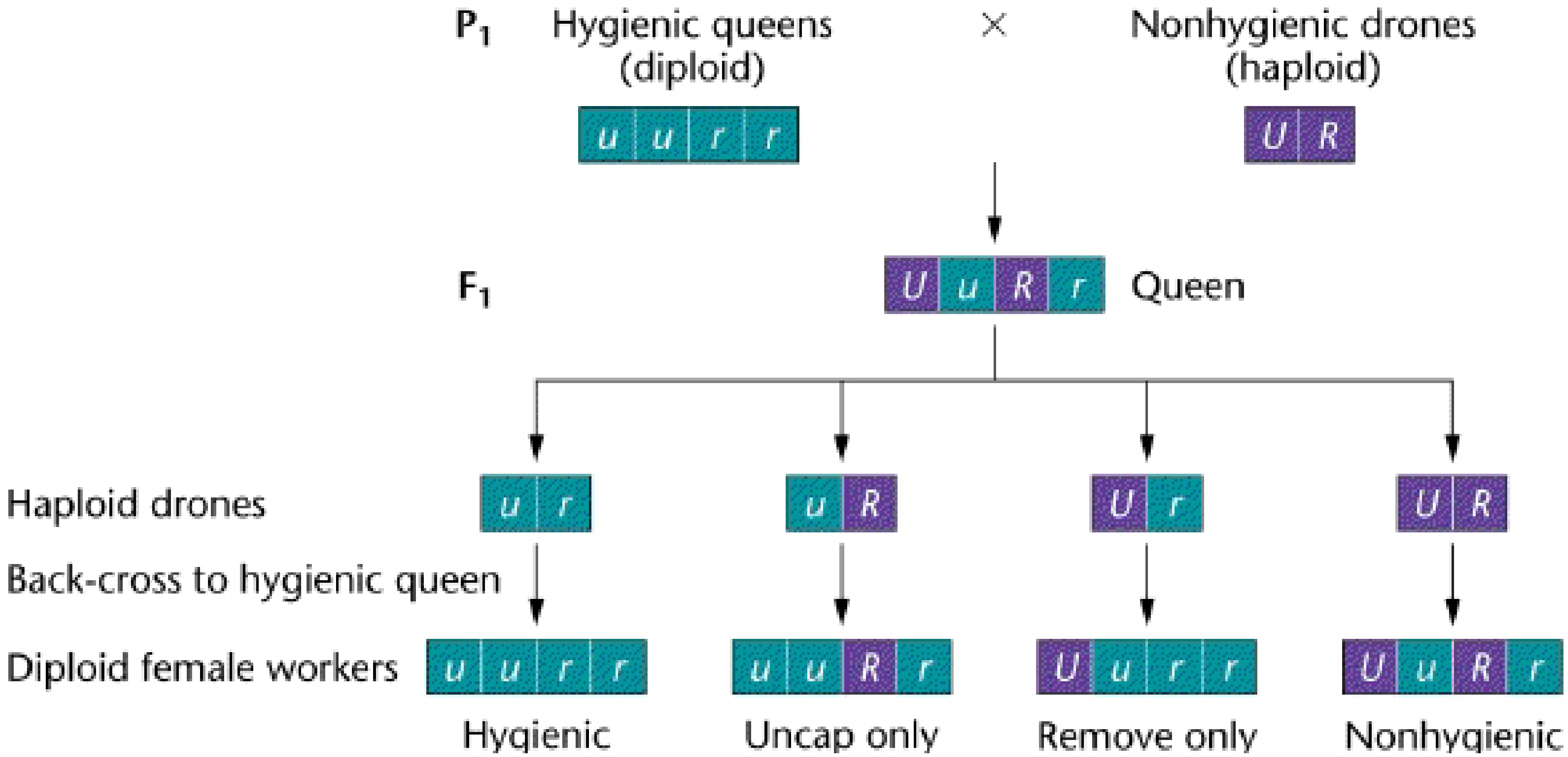
Nest-Cleaning behavior in honeybees

- Honeybee nests can get *Bacillus* infection (foulbrood disease 腐蛆病)
- Worker bees clean them with two "hygienic" behaviors:
  - Uncap cell
  - Remove infected larvae

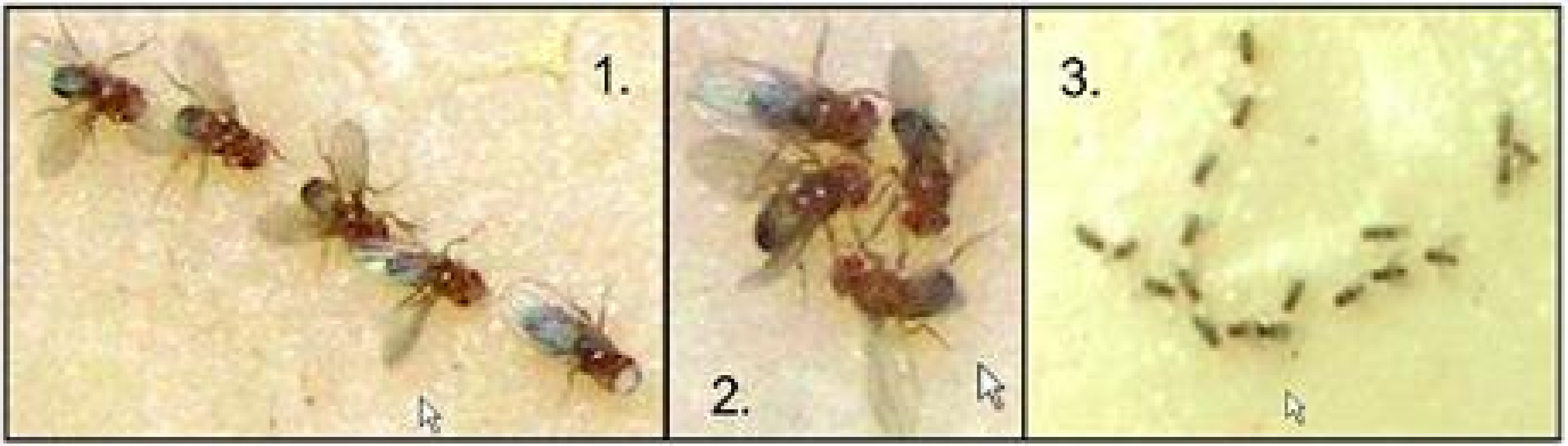


1964, Walter Rothenbuhler




P1
Hygienic queens (diploid)
×
Nonhygienic drones (haploid)
u u r r
U R
F1
U u R r
Queen
Haploid drones
u r
u R
U r
U R
Back-cross to hygienic queen
Diploid female workers
u u r r
u u R r
U u r r
U u R r
Hygienic
Uncap only
Remove only
Nonhygienic

Sex Preference in *Drosophila*



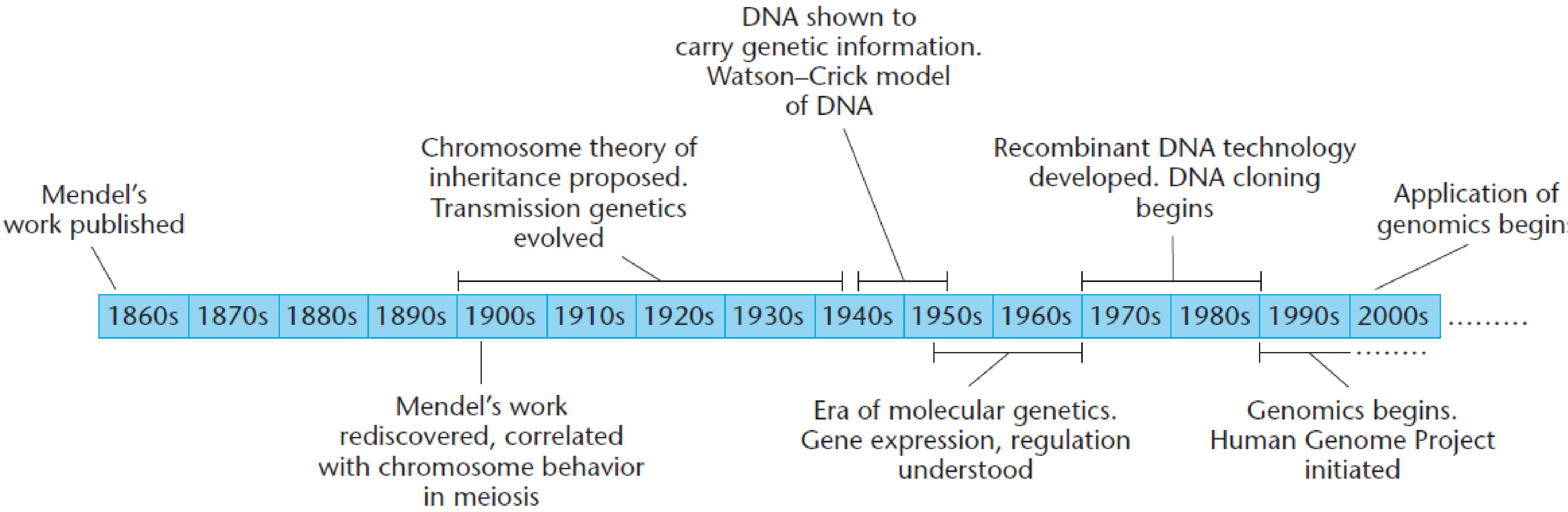
----*fruitless* (*fru*) gene, male-sterile mutation

- **Biological rhythms in *Drosophila* and mice**
- **Nurturing behavior in mice**
- **Single-gene mutations and human behavior**
- **Complex human behavior**

遗传学是生命科学的核心！

？

Genetics Has a Rich and Interesting History

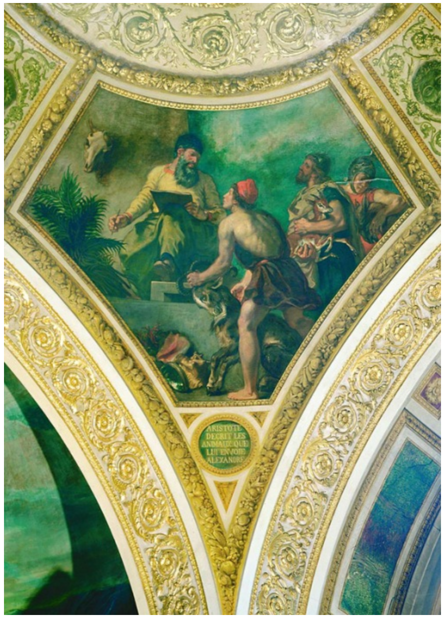


1. Prehistory

Domesticated animals and cultivated plants （10,000 and 12,000 years ago）

Northwest Palace of Assurnasirpal II (883–859 B.C.)

2. Early Written Records



The Greek Influence:

- **Hippocrates (460-370 B.C.)**

  Active “humors” in various parts of the body served as the bearers of hereditary traits.

- **Aristotle (384 – 322 B.C.)**

  People sometimes resemble past ancestors more than their parents

  Acquired characteristics such as mutilated body parts are not passed on

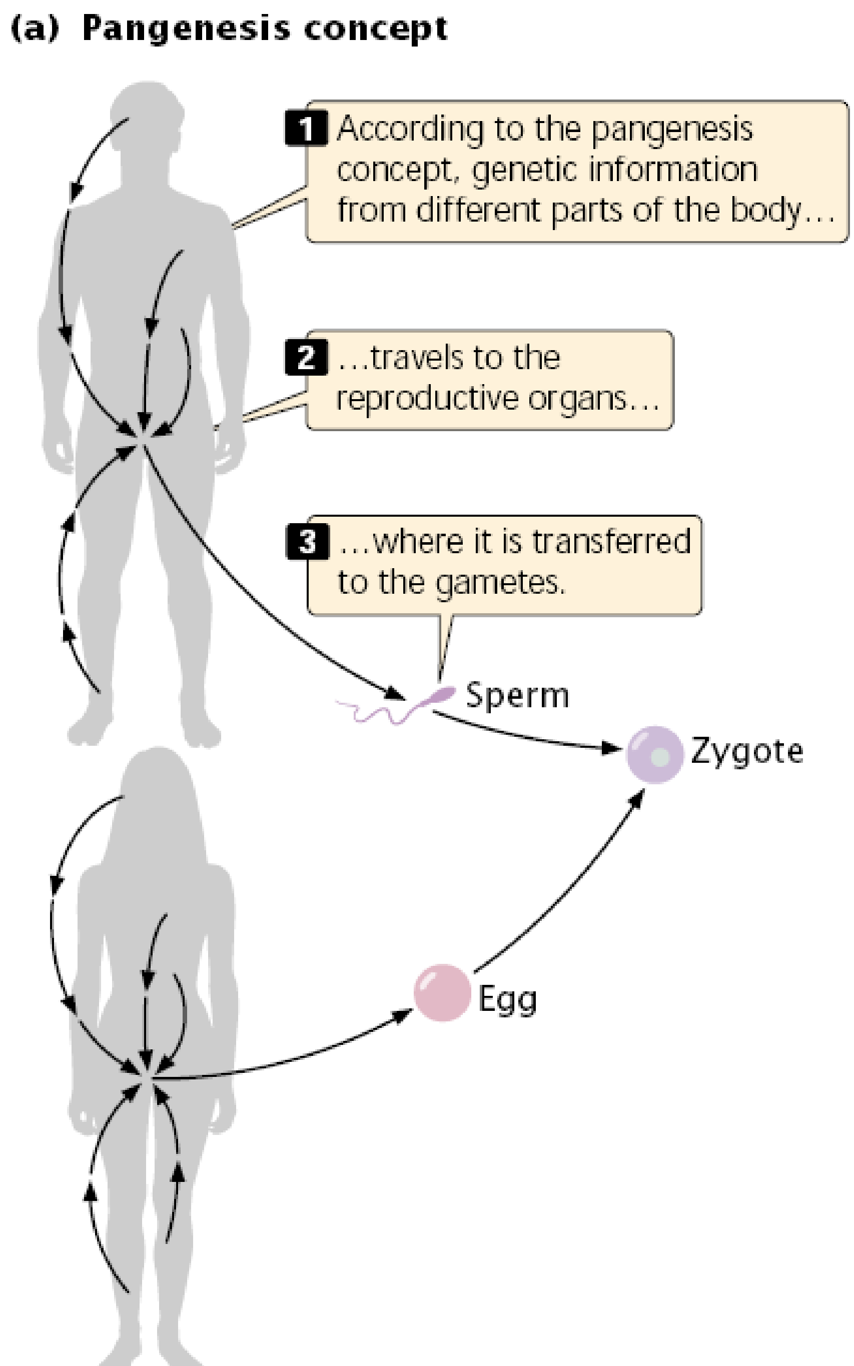
  Both males and females made contributions to the offspring

3. The Rise of Modern Genetics

Microscopes (the late 1500s)

Robert Hooke discovered cells in 1665

- **Theory of pangenesis （泛生论)**
- **Preformationism (先成说)**
- **The theory of epigenesis (渐成说)**



The homunculus: A myth. Well into the nineteenth many prominent microscopists believed they saw a fully miniature fetus crouched within the head of a sperm.

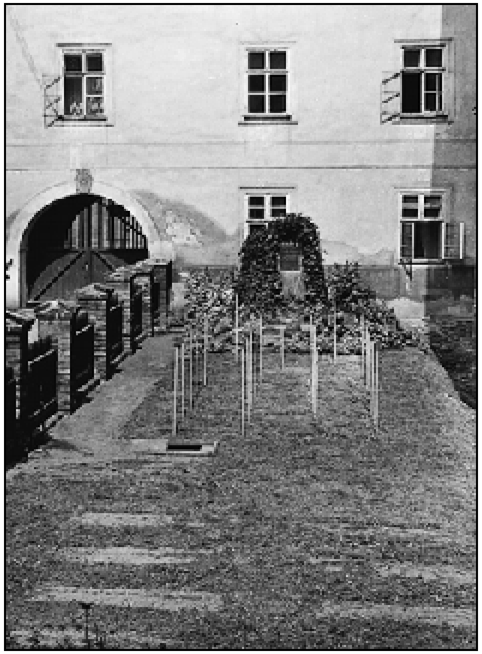
- **Charles Darwin and Evolution**

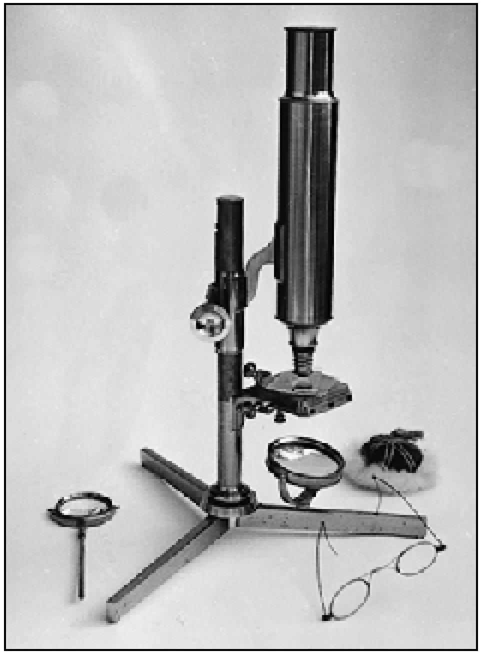
  On the Origin of Species (1859)

  Variations in Animals and Plants under Domestication (1868)

4. The foundation of Modern Genetics

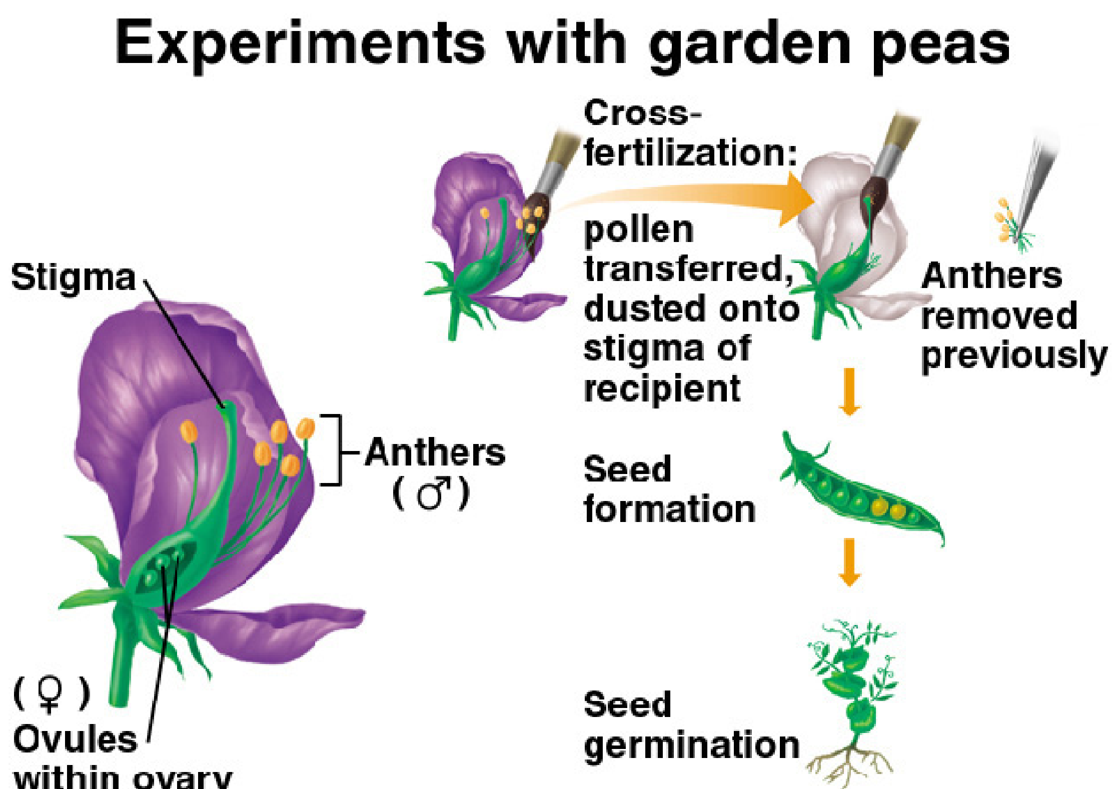
- Gregor Mendel (1822-1884)

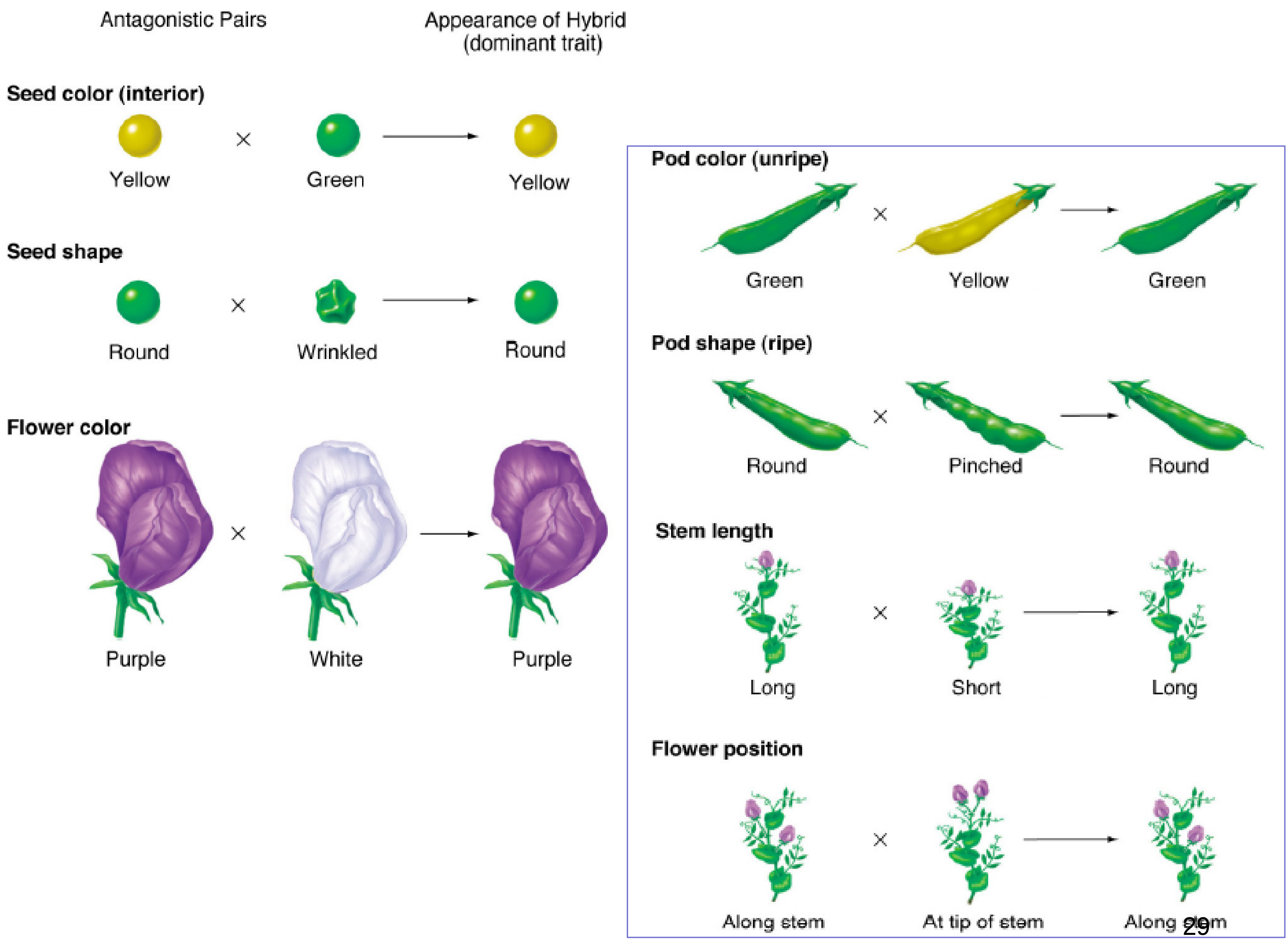


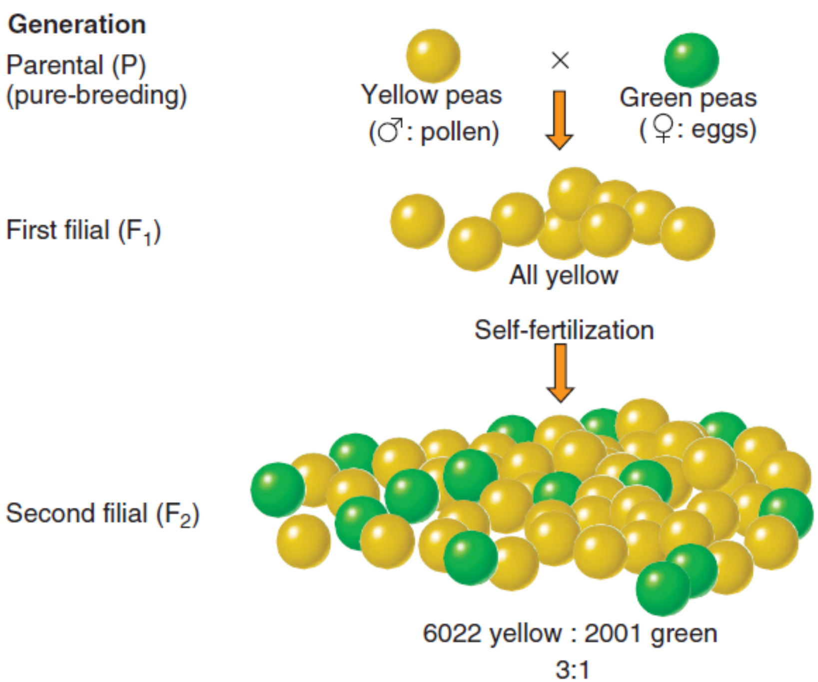


豌豆杂交试验

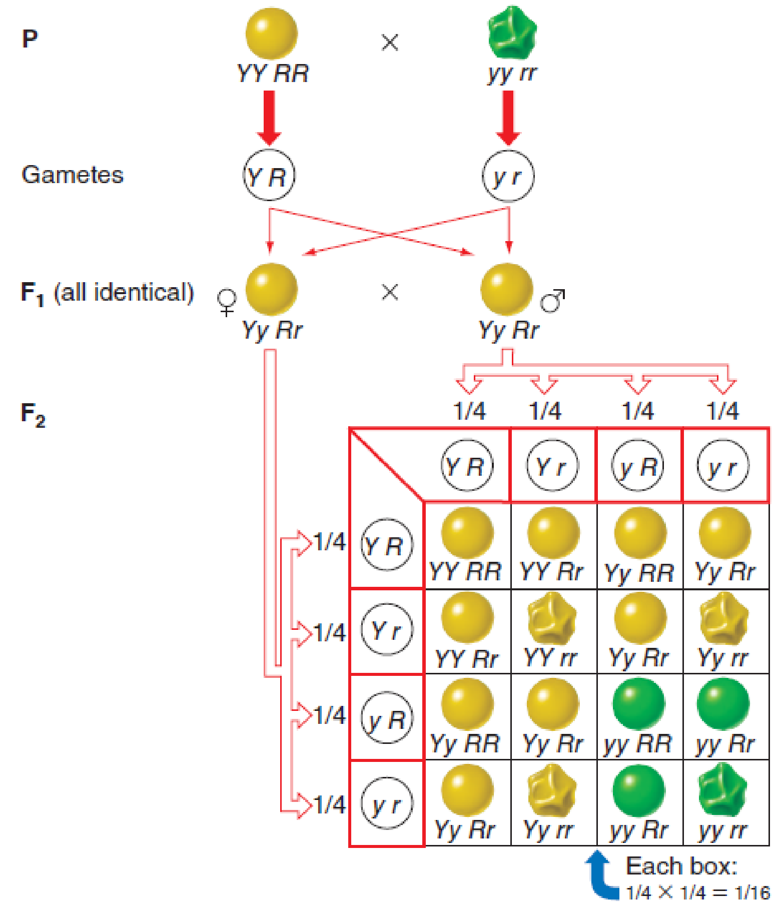
- Mendel chose true-breeding (=**homozygous**) garden peas for his experiments
- Mendel first worked with single-character crosses (**Monohybrid cross**)




Antagonistic Pairs
Appearance of Hybrid (dominant trait)
Seed color (interior)
Yellow
Green
Yellow
Seed shape
Round
Wrinkled
Round
Flower color
Purple
White
Purple
Pod color (unripe)
Green
Yellow
Green
Pod shape (ripe)
Round
Pinched
Round
Stem length
Long
Short
Long
Flower position
Along stem
At tip of stem
Along stem



Monohybrid Crosses Reveal Units of Inheritance and the Law of Segregation



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

Dihybrid Crosses Reveal the Law of Independent Assortment

- Mendel completed his experiment in 1863 and spend the next two years analyzing and summarizing the data

- In 1865, he presented the results before the Natural History society

- In 1866, Mendel published his classic paper, "*Experiment in Plant Hybrid*"

Versuche über Pflanzen-Hybriden.

Von

Gregor Mendel.

(Vorgelegt in den Sitzungen vom 8. Februar und 8. März 1865.)

Einleitende Bemerkungen.

Künstliche Befruchtungen, welche an Zierpflanzen desshalb vorgenommen wurden, um neue Farben-Varianten zu erzielen, waren die Veranlassung zu den Versuchen, die hier besprochen werden sollen. Die auffallende Regelmässigkeit, mit welcher dieselben Hybridformen immer wiederkehrten, so oft die Befruchtung zwischen gleichen Arten geschah, gab die Anregung zu weiteren Experimenten, deren Aufgabe es war, die Entwicklung der Hybriden in ihren Nachkommen zu verfolgen.

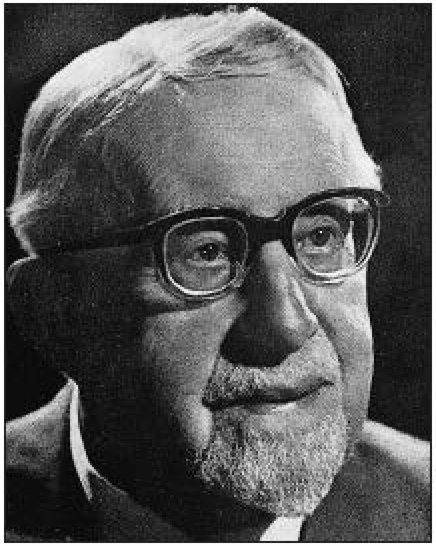
3. Versuch. Farbe der Samenschale. Unter 929 Pflanzen brachten 705 violett-rothe Blüthen und graubraune Samenschalen; 224 hatten weisse Blüthen und weisse Samenschalen. Daraus ergibt sich das Verhältniss 3,15 : 1.

4. Versuch. Gestalt der Hülsen. Von 1181 Pflanzen hatten 882 einfach gewölbte, 299 eingeschnürte Hülsen. Daher das Verhältniss 2,95 : 1.

Mendel's work was rediscovered in 1900

(b) Carl Correns

(c) Hugo de Vries



(d) Eric von Tschermak

Mendel was Considered the "**Father of Heredity**"

What did Mendel do superiorly to those who preceded him?

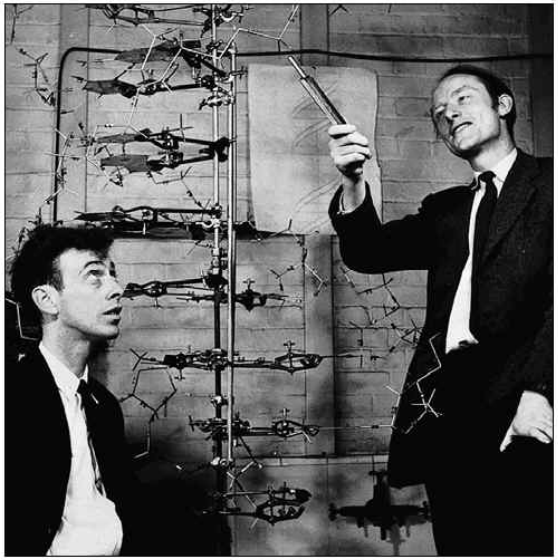
- Choose true-breeding garden peas, they were normally self-fertilizing
- Examined the inheritance of clear-cut alternative forms of particular traits
- Isolated and perpetuated lines of peas that bred true
- Carefully controlled his matings
- Worked with large numbers of plants, subjected to statistical analysis, and then compared his results with predictions based on his models.

5. Genetics progressed from Mendel to DNA in less than a century

- The chromosome theory of inheritance
- Genetic variation
- The search for the chemical nature of genes: DNA or proteins?

6. Discovery of the double helix launched the era of molecular genetics

- The structure of DNA and RNA
- Gene expression: From DNA to phenotype
- Protein and biological function
- Linking genotype to phenotype



7. Development of recombinant DNA technology began the era of cloning

8. Genomics, proteomics, and bioinformatics are new and expanding fields

Applications of Genetics

——Genetics，Better life for all

1. Genetics in Agriculture

- Genetic breeding

The Green Revolution used genetic techniques to develop new strains of crops that greatly increased world food production during the 1950s and 1960s.

Nobel Peace Prize in 1970

Development of superior breeds of livestocks

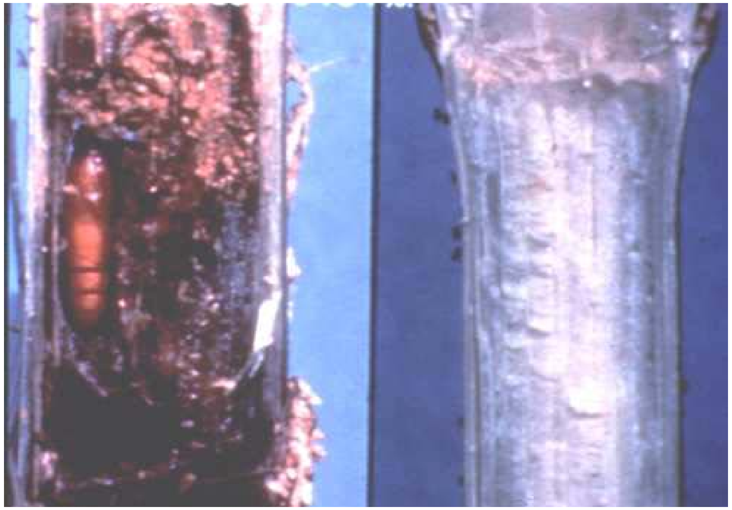
- Genetic Engineering

Genetically Modified Organisms (GMO)

Agriculture Transgenics On the Market

Insect resistant cotton – Bt toxin kills the cotton boll worm

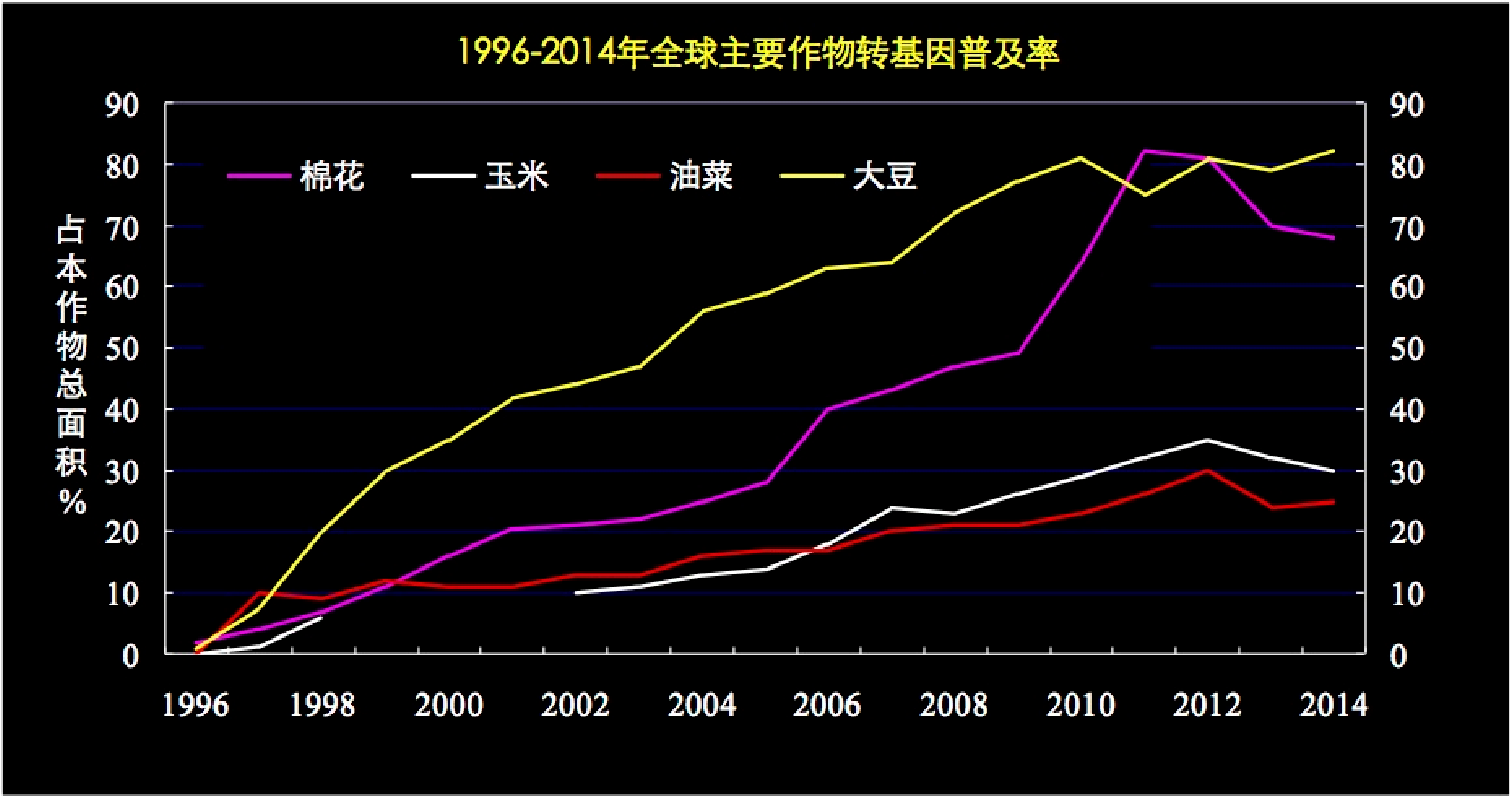
- ***transgene = Bt protein***



Normal **Transgenic**

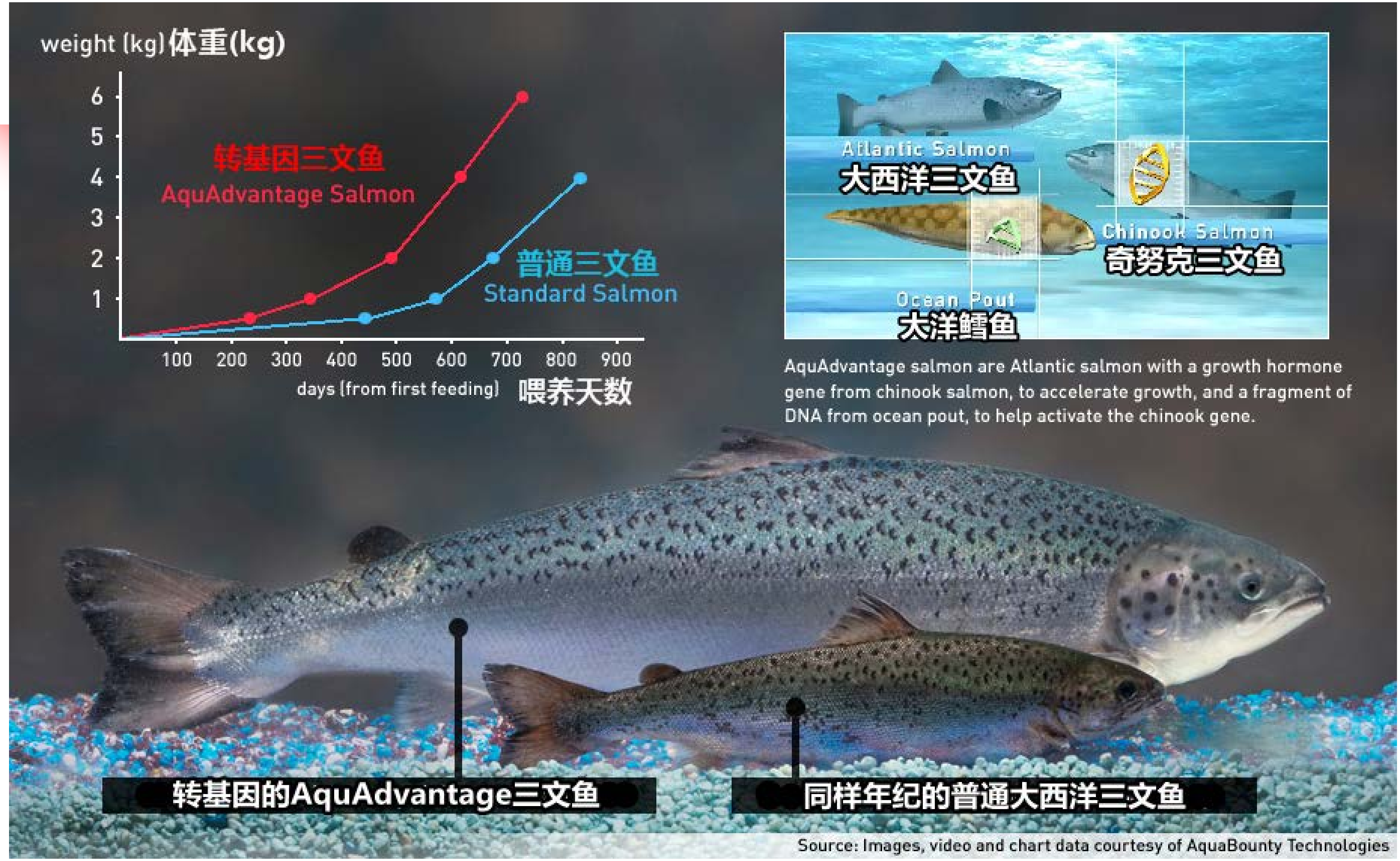
Insect resistant corn – Bt toxin kills the European corn borer

- ***transgene = Bt protein***



1996-2014年全球主要作物转基因普及率
棉花
玉米
油菜
大豆
占本作物总面积%
90
80
70
60
50
40
30
20
10
0
1996
1998
2000
2002
2004
2006
2008
2010
2012
2014

转基因三文鱼



2015年11月19日，美国食品药品监管局（FDA）公布全球首例转基因食品动物——转基因三文鱼上市

Nonbrowning Arctic® Apples

The team uses gene silencing to turn down the expression of polyphenol oxidase (PPO), which virtually eliminates PPO production.
The Arctic Apples will arrive in select midwestern U.S. stores next month (Feb,2017).

2．Genetics and Medicine

“人类所有的疾病都与**DNA**有关”

- 遗传疾病——医学遗传学

染色体病：染色体结构数目异常而导致的遗传病
单基因病：多指症，白化病，早老症
多基因病：哮喘，原发性高血压，糖尿病

TABLE 1.1 Some of the Most Common Single-Gene Traits in Humans

Disease	Effect	Incidence of Disease
Caused by Recessive Allele		
Thalassemia (chromosome 16 or 11)	Reduced amounts of hemoglobin; anemia, bone and spleen enlargement	1/10 in parts of Italy
Sickle-cell disease (chromosome 11)	Abnormal hemoglobin; sickle-shaped red cells, anemia, blocked circulation; increased resistance to malaria	1/625 African Americans
Cystic fibrosis (chromosome 7)	Defective cell membrane protein; excessive mucus production, digestive and respiratory failure	1/2000 Caucasians
Tay-Sachs disease (chromosome 15)	Missing enzyme; buildup of fatty deposit in brain; buildup destroys mental development	1/3000 Eastern European Jews
Phenylketonuria (PKU) (chromosome 12)	Missing enzyme; mental deficiency	1/10,000 Caucasians
Albinism (chromosome 11)	Missing enzyme; unpigmented skin, hair, and eyes	1/10,000 in Northern Ireland
Caused by Dominant Allele		
Hypercholesterolemia (chromosome 19)	Missing protein that removes cholesterol from the blood; heart attack by age 50	1/122 French Canadians
Huntington disease (chromosome 4)	Progressive mental and neurological damage; neurologic disorders by ages 40–70	1/25,000 Caucasians

Cancer is a genetic disorder at the somatic cell level

我国主要单基因病患病率（1980s）

疾病	调查人数	患者数	患病率	调查者
先天性红绿色盲（男）	87,521	4439	50.7‰(1:20)	全国各地普查
先天性红绿色盲（女）	38,818	315	8.1‰(1:123)	全国各地普查
高度近视	26,084	248	9.5‰(1:105)	眼遗传协作组
β-地中海贫血	356,849	2375	6.7‰(1:150)	血红蛋白协作组
先天性智力发育不全（儿童）	299,646	1773	5.9‰(1:169)	湘、黔、川、冀等
先天性智力发育不全（群体）	1,383,174	2504	1.8‰(1:552)	京、沪、豫、宁等
先天性睑下垂	86,190	131	1.5‰(1:658)	眼遗传协作组
α-地中海贫血	203,913	217	1.1‰(1:940)	血红蛋白协作组
多指、趾	430,684	274	0.64‰(1:1,572)	沪、豫、武汉等
先天性聋哑	638,418	379	0.59‰(1:1,685)	豫、粤、鲁、冀等
先天性白内障	53,170	28	0.53‰(1:1,899)	眼遗传协作组
视网膜色素变性	107,460	31	0.29‰(1:3,467)	眼遗传协作组
鳞癣	463,929	208	0.45‰(1:2,230)	武汉、川、冀等
先天性小眼球	154,529	16	0.10‰(1:9,658)	眼遗传协作组
视网膜母细胞瘤	124 万	105	0.085‰(1:11,810)*	上海
白化病	985,990	50	0.051‰(1:19,720)	武汉、豫、辽、冀、川等
软骨发育不全	452,699	18	0.04‰(1:25,150)	武汉、河北
血友病A	661,616	22	0.033‰(1:30,074)	武汉、豫、冀等
马凡综合征	688,126	19	0.028‰(1:36,217)	眼协作组、武汉、豫
先天性眼组织缺损	220,948	6	[illegible]027‰(1:36,825)	眼协作组、武汉
进行性肌营养不良	661,616	17	0.026‰(1.38,919)	武汉、豫、冀
先天性青光眼	429,865	7	0.016‰(1:61,409)	眼协作组、豫、武汉
成骨不全	661,616	10	0.015‰(1:66,162)	武汉、冀、豫等
抗维生素D佝偻病	484,559	5	0.010‰(1:96,912)	河南、河北
先天性无虹膜	289,286	3	0.010‰(1:96,429)	眼协作组、武汉
肝豆状核变性	661,616	5	0.0076‰(1:132,323)	武汉、冀、豫等
神经纤维瘤病	484,559	3	0.0062‰(1:161,520)	河南、河北

* 为活产儿中发病率。

这些遗传病患者看似和我们无关，实质是替每个健全人承担了遗传风险

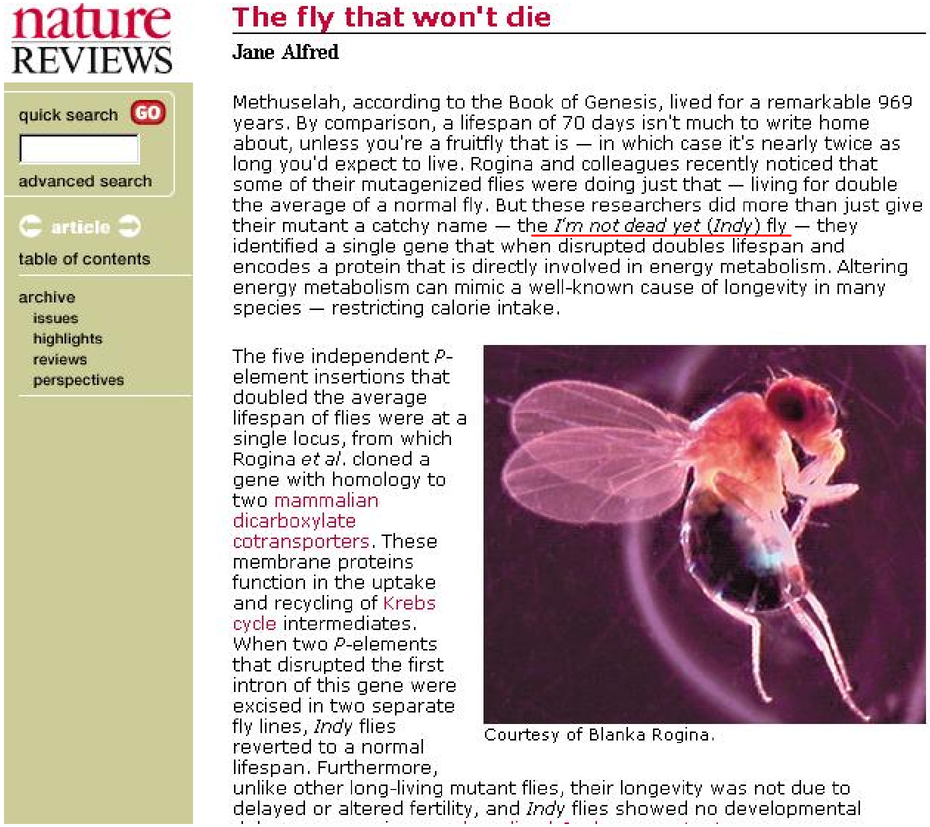
关爱弱势人群是每一个健全人的基本素质

Recombinant Proteins in Medicine

- Insulin, interferon, interleukin......

- Vaccines: HBV......

- Gene diagnosis and gene therapy
  - 新生儿免费耳聋基因筛查
  - 基因组测序
  - 基因编辑修复患者干细胞的致盲基因、清除T淋巴细胞的艾滋病病毒
- Gene and longevity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reviews
perspectives

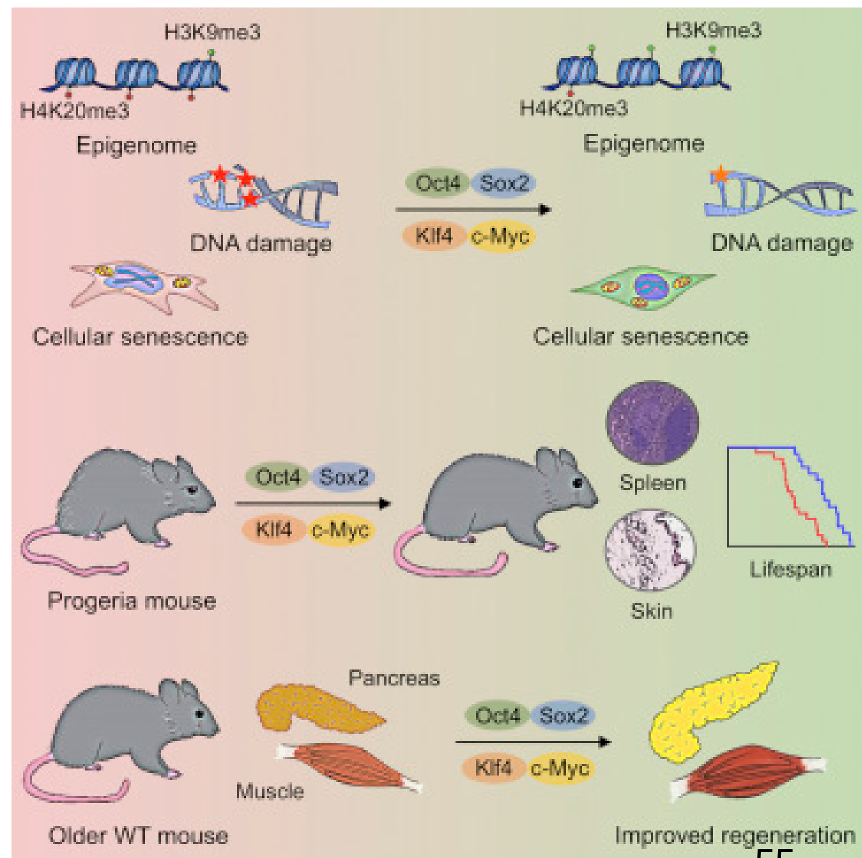
The fly that won't die

Jane Alfred

Methuselah, according to the Book of Genesis, lived for a remarkable 969 years. By comparison, a lifespan of 70 days isn't much to write home about, unless you're a fruitfly that is — in which case it's nearly twice as long you'd expect to live. Rogina and colleagues recently noticed that some of their mutagenized flies were doing just that — living for double the average of a normal fly. But these researchers did more than just give their mutant a catchy name — the *I'm not dead yet (Indy)* fly — they identified a single gene that when disrupted doubles lifespan and encodes a protein that is directly involved in energy metabolism. Altering energy metabolism can mimic a well-known cause of longevity in many species — restricting calorie intake.

The five independent *P*-element insertions that doubled the average lifespan of flies were at a single locus, from which Rogina *et al*. cloned a gene with homology to two mammalian dicarboxylate cotransporters. These membrane proteins function in the uptake and recycling of Krebs cycle intermediates. When two *P*-elements that disrupted the first intron of this gene were excised in two separate fly lines, *Indy* flies reverted to a normal lifespan. Furthermore, unlike other long-living mutant flies, their longevity was not due to delayed or altered fertility, and *Indy* flies showed no developmental

Courtesy of Blanka Rogina.



In Vivo Amelioration of Age-Associated Hallmarks by Partial Reprogramming. ***Cell***. 2016, 67(7):1719-1733

3. Genetics and Society

Genetics Today

How geneticists study life today?

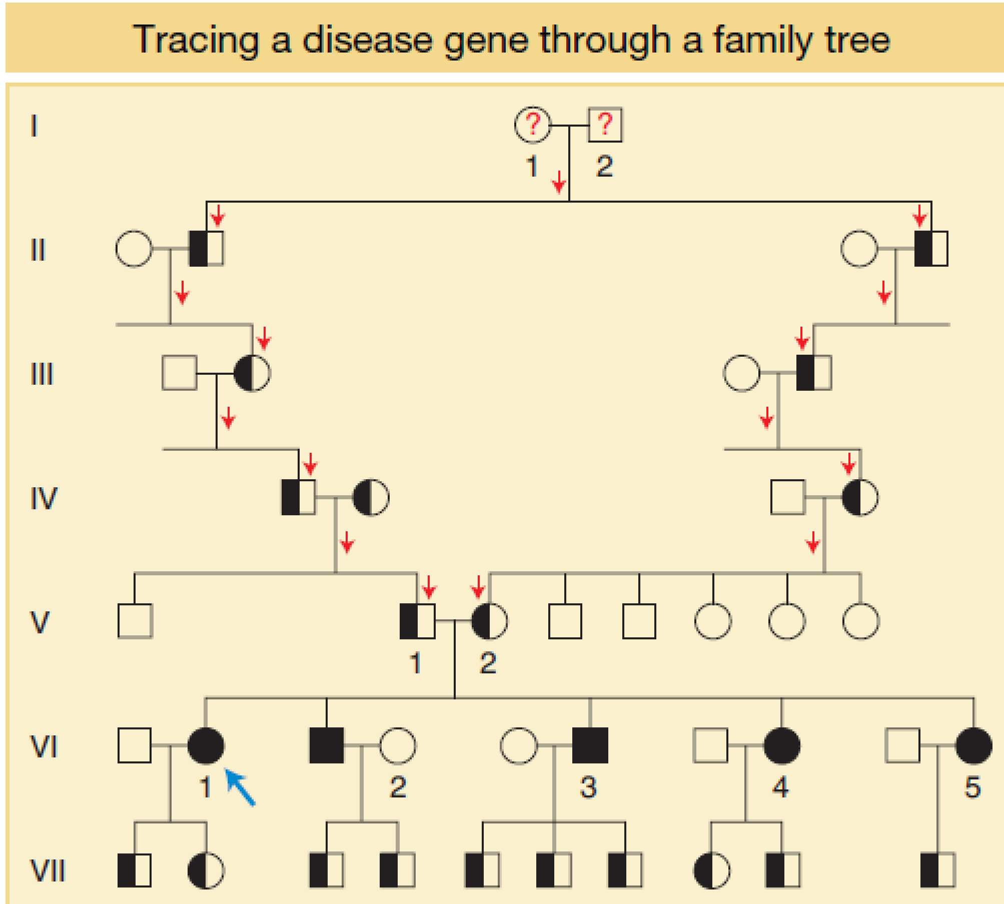
Case I : From classical genetics to medical genomics

Louise Benge has an undiagnosed disease

(a) Louise Benge developed an undiagnosed disease experiencing pain in her legs as a young woman.
(b) An X ray revealed that Louise Benge's disease condition caused calcification of the arteries in her legs.

Undiagnosed Diseases Program (UDP)

- Benge had a very low level of an enzyme called CD73. This enzyme is involved in signaling between cells, and specifically it sends a signal that blocks calcification.
- The disease was named “arterial calcification due to deficiency of CD73,” or ACDC.



- ACDC only appears if an individual carries two defective alleles.
- Benge's parents were third cousins.

- The UDP team then looked in the genome for the mutant gene.
- They used a DNA microarray to study the genome-wide SNP.
- The UDP team found exactly the small chromosome segment harboring CD73 gene.
- After determining the DNA sequence of the defective CD73 gene, the team found the defective gene encoded only a short, or truncated, protein

- The medicine etidronate can substitute for CD73 in signaling cells to keep the calcification pathway turned off.
- Clinical trials with etidronate are currently underway for ACDC patients and are scheduled for completion in 2017.

Case II : When rice gets its feet a little too wet

Rice growing in a flooded field or paddy

The ability of rice to grow in flooded fields offers it an advantage: rice can survive modest flooding (up to 25 cm of standing water) in the paddies, but most weeds cannot. So rice farmers can use flooding to control the weeds in their field while their rice thrives.

- In the early 1990s, David Mackill identified a remarkable variety of rice called **FR13A** that could survive submergence and even thrive after the plants remained fully submerged in deep water for up to two weeks.
- Mackill set out to transfer **FR13A**'s genetic factor(s) for submergence tolerance into a rice variety with a higher yield and higher grain quality, and succeeded.
- But the genetic basis for why FR13A was submergence tolerant remained obscure.

- Mackill and his team conducted a form of genetic analysis called quantitative trait locus (**QTL**) mapping.
- They found that FR13A exceptionalism was mostly due to a single genetic locus or QTL on one of the rice chromosomes. He named this locus **SUB1** for “submergence tolerant.”
- What is the molecular nature of **SUB1**?

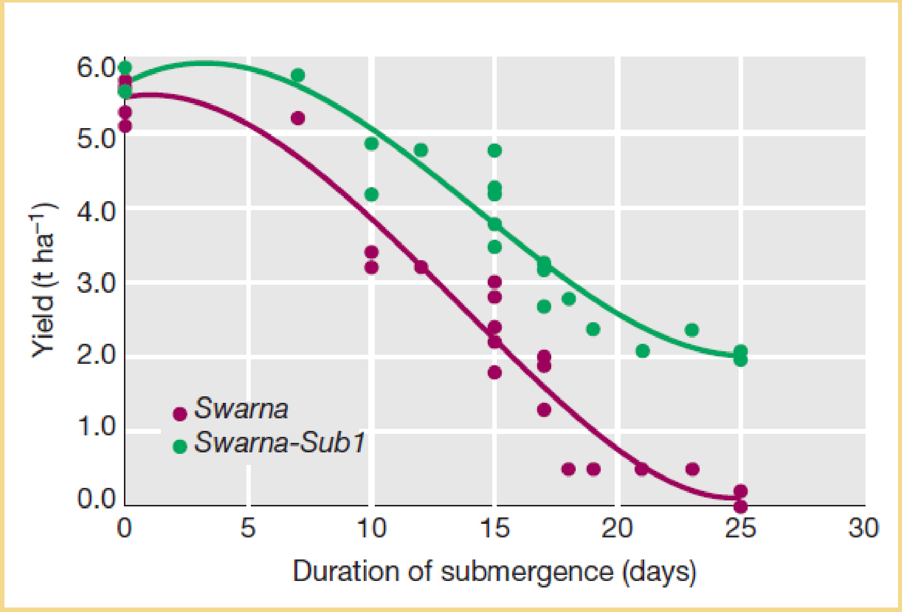
- The expanded team determined that it encompasses a member of a class of genes called *ethylene response factors* (***ERFs***). ERF genes encode regulatory proteins that bind to regulatory elements in other genes and thereby regulate their expression.
- They determined that the allele of ***SUB1*** in FR13A is switched on in response to submergence, while the allele of ***SUB1*** found in submergence-sensitive varieties is not switched on by submergence.
- How does switching on ***SUB1*** enable FR13A to survive complete submergence?

- Ethylene signals the plant to escape submergence by elongating its leaves and stems to keep its “head” above water.
- For **ordinary rice plants**, this escape strategy works fine as long as the water is not so deep. If the flood waters are too deep, the plant cannot grow enough to escape. It uses up all its energy reserves , becomes spindly and weak, and eventually dies.
- In **FR13A** plants that become submerged, the ***SUB1*** is switched on in response to the elevated ethylene levels, lead to the genes involved in stem and leaf elongation being switched off. Then, FR13A plant stops the elongation growth response, and remains in a quiescent, submerged state for up to two weeks and then emerge healthy and resume normal growth when the flood waters recede.

- The team repeated Mackill's early breeding work to transfer the flood tolerance into superior varieties with surgical precision.

Flood-intolerant and flood-tolerant rice

SUB1 gene increases rice yield under flooding



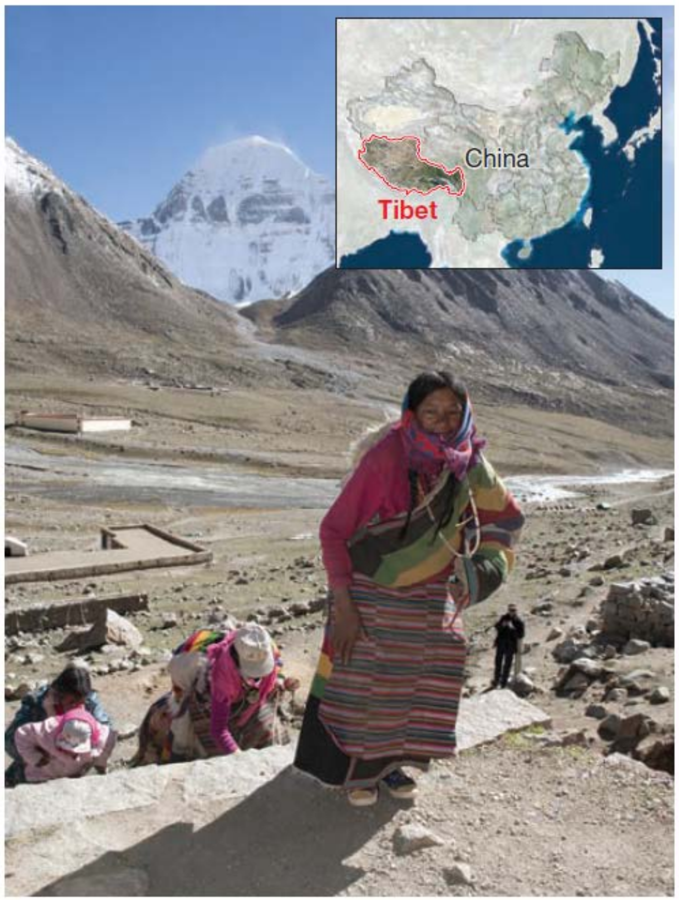
This field was flooded for 10 days

In 2008, only 700 farmers were growing SUB1 enhanced rice. By 2014, the number climbs to 5 million.

Case III: Recent evolution in humans

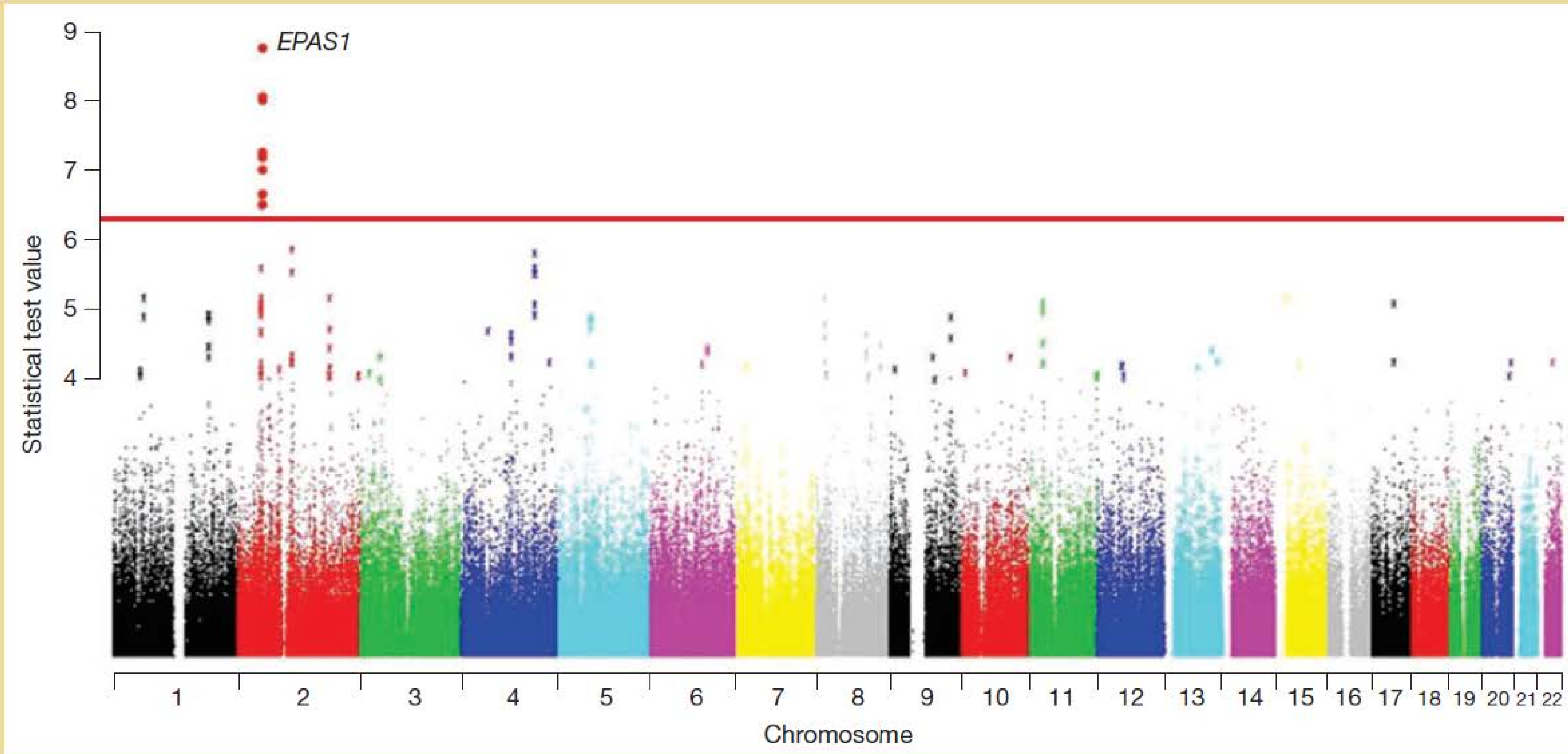
--Adaptation to high altitude

Tibetans are genetically adapted
to life at high elevation



- The high Tibetan Plateau was colonized by people about 3000 years ago, and the people who colonized Tibet are closely related to the modern Han Chinese.
- A research team compared Tibetans to Han Chinese at over 500,000 SNPs across the genome (*PNAS*, 2010).
- Another team sequenced 50 exomes of ethnic Tibetans (*Science*, 2010).

Tibetans have a special variant of the *EPAS1* gene



- The SNPs in one gene, ***EPAS1***, stood out.
- ***EPAS1*** gene regulates the number of red blood cells (RBCs) that our bodies produce. When oxygen levels in our tissues are low, *EPAS1* signals the body to produce more RBCs.
- Tibetans have a special variant of ***EPAS1*** that helps them adapt to life at high elevation.

- Re-sequencing the region around ***EPAS1*** in 40 Tibetan and 40 Han individuals, the authors suggested that the adaptation was likely to be due to the introduction of genetic variants from archaic Denisovan or Denisovan-related individuals from the Altai Mountains into the ancestral Tibetan gene pool (***Nature***, 2014).

“Nothing can be understood in life science, except in the light of Gene.”

The figures and tables are cited from:

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