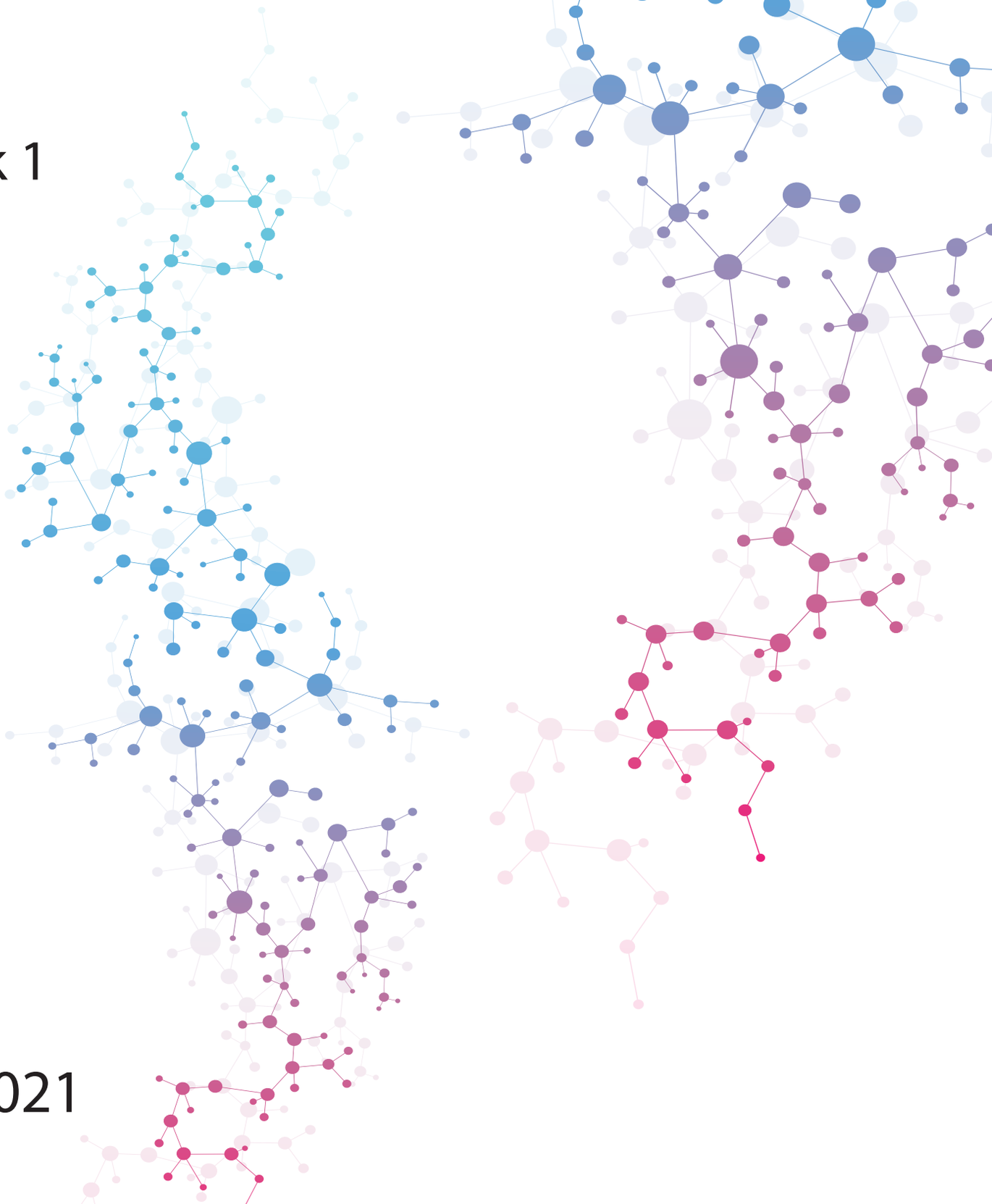
HMB265:

General & Human Genetics

Week 1

Fall 2021



Why do we care about genetics?

1) Medicine: - treatment
   - diagnosis & prediction
   - gene therapy
   - pharmacogenomics
   → Personalized medicine
2) Agriculture: genetic engineering help to improve traits, survival, etc.
3) Conservation
4) Biology

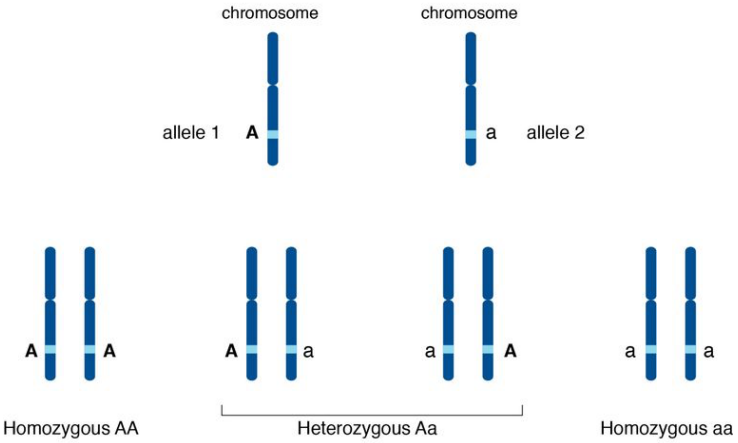
Two hypotheses to explain inheritance (其实是错误的):

1) Uniparental: One parent contributes more
   (Aristotle 认为是 male, 后代会长得和父亲一样)
2) Blended inheritance: 红 + 白 = 粉
   (这个 hypothesis only explained single offspring，但是无法解释 siblings 和 next generation)

Model Organism:

1) short generation time
2) able to inbred (self-fertilize)
3) simple reproductive biology 并且一定要 discrete traits
4) easy to breed/grow (ex. Small in size)
5) large number of progeny

Terminology:



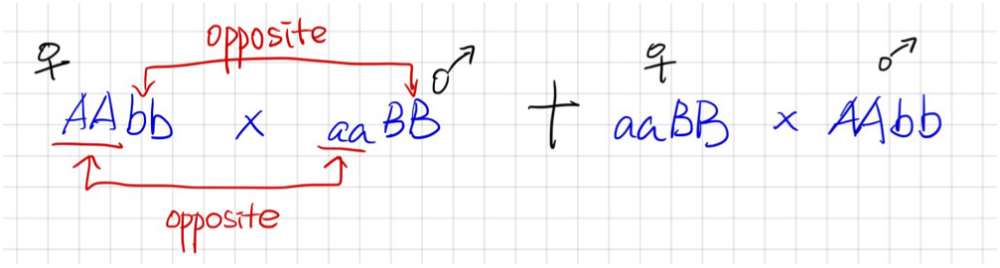
我是重点啊！答应我一定要会好吗

https://www.thoughtco.com/allele-a-genetics-definition-373460

- Locus - genetically defined location, behave like one gene
- Allele - alternative form at a given locus
- Dominant - one allele that manifests itself regardless of the other allele that is present.
  (indicated by an uppercase letter)

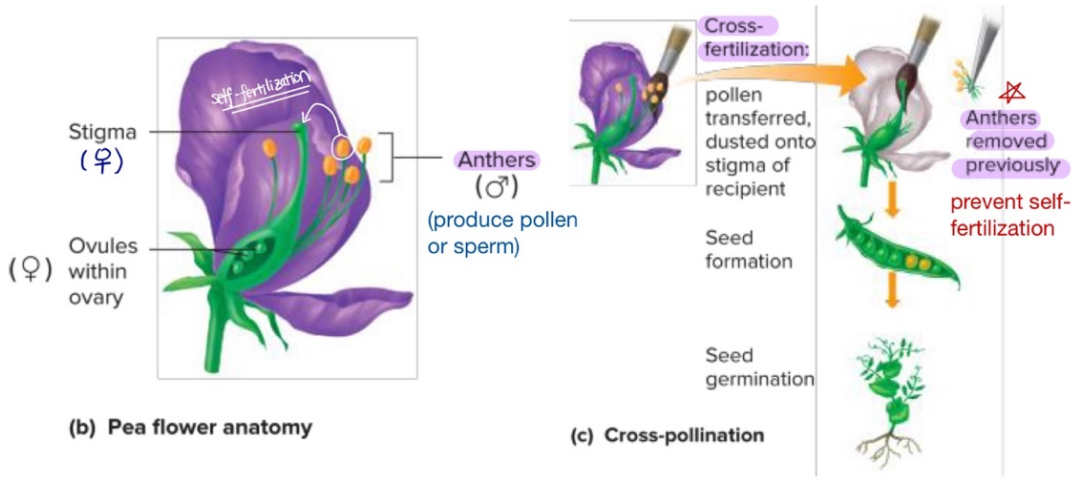
- Recessive – an allele whose effect is "masked" when the dominant allele is present.
  For the recessive allele to manifest itself, all alleles at a locus must be Recessive (ex. aa)
  (indicated by a lowercase letter)
- Homozygous – both alleles at a given diploid locus are the same
  (AA or aa)
- Heterozygous – one dominant and one recessive at a diploid locus
  (Aa)
- Monohybrid – one hybrid locus (e.g. AABBccDd)
- Dihybrid – 2 hybrid loci (e.g. AaBbCCDD)

- True-breeding – homozygous at the loci/locus
  (AA or aa)
- Reciprocal crosses – cross 2 true-breeding lines that are opposite to each other and do another round that reverse the trait between the male and the female . Tell us that both parent contribute equally to offspring (independent).



- Test Cross – unknown genotype X homozygous recessive genotype
  (to find the unknown genotype (ex. aabb))

- Self-fertilization vs. cross-fertilization:



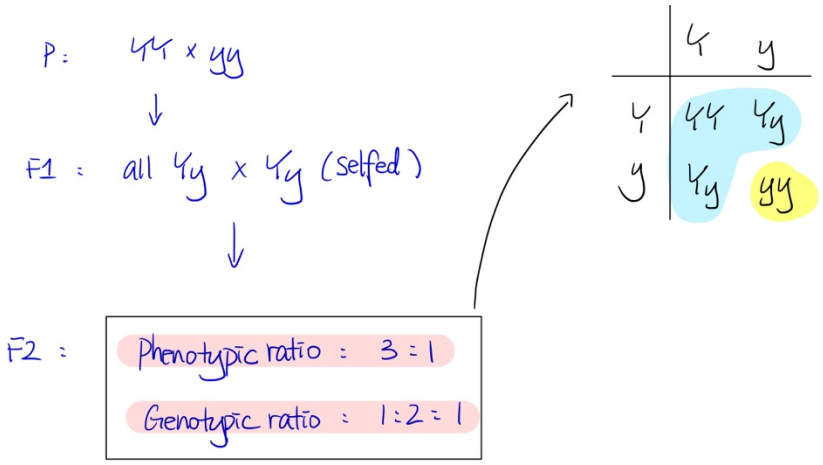
Mendel 最后选择了 Pisum sativum 来作为他的 model organism 因为:

- short generation time
- 可以 inbred
  (得到一个 pure-breeding line (也叫 true-breeding，就是紫花 self-fertilize always 得到紫花，世世代代的 traits 都没有变化)
  (可以把 2 个 pure-breeding lines cross-fertilized 来形成一个 hybrids (monohybrid cross))
- 可以做 reciprocal cross
- traits are discrete (7 antagonistic pairs: no intermediate form)
- easy to grow
- large number of progeny

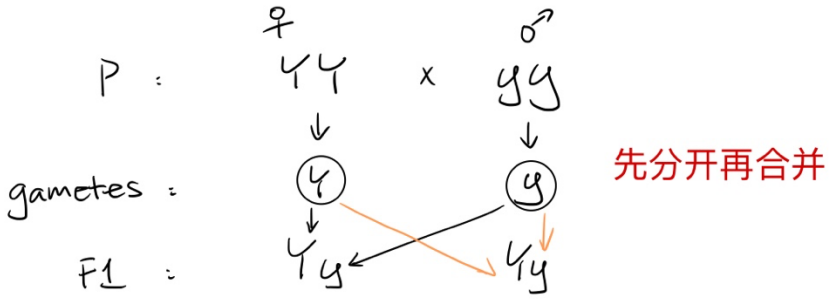
Monohybrid Cross:

- Examining only one single trait
- YY x yy
- All F1 generation show the dominant phenotype
- F2 generation: phenotype ratio = 3 : 1
  genotype ratio = 1 : 2 : 1
- Law of Segregation = explains how genes are transmitted:
  (1. Two members of a gene pair segregate from each other into the gametes
  2. Then unite at random)
  先分开再合并 (在 gamete formation 的时候分开，fertilization 的时候合并)

灵魂画手时间:
Punnett Square:



Law of Segregation:

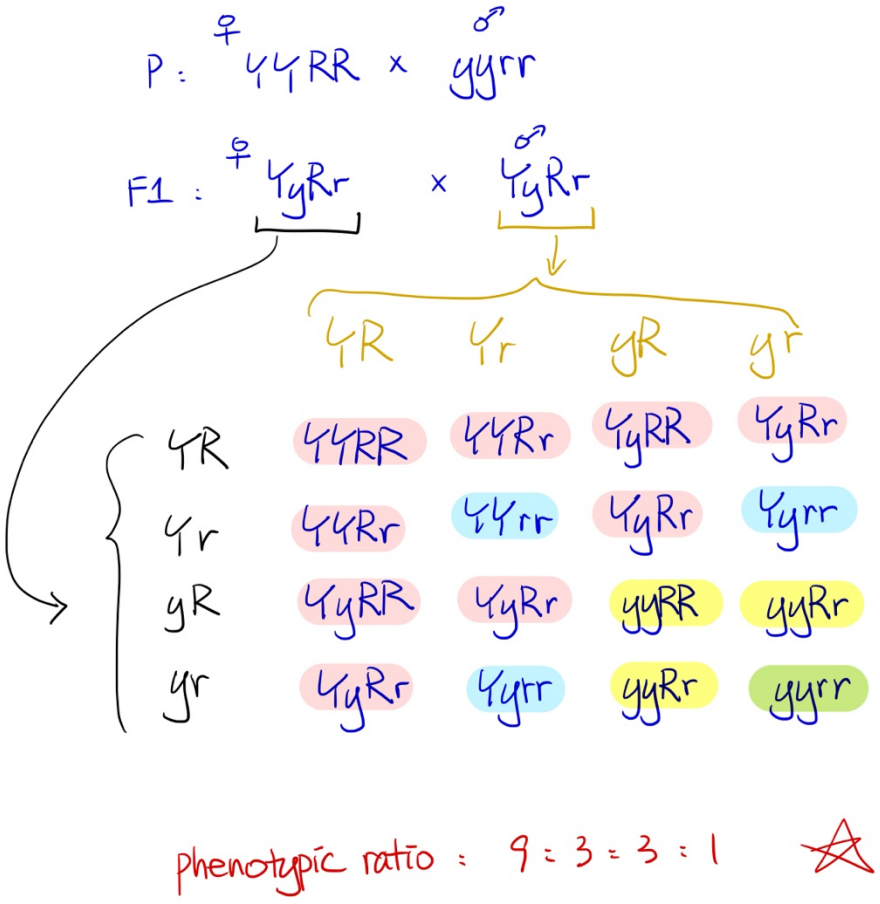


先分开再合并

Dihybrid Cross:

- Examining two traits
- ex) RRYY X rryy
- All F1 generation show dominant phenotype
- F2 generation show 9 : 3 : 3 : 1 phenotypic ratio
- Law of Independent Assortment = During gamete formation, the segregation of alleles at one locus is independent of the segregation of alleles at another locus (分开找 Yy, Rr 各自的 prob. 然后再乘起来)

灵魂画手时间:



Law of Probability for multiple genes:

- 2^n = number of possible gamete combinations for each parent
  Thus, 2^n X 2^n = number of genotypes
- "and" events = multiplication (product rule)
  "or" events = addition (sum rule)

(一般情况下题目问到 what is the prob. of obtaining the genotype RrYyTtss? 用 product rule;
而问到 prob. of obtaining either RRYYTTSS or rryyttss 则要用 sum rule)

1) P: RrYyTtSs X RrYyTtSs
   What is the prob. of obtaining the genotype RrYyTtss?

2) P: RrYyTtSs X RrYyTtSs
   What is the prob. of obtaining the genotype RRYYTTSS or rryyttss?

3) Female: AaBbccDDEe X Male: aaBbCcddEe
   What proportion of the progeny will phenotypically resemble the female parent?

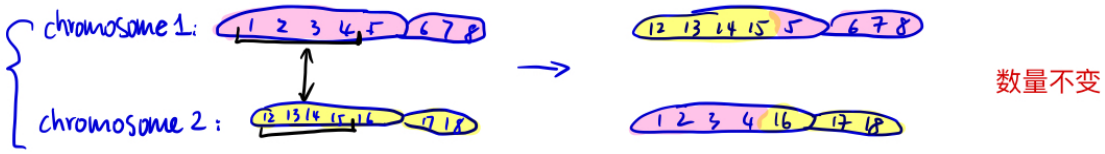
LECTURE 3: Molecular Basis of Genetic Polymorphisms & Their Detection

Mutations:

- Genes change from one allelic form to another
- Genes mutate randomly and spontaneously, or can be induced by a mutagen
- 只有在 germline cells 里的 mutations 才会被遗传，而在 somatic cells 里的不会
- Mutations are the source of allelic variation
- Mutate allele has a frequency of <1%
- 不同的 genes 有着不同的 mutation rate
- Mutations affecting phenotype occur very rarely
- Wild-type allele: frequency ⩾1%
- Mutant allele: frequency < 1%
- Monomorphic: gene with only one wilt-type allele
- Polymorphic: gene with more than one wild-type allele
- Forward mutation: change wild-type to a different allele
- Reverse mutation: change from mutate allele back to wild-type allele
- Forward mutation 的 rate almost always 高于 reverse mutation 的 rate

Classification of mutations by effect on DNA molecule:

1) Substitution: = point mutation = single nucleotide polymorphism (SNP)
   Change in only one nucleotide
2) Deletion: one or more DNA pairs is lost
3) Insertion: one or more DNA pairs is added
4) Inversion: rotate a piece of DNA
5) Reciprocal translocation: parts of nonhomologous chromosomes change places



6) Chromosomal rearrangements: affect many genes at one time

Effects of Mutations:

- Mutations will produce two different alleles of a gene
- Causing changes in DNA (gene) expression (affect transcription, splicing, translation and folding)
- Affect protein function
- Thus, affect phenotype

Classification of mutations by <u>effect on gene expression:</u>

1) Null Mutation: cause non-functional protein (最严重)
2) Leaky Mutation: cause loss of function (还能工作)
3) Silent Mutation: does not affect the function of protein (没影响)

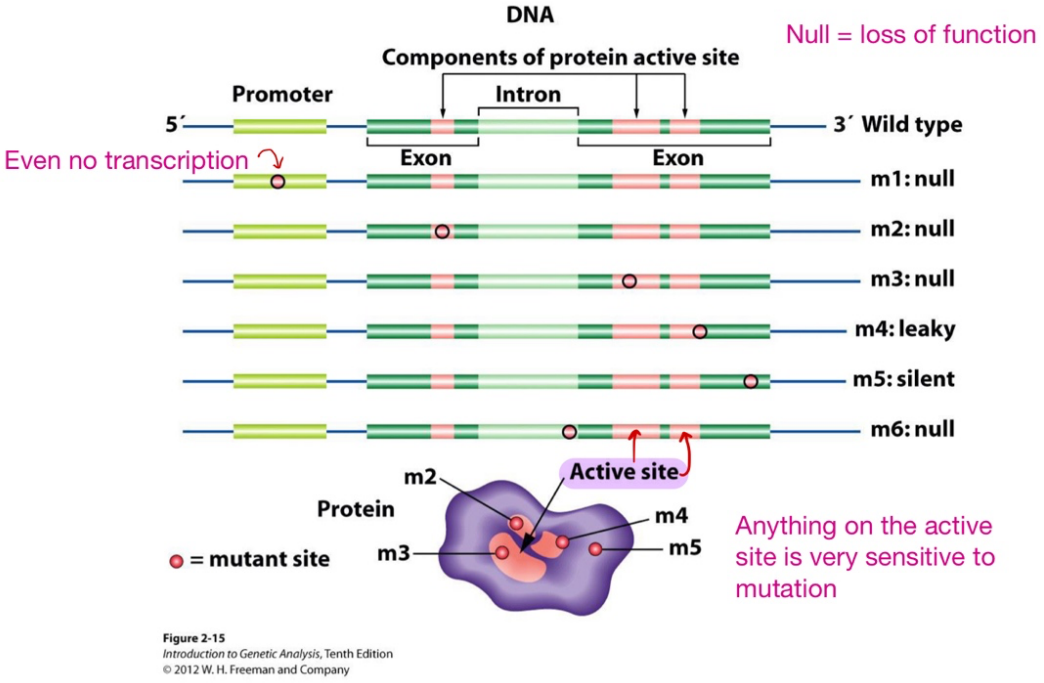


Figure 2-15
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Note: - 在 promoter 上的 mutation 连 transcription 都没有，直接 loss of function
- 在 active site 上的也都是 null，因为 active site is very sensitive to mutation
- 在 intron 的头或尾的 mutation 也比较严重，因为会导致无法 recognize splice site

The gene basis of Mendel's "antagonistic pairs":

a) Pea shape:
   - R 有 Sbe1，r 没有 Sbe1
   - RR 和 Rr 都会 produce Sbe1，从而 produce Amylopectin (round shape)
   - rr 不会 produce Sbe1，produce non-functional starch (wrinkled shape)

b) Pea stems:
   - LE can produce high activity of gibberellin (GA) 3β-hydroxylase → long stems
   - le produce low activity of gibberellin (GA) 3β-hydroxylase → short stems

Genetic basis of single-gene disorders: PKU

- PKU is caused by mutations in the PAH gene
- Resulting in low level of enz. phenylalanine hydroxylase production
- Causing a build up of toxic compound phenylpyruvic acid.
- Phenylpyruvic acid can interfere with nervous system development.
- Normally phenylalanine will be convert into tyrosine.

Classification of mutations by <u>effect on phenotype:</u>

1) Haplosufficiency
   - 50% of the protein product is sufficient to give wt phenotype.
   - Mutation is recessive
2) Haploinsufficiency
   - 50% of the protein product is not enough to give wt phenotype.
   - Mutation is dominant
3) Dominant negative
   - Mutant allele will produce a mutant protein that bind and inactivate a wt protein in a dimer. Function like an antagonist.

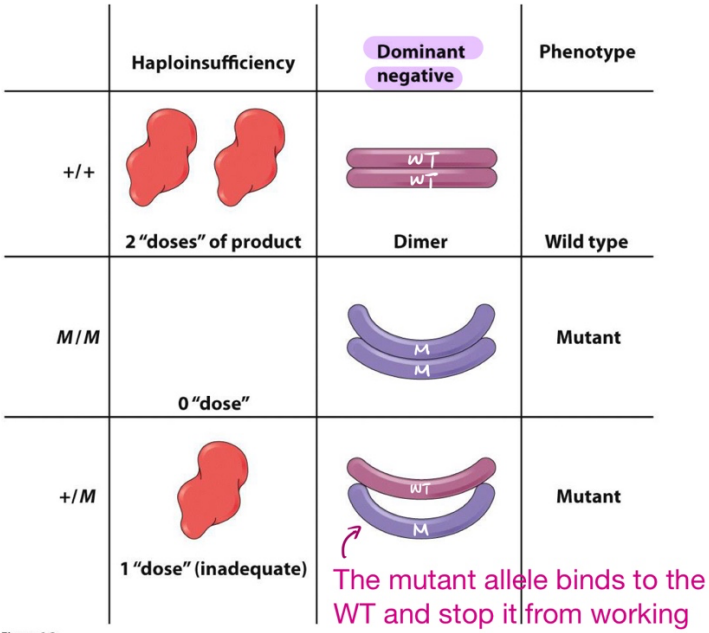

Figure 6-2
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Detection of allelic polymorphism at the molecular level:

1) PCR & DNA sequencing
   - 我们一般先用 PCR 来做 amplification，再做 DNA sequencing
   - Use SNP detection approaches at identified SNP to screen at-risk relatives
2) New Technologies:
   - Next-generation sequencing: cheaper & can allow massive amounts of sequencing

Principles of allele detection:

1) Attempting to visualize allelic polymorphism
2) At the level of DNA sequence
3) Can detect polymorphism from DNA to protein level
4) Analysis performed on diploid nuclear genome