单基因遗传病
Monogenic Diseases

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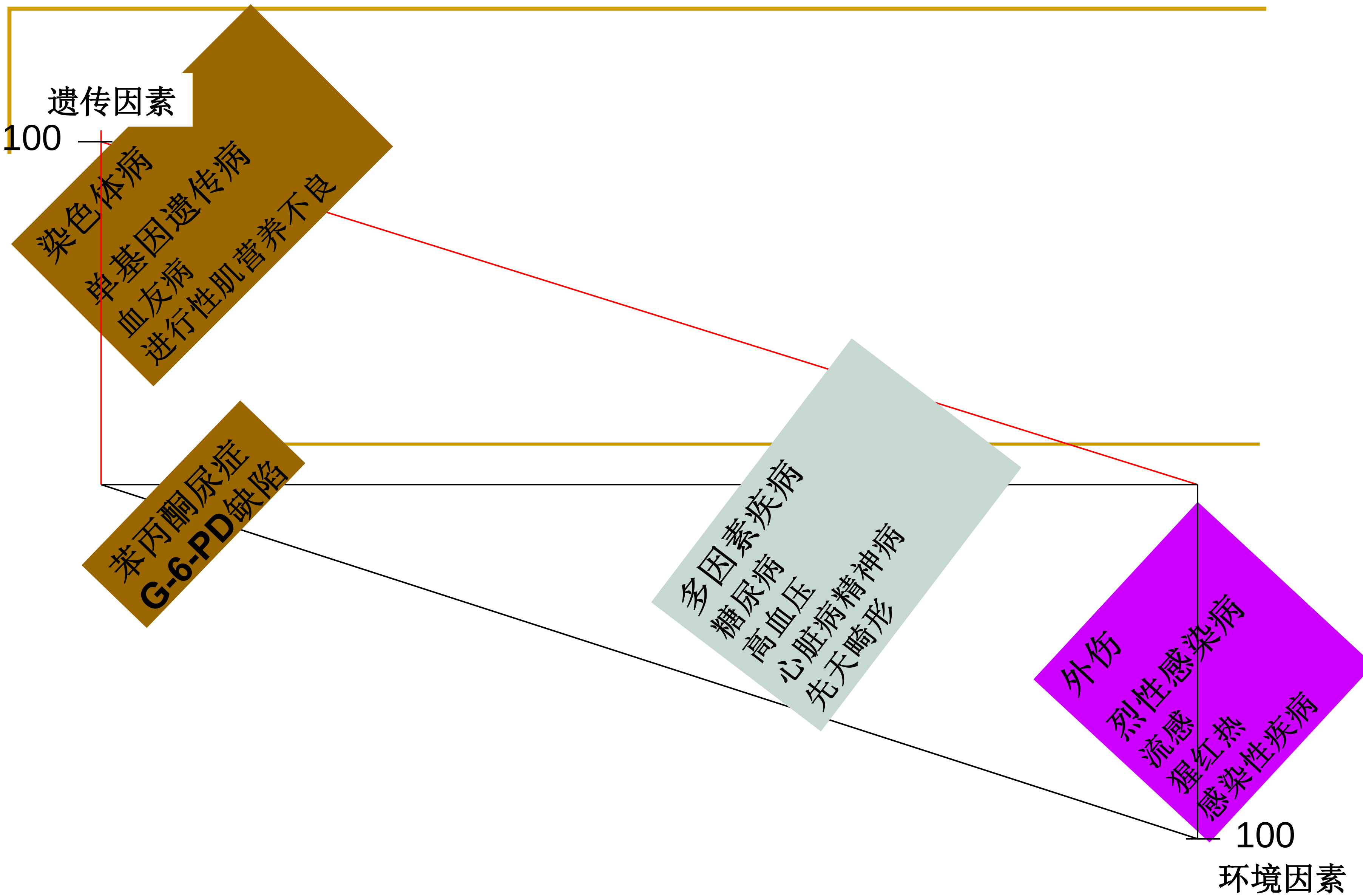
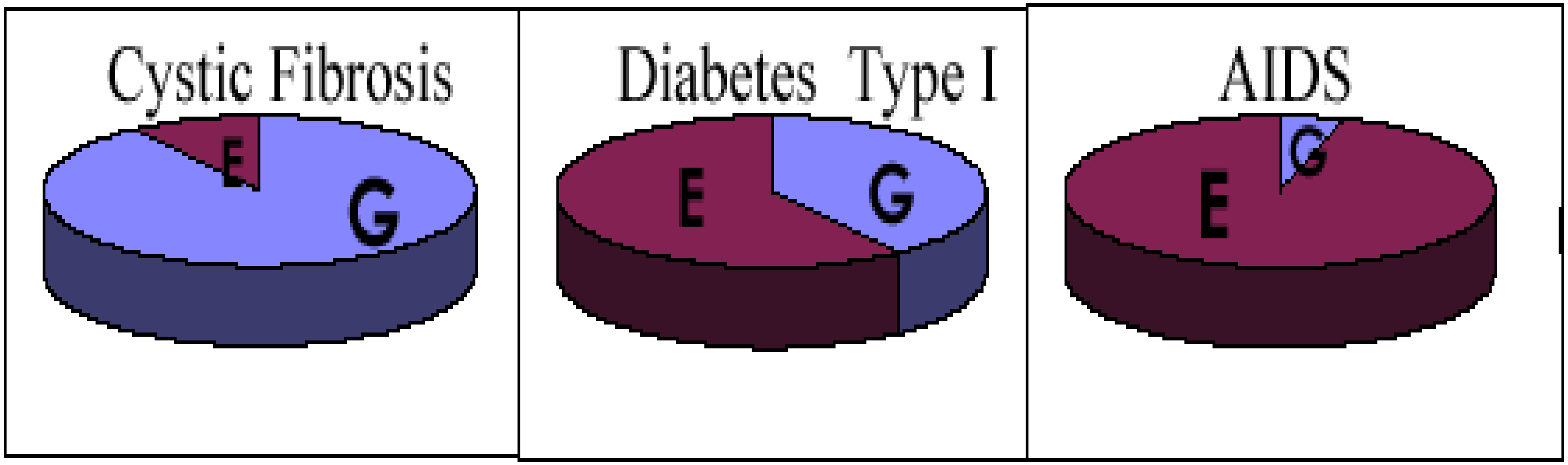
疾病发生中的遗传因素和环境因素



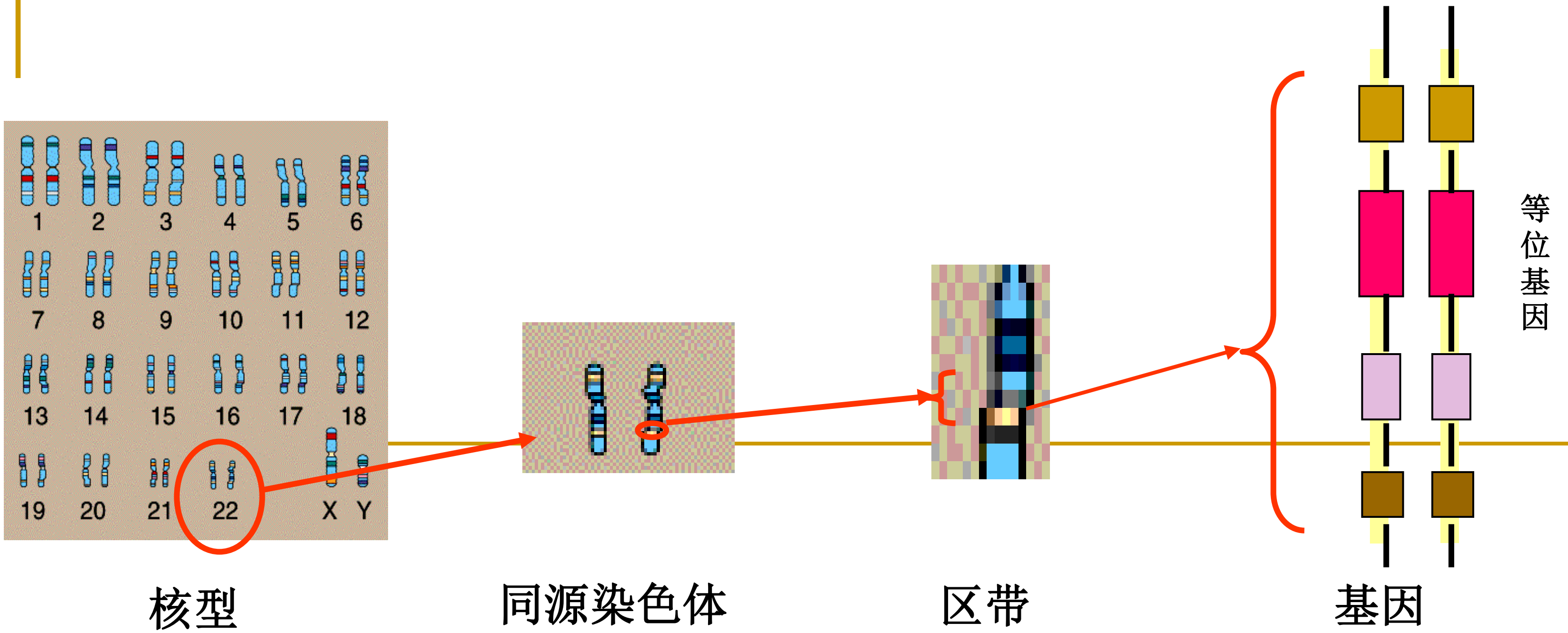
Genes Play an Important Role In All Human Disease



Patterns of Human Inheritance

- Monogenic, rare diseases
  - Mundelein
    - Autosomal dominant
    - Autosomal recessive
    - X- linked
  - Non-Mendelian
    - Y-linked
    - Mitochondrial diseases
- Multifactorial
    - Common diseases
    - Somatic diseases
- Chromosomal

染色体、基因、等位基因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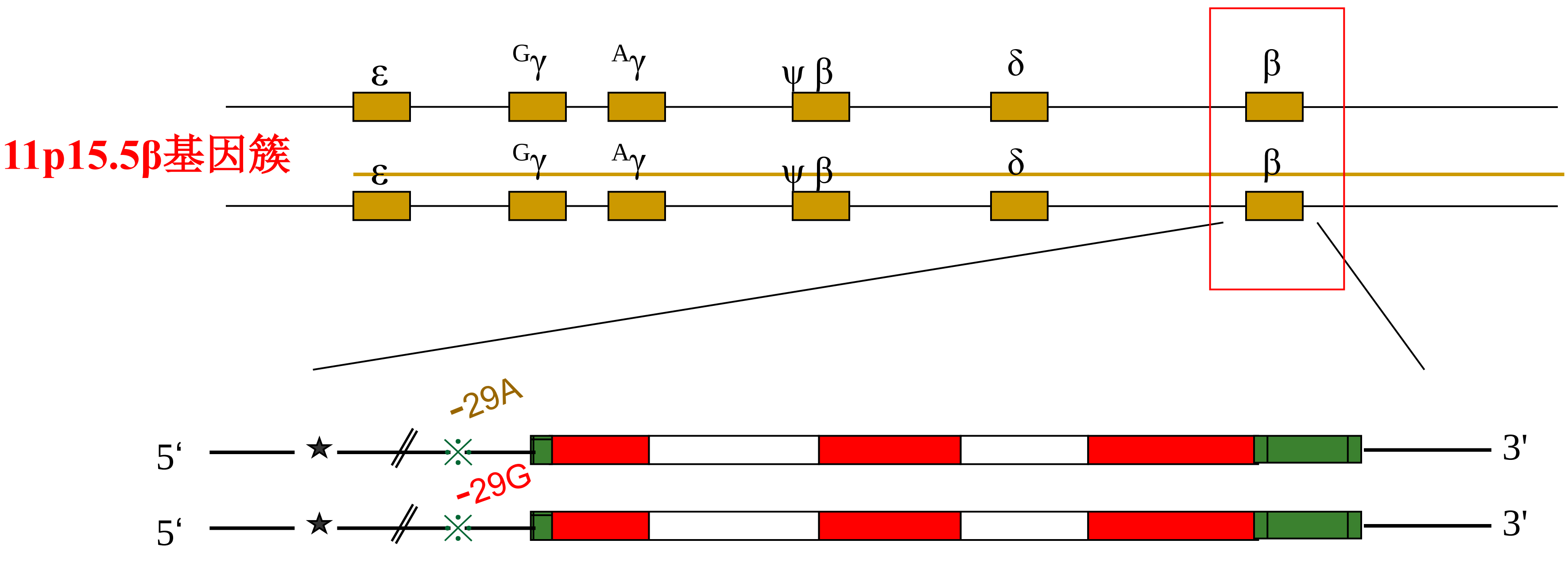
21
22
X
Y
等位基因
核型
同源染色体
区带
基因

等位基因(allele)

同一基因座的不同形式或多态性DNA标记位点的多态性DNA片段，彼此称为等位基因(allele)。



基因突变

- 类型：基因突变在遗传物质的改变上，无非两种情况：
  - 量（DNA长度增加或减少）
  - 质（核苷酸的取代）
- 后果：
  - 导致基因功能异常的突变称为致病突变(disease-producing mutation)，
  - 不引起基因功能改变的称为多态性(natural variation或DNA polymorphisms)。

表现型与基因型

- 人们通常观察到的是个体的表现型(phenotype)
- 基因型(genotype）：个体在一个基因座上两个等位基因的组成类型;
  - 基因型决定表型，取决于两个等位基因在表型产生中的作用是否相同（显隐性）。

Genotype

Definition：The genetic constitution of an individual cell or organism.

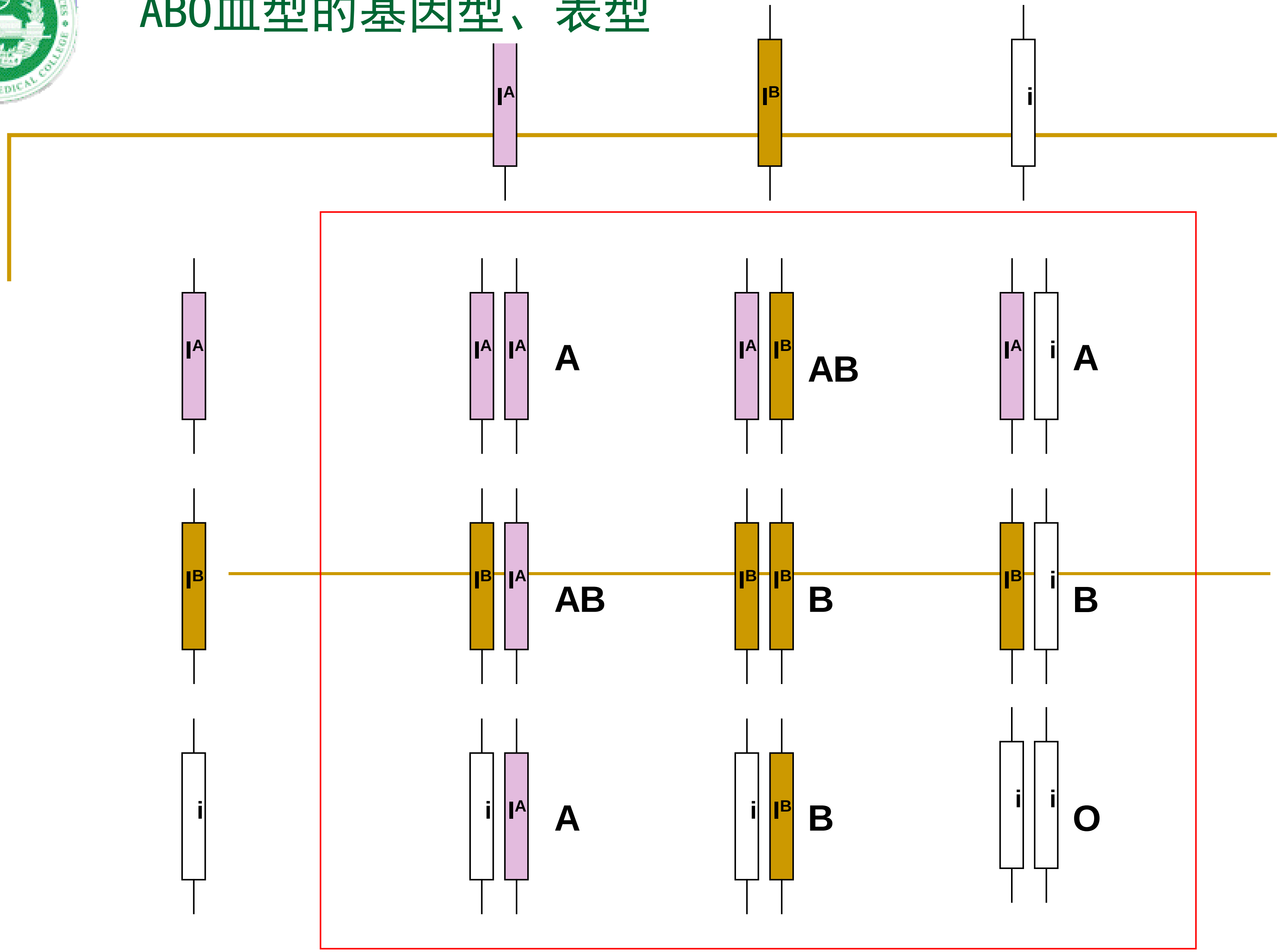
- Homozygous： two identical alleles at a locus
  - Functionally（normal，mutant）
  - Structurally（ identical sequence ）
- Heterozygous： two different alleles at a locus, usually one mutant & one wild-type
  - Compound heterozygous: two different alleles, both usually mutant at a locus
  - Double heterozygous: heterozygous at two different loci

Phenotype

Definition: The observable character of a cell or organism

- Dominant vs recessive
  - Dominant: Mutation of one gene copy (allele) that results in a disease phenotype；
  - Recessive: Mutation of both alleles of the gene which gives rise to a disease phenotype；
  - Co-dominant: character expressing for both alleles of the heterozygote

ABO血型的基因型、表型

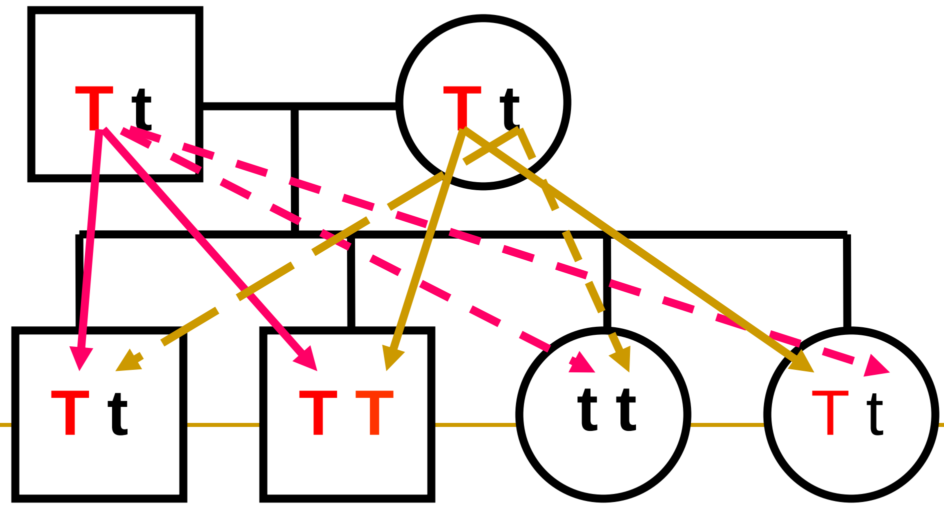


Hereditary pattern of disease

Denpends on

- Which chromosome it located
- The dominant or recessive of the alleles

等位基因‘T’在家系中的传递

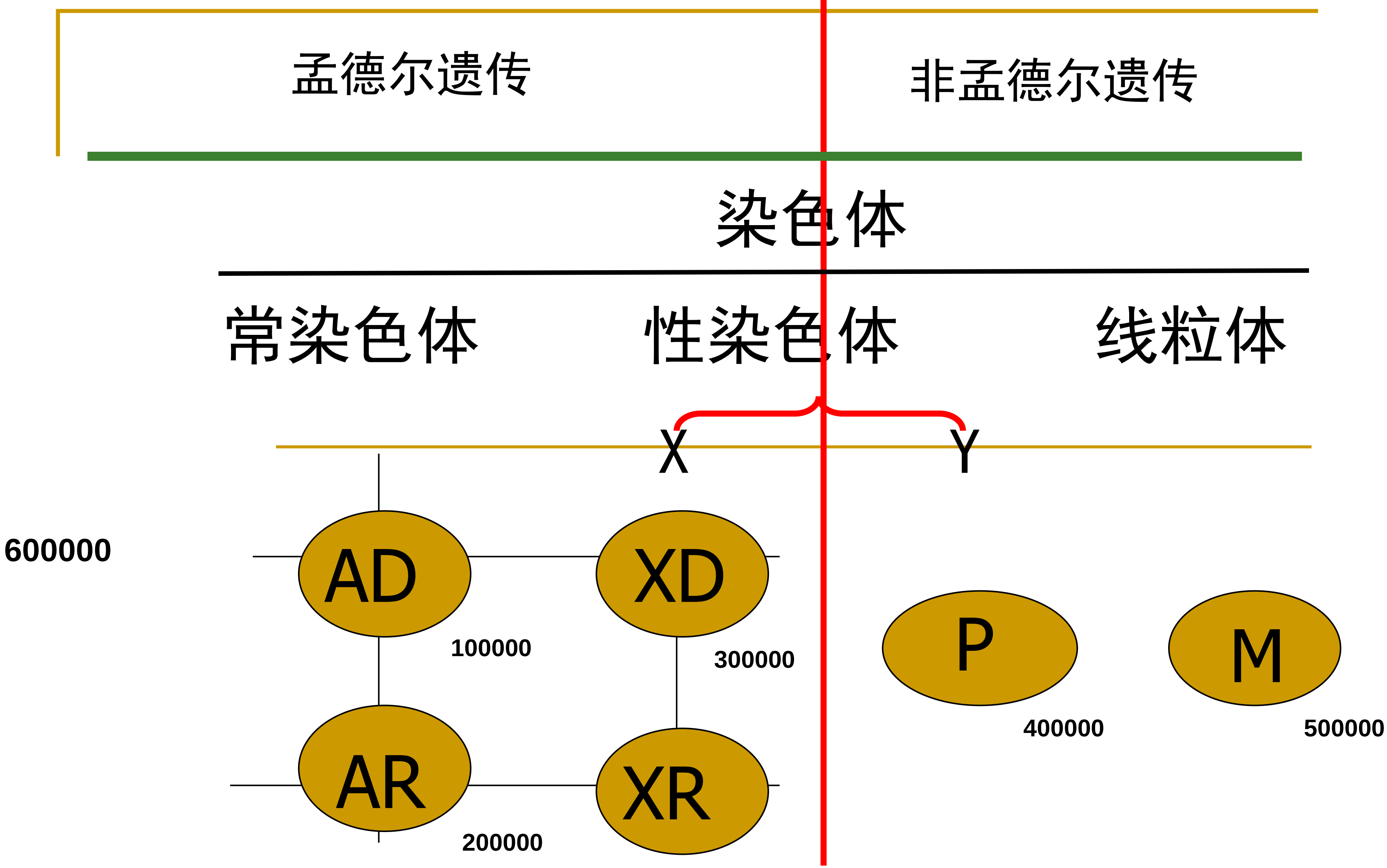


世代传递的是等位基因

- 父母只将其½遗传物质传递给子代（男性特殊，X染色体传给女儿、Y染色体传给儿子）
- 从祖先传递给后代而共享的遗传物质被逐代稀释（≦$½^n$)
  - 共享的染色体区域越来越短（不断互换的结果）
  - 姓氏中男性唯一保持不变的是Y染色体
  - 线粒体由女性传递
- 性状（疾病，表型）不一定世代传递（取决于基因型，显隐性）

Hereditary pattern of disease

世代传递着的是基因突变而不是疾病



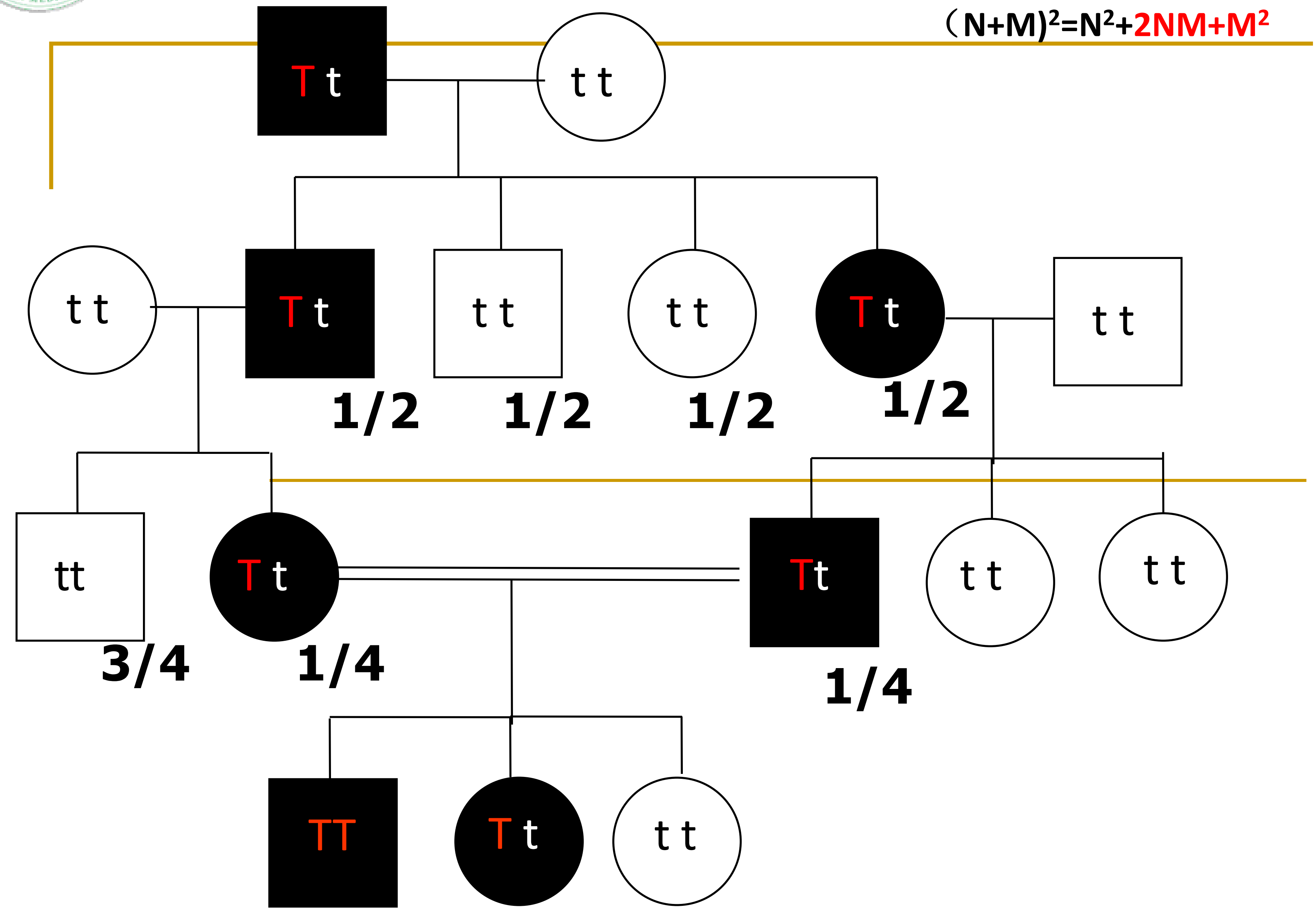
Autosomal dominant disease

- **Gene located on the chromosomes 1 to 22,**
- **the heterozygote is affected,**
- **Homozygous case is rare, the phenotype is more several than heterozygote.**

显性疾病:

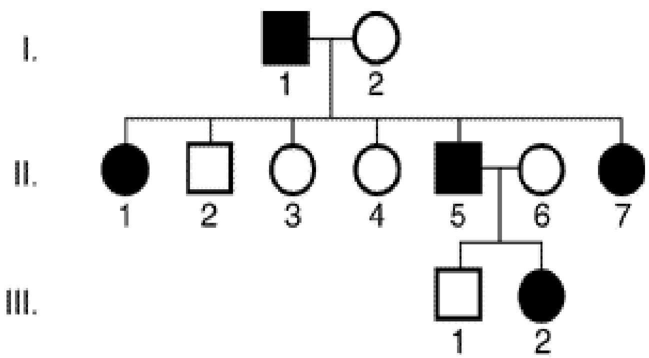
Ex: 家族性高胆固醇血症

$(N+M)^2=N^2+2NM+M^2$



Autosomal dominant disease

- Inheritance from only one parent
- Vertical transmission
- Males and females equally affected
- Affected parent has 50% chance of transmitting the trait to each offspring
- At least one male to male transmission
- More severe phenotype associated with higher frequency of sporadic or non-inherited cases

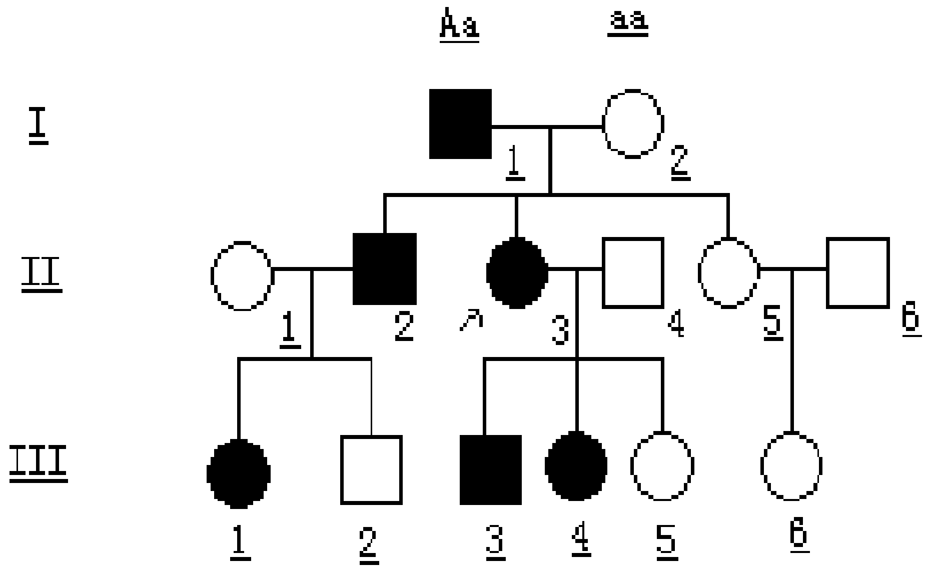


Autosomal Dominant Inheritance

- Molecular pathophysiology
- Dominant loss of function
- Dominant gain of function:a mutation that causes inappropriate expression or function of the gene product
- Dominant negative effect :a mutation which results in a mutant gene product that can inhibit the function of the wild-type gene product

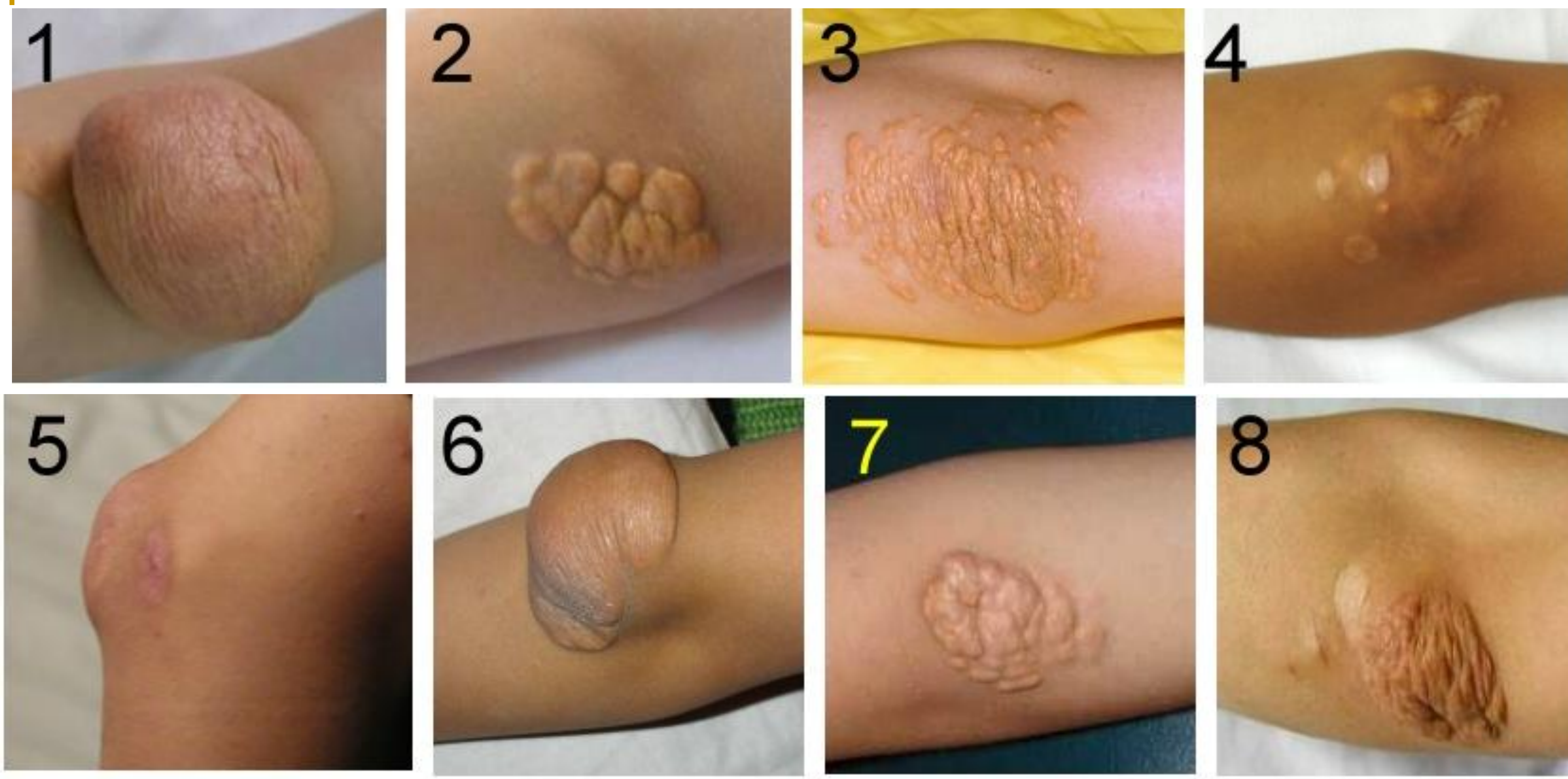
Incomplete dominance

semidominance: the phenotype is more severe in homozygote (AA) than heterozygote (Aa)



Familial hypercholineterinemia

家族性高胆固醇血症纯合子
--肘部黄色瘤



Irregular dominance

Definition: the heterozygote may express the corresponding phenotype or not express, or expressed at different extent。

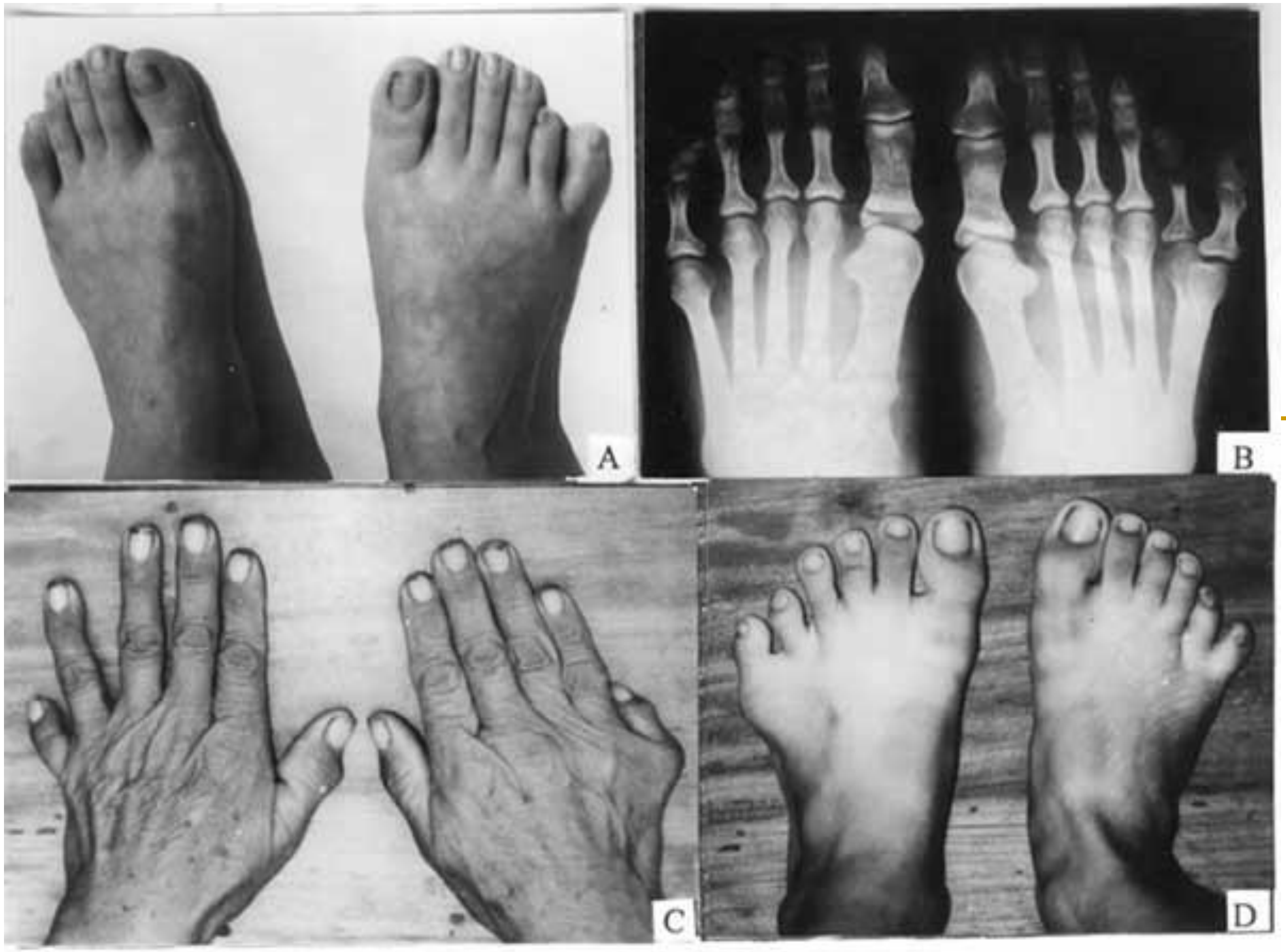
- **Causes for irregular dominance：**
  - **Penetrance外显率**
  - **Expressivity表现度**

Penetrance

Definition: A term indicating the likelihood that a given gene will actually result in disease.

- **Completed penetrance：the penetrance is 100%**
- **decreased penetrance：part of the individuals are affected, but the others are not affected.**
  - **the highest penetrance are 70~80%**
  - **the lowest are 20~30%**

Variable expressivity

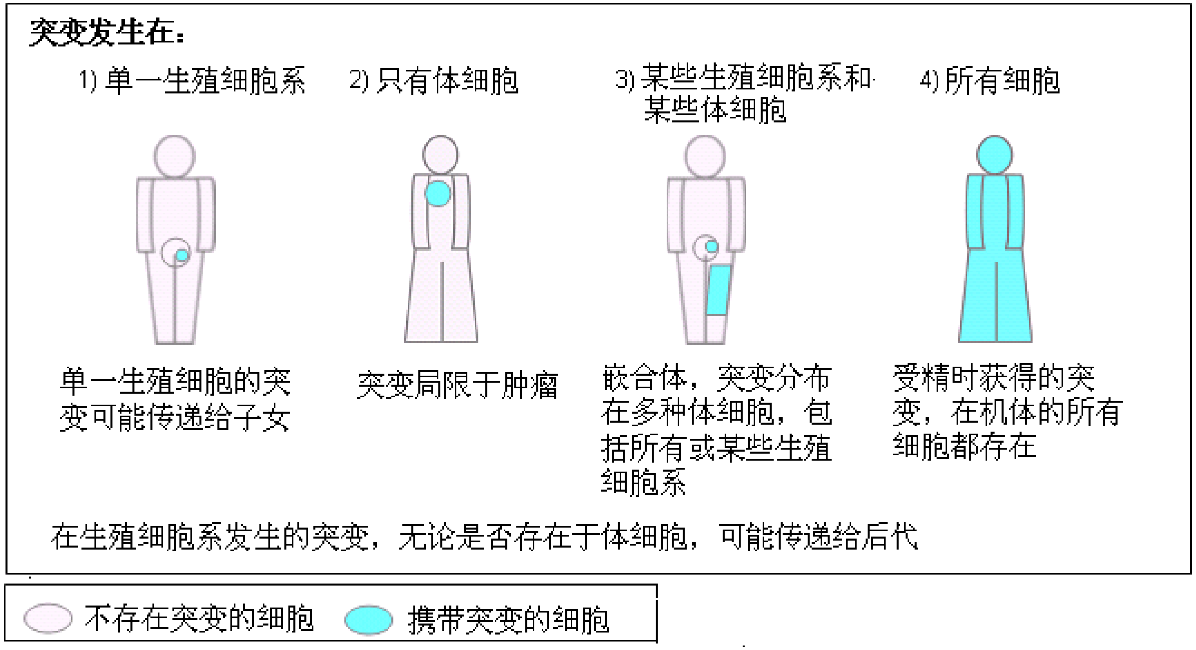


软骨发育不良

发病率1/10000~40000，80%为新生突变。99%病例为 *FGFR3* (Ch.4)
G380R(98%为1138位 G>A, 1%为G>C)

新生突变

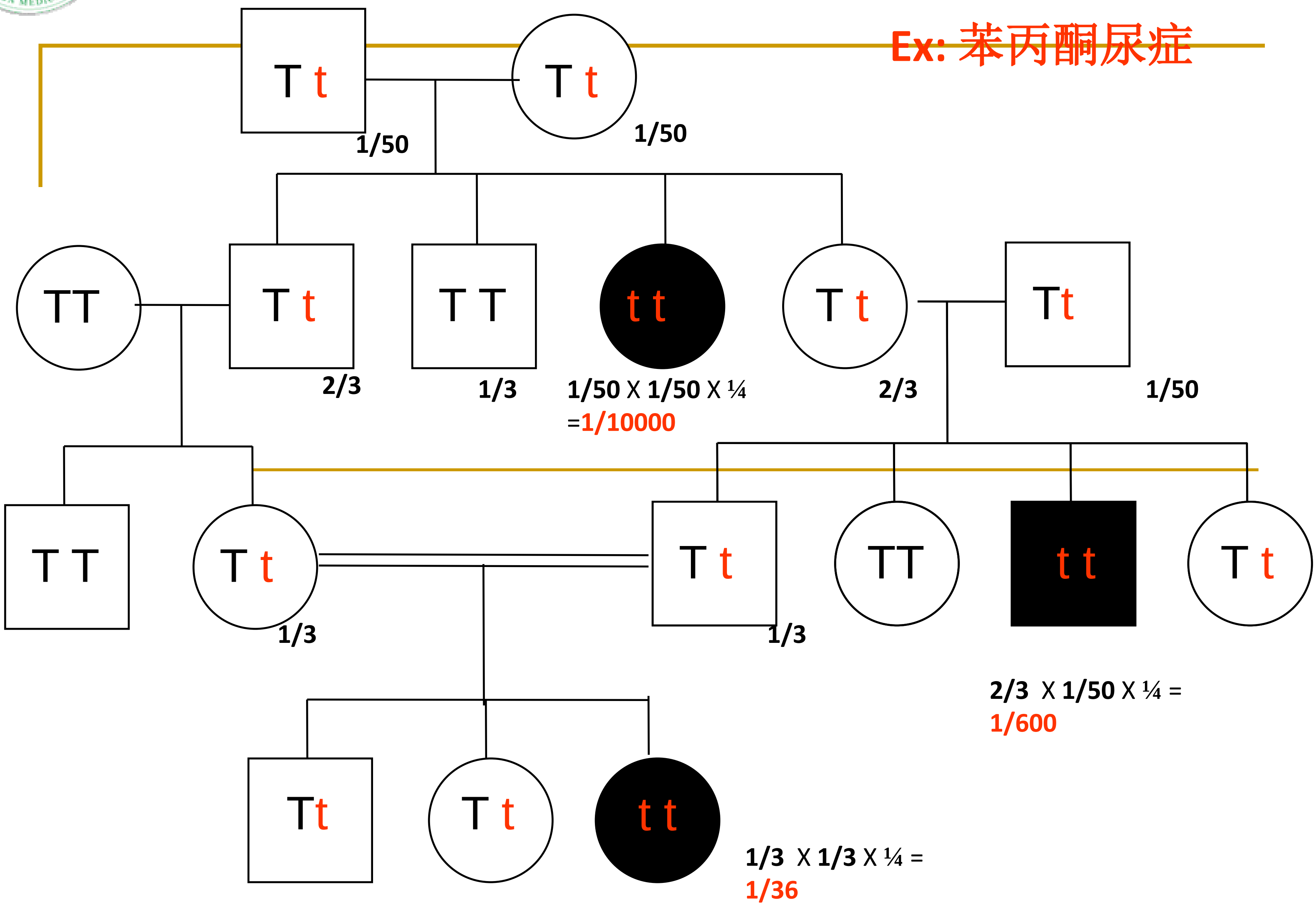
- 严格意义上的新生突变——减数分裂事件
- 个体发育过程中的突变
  - 体细胞嵌合
  - 生殖腺嵌合



Autosomal Recessive Inheritance

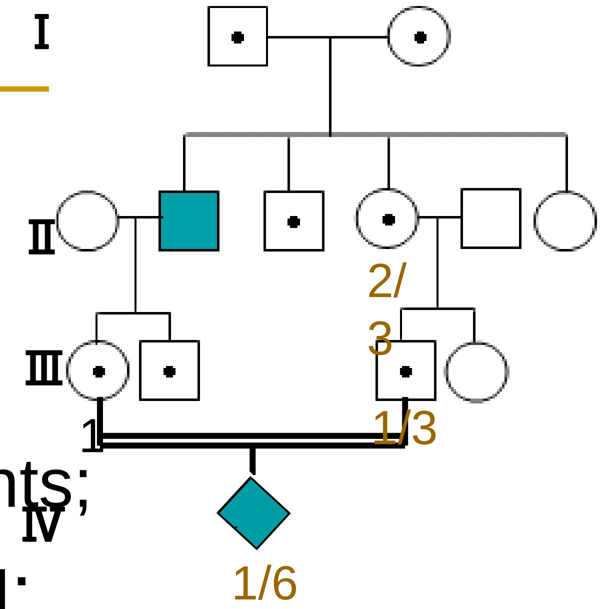
- The mutant gene located on chromosomes 1-22,
- Heterozygote is not affected
- Homozygote is affected

常染色体隐性遗传:



Ex: 苯丙酮尿症
T t
T t
1/50
1/50
TT
T t
T T
t t
T t
Tt
2/3
1/3
1/50 X 1/50 X ¼
=1/10000
2/3
1/50
T T
T t
T t
TT
t t
T t
1/3
1/3
2/3 X 1/50 X ¼ =
1/600
Tt
T t
t t
1/3 X 1/3 X ¼ =
1/36

Autosomal Recessive Inheritance



- **Characters:**
  - Horizontal pattern in a pedigree;
  - Inheritance from both healthy parents;
  - Males and females equally affected;
  - One fourth of the sibling are affected;
  - Offsprings are usually normal, unless the patient is married to a heterozygote;
  - Increased incidence in consanguineous marriage。

苯丙酮尿症

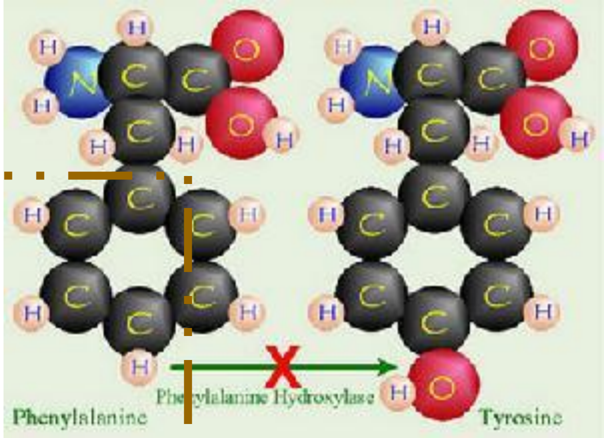
http://www.google.com.hk

Phenylketonuria, PKU I

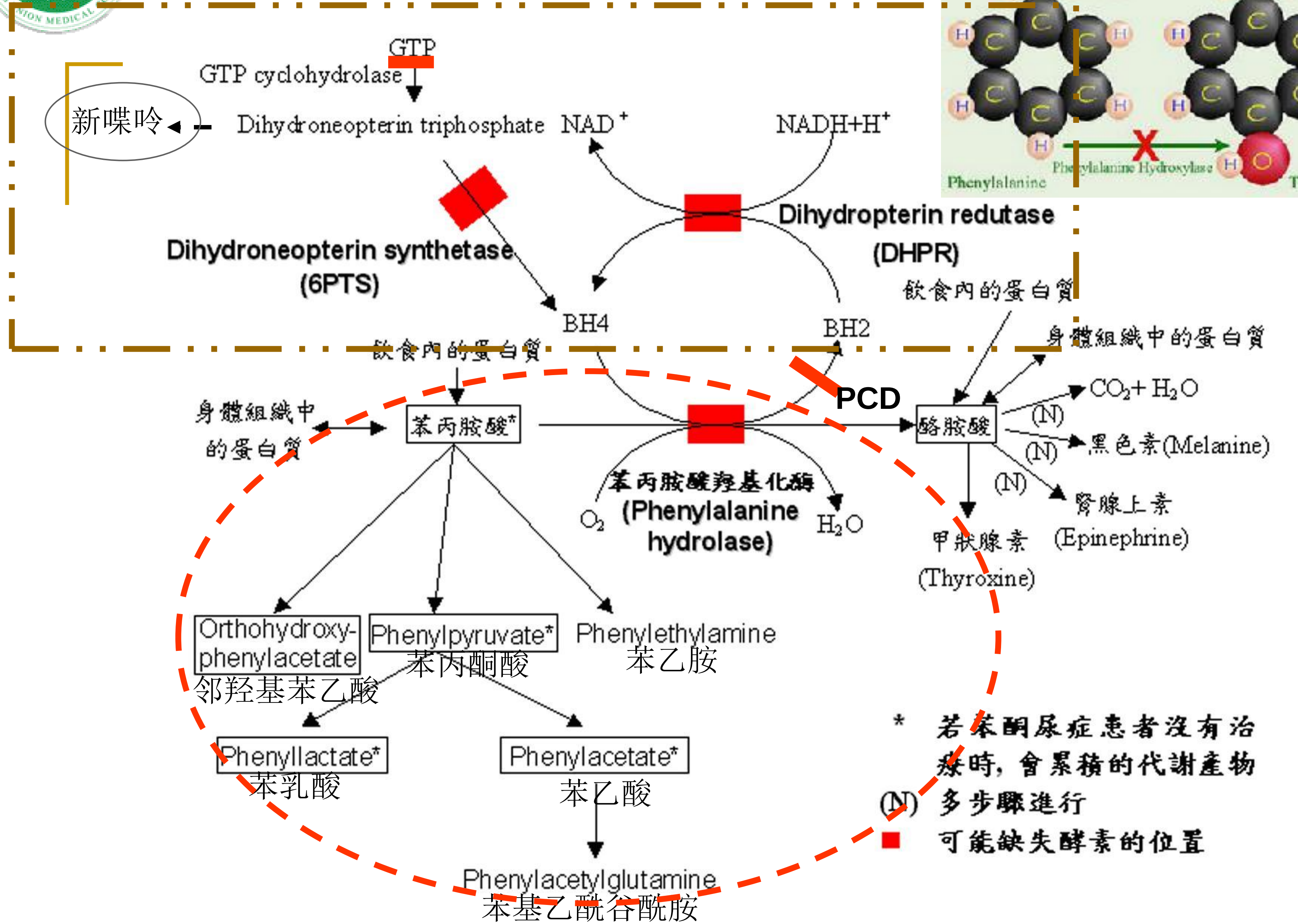
- PKU is caused by a complete or near-complete deficiency of phenylalanine hydroxylase activity; without dietary restriction of phenylalanine, most children with PKU develop profound and irreversible mental retardation.
- **The incidence of HPA is 1/11144 in China.**

甘肃	7.76
新疆	7.18
山西	3.00

高苯丙氨酸血症



Phenylalanine
Phenylalanine Hydroxylase
Tyrosine



GTP
GTP cyclohydrolase
新喋呤
Dihydroneopterin triphosphate
NAD^+
$NADH+H^+$
Dihydropterin redutase
(DHPR)
Dihydroneopterin synthetase
(6PTS)
BH4
BH2
飲食內的蛋白質
飲食內的蛋白質
身體組織中的蛋白質
身體組織中
的蛋白質
PCD
苯丙胺酸*
酪胺酸
CO_2+H_2O
(N)
黑色素(Melanine)
(N)
(N)
腎腺上素
(Epinephrine)
甲狀腺素
(Thyroxine)
苯丙胺酸羥基化酶
(Phenylalanine
hydrolase)
O_2
H_2O
Orthohydroxy-
phenylacetate
邻羟基苯乙酸
Phenylpyruvate*
苯丙酮酸
Phenylethylamine
苯乙胺
Phenyllactate*
苯乳酸
Phenylacetate*
苯乙酸
Phenylacetylglutamine
苯基乙酰谷酰胺
* 若苯酮尿症患者沒有治療時，會累積的代謝產物
(N) 多步驟進行
可能缺失酵素的位置

BH4 缺陷

- **BH4** 合成缺陷：
  - 三磷酸鸟苷环化水解酶（**guanosine triphosphate cyclohydrolase，GTPCH)**缺陷；
  - **6-**丙酮酰四氢生物喋呤合成酶（**pyruvoyl tetrahydrobiopterin synthase，PTPS)** 缺陷；
- **BH4** 循环缺陷：
  - 二氢生物喋啶还原酶（**dihydropteridine reductase，DHPR)**缺陷；
  - 喋呤**-4α**甲醇胺脱水酶（**pterin-4 a carbinolamine dehydratase，PCBD1)**缺陷。
- 常染色体隐性遗传
- **BH4** 还参与酪氨酸、 色氨酸羟化反应和儿茶酚胺、五羟色胺、含氮氧化物生物合成 。故该型患者症状更重，得名“恶性”

中国人BH4

诊断	地区	PAH 发病率*	BH_4/HPA 比例
PTS缺陷	台湾	1/31,000	19% *
	广州	1/33,000	20%
	上海	1/17,000	10 ~ 16%
	北京	1/11,000	6 ~ 7%
DHPR缺陷	台湾(2个家庭，3个患者)		

* 根据新生儿筛查数据

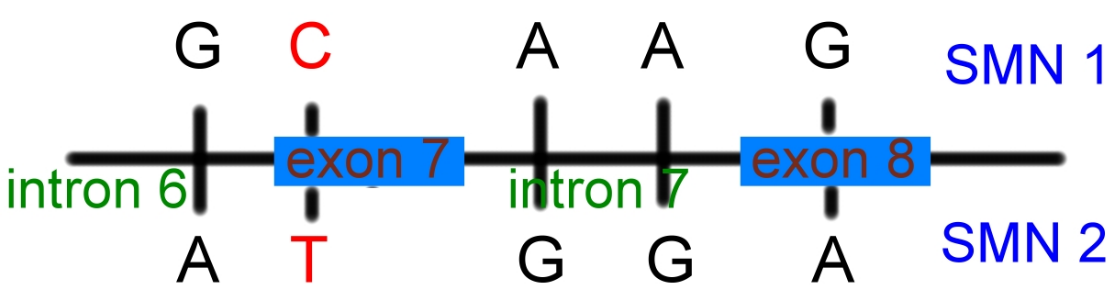
最新研究显示：
上海PTPSD占97%

肖广仁2008.9

“软孩”

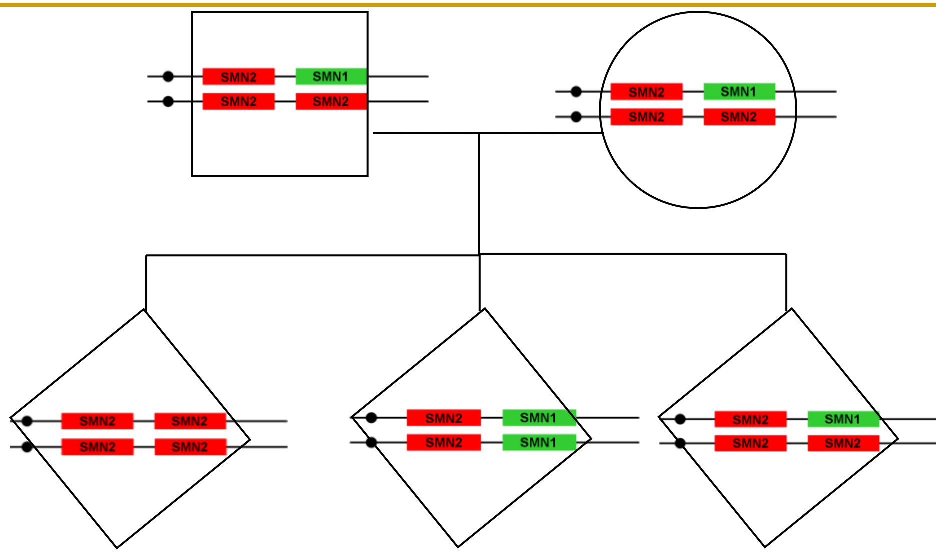
SMN 基因

- 两个基因有高度的同源性，都广泛表达，选择性剪接产生较小的异型体：
  - SMN1
    - 全长有功能的 1.7 kb mRNA (~90%)
    - 缺外显子 5 (10%)
  - SMN2，因外显子7 +6位 C→T 取代，导致选择性剪接而使外显子7跳越，失去功能
    - 转录本缺外显子 5 或 7;
    - 转录本缺外显子5和7
    - 全长 SMN mRNA (20-30%)



SMN1基因突变

- 90~98% 的患者纯合缺失外显子 7（大部分还缺失外显子 8）；
- 错义突变
- 还有一些微小的缺失和重复



X-linked Inheritance

- Male is hemizygous, and is always affected
- No male to male transmission
- Heterozygous females nearly always
  - affected, if XD
  - unffected, if XR
- Females typically less severely affected than males

X连锁显性遗传病

- X-连锁低磷酸血症（hypophosphatemia，抗维生素D 佝偻病）

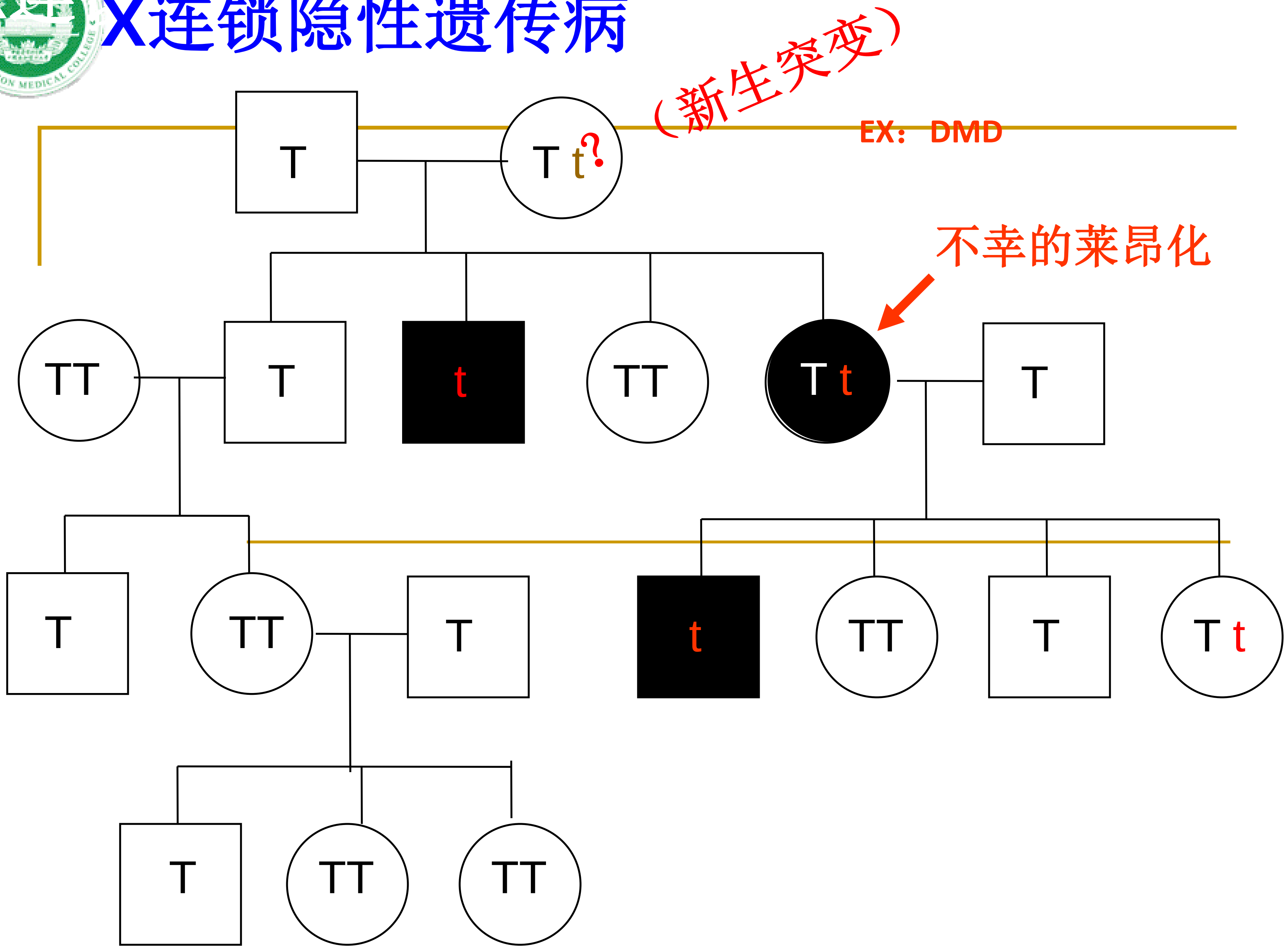
pathophysiology:
 - decreased reabsorption of phosphate by the renal tubule (causing hypophosphatemia) (otherwise the renal function is normal);
 - decreased absorption of calcium and phosphorous from the GI tract;


diff dx:
 - metaphyseal chondrodysplasia
 - hypophosphatasia:
 - in contrast to vitamin D resistant rickets, hypophosphatasia shows a reduction in serum alk phos;

Hemizygous lethal in males

- Only females affected
- Affected females
  - have fewer sons than expected
  - Half of the daughters are affected
- Affected females have increased frequency of spontaneous abortions
- **Example:** 色素失调病和**Goltz**综合征

X连锁隐性遗传病



X-linked Recessive Inheritance

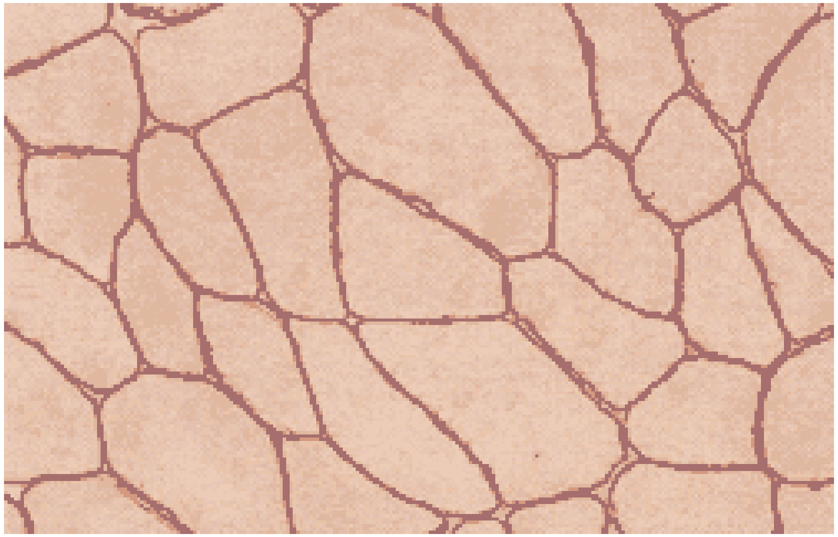
- **Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy (BMD);**
- **Hemophilia A**

- ***de novo* mutation**
- **Gonad mosaicism**

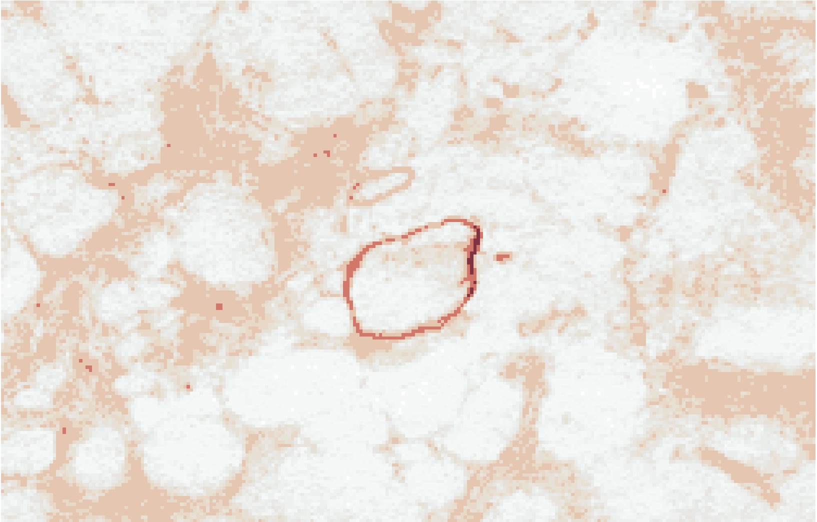
Gowers 征

腓肠肌肥大

Dystrophin 免疫组化检测



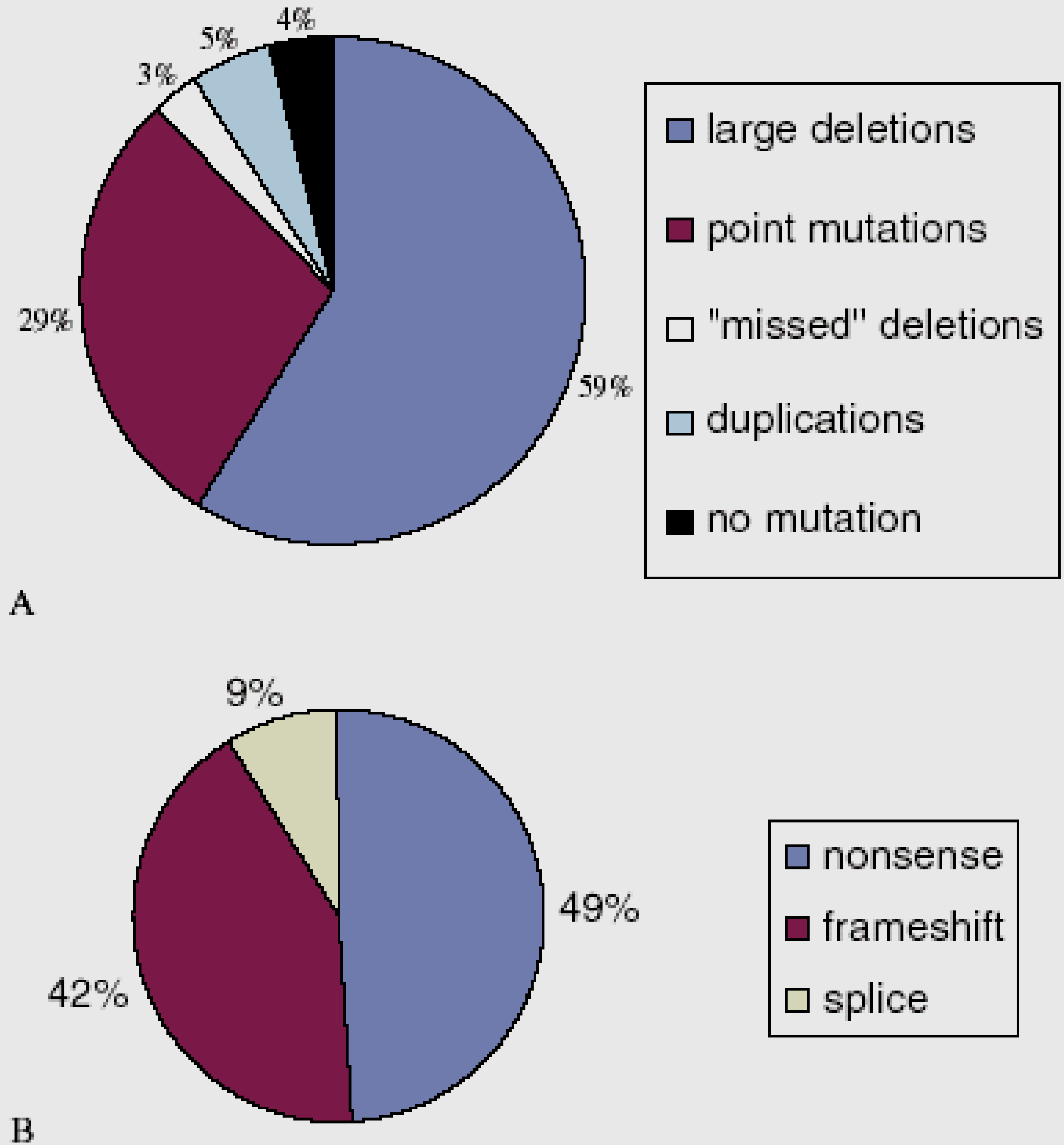
正常肌肉



患者

Western 印迹杂交

DMD突变类型


4%
5%
3%
29%
59%
large deletions
point mutations
"missed" deletions
duplications
no mutation
A
9%
49%
42%
nonsense
frameshift
splice
B

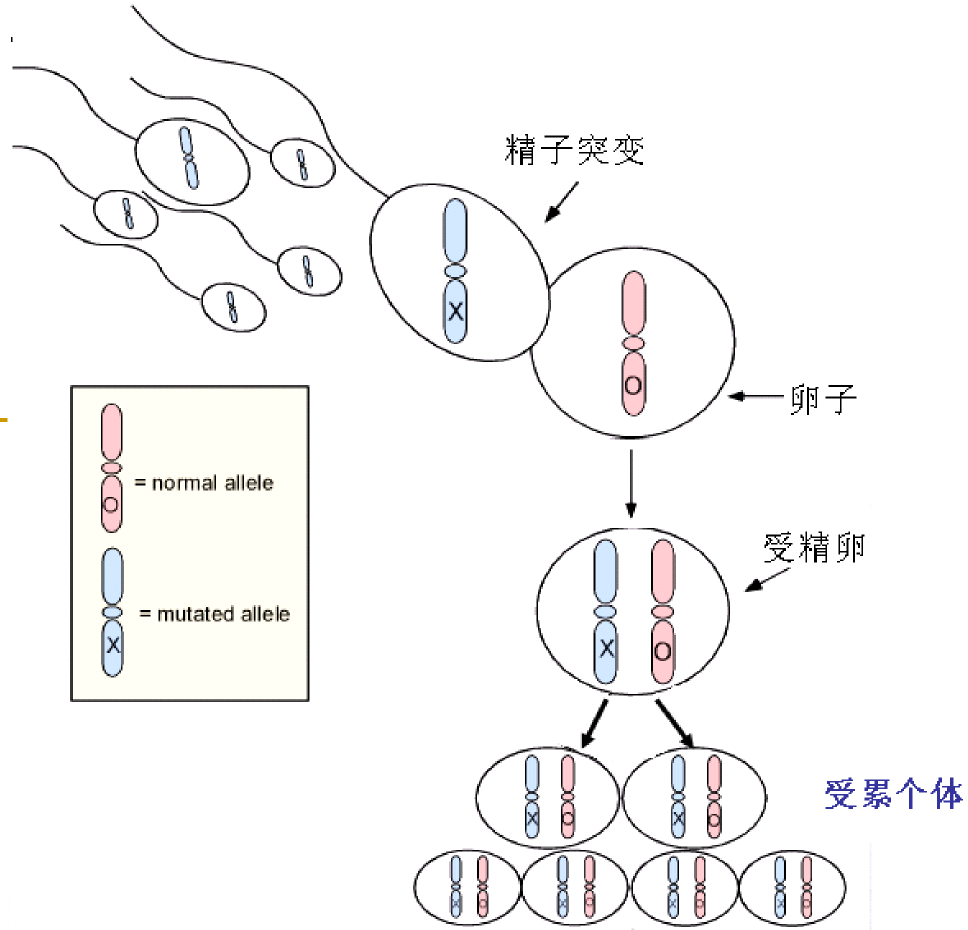
肌营养不良病的遗传异质性

- **DMD**
- **SMA**
- **MD(Myotonic Dystrophy，强直性肌萎缩）**
  - 此疾病除了进行性肌无力外，还有其他特征，如肌强直（肌肉收缩之后不能松弛，常发生早发性白内障，心脏受累，受累的肌肉有面部、前臂和小腿肌肉。
  .
- **肢带型肌萎缩（LGMD）**
  - 由许多基因缺陷引起
- **面肩肱型肌萎缩（FSHD）**
  - 面部肌肉无力，患者不能吹口哨，睡觉时不能闭眼
- **先天性肌病Congenital Myopathy**
  - Nemaline Myopathy. Central Core Disease, Myotubular Myopathy.

遗传异质性(heterogeneity)

- Definition (1): The same clinical phenotype causing by different loci (locus heterogeneity)
  - There are more than 100 loci responsible for deafness
  - APKD: PKD1(Ch.16)、PKD2(Ch4.)、PKD3
- Definition (2): different mutant alleles of the same locus cause different phentoypes (allele heterogeneity)
  - β hemoglobin gene mutations: abnormal hemoglobins, sickle cell anemia, β thalassemia
  - Osteogenesis imperfecta: mutation of COL1A1 (dominant negative mutation)

新生突变来源于外祖父时，要警惕父源生殖腺嵌合

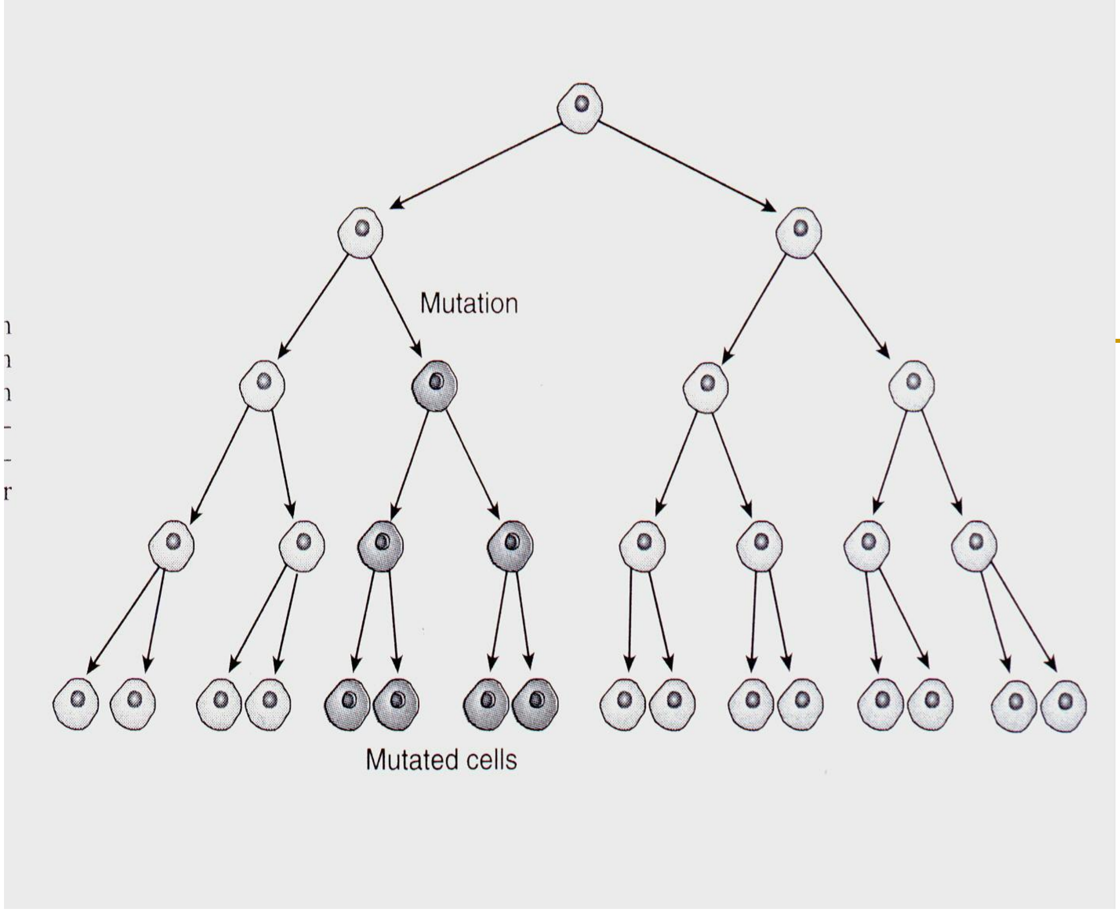


X chromosome inactivation ——Lyonization

- Lyon hypothesis (Lyon，1961): most part of one X chromosome in human female is heterochrmatide without genetic activity.
  - X inactivation occurred in the early embryonic stage.
  - The inactivation is random for either X chromosome (paternal or maternal) if they are both normal
  - The daughter cells remain the inactivation pattern
  - Since there are handrens of cells in the embryo when lyonization occurs, all females are composed of two cell lines.

Mosaicism

Definition: Presence in an individual or a tissue of at least two cell lines that differ genetically



Mosaicism

- Chimera: two cell lines in the same organism resulted in fussing of two zygotes, fertilizing eggs or egg and the polar body.
- Mosaic: numberary or structural abnormalities of chromosome caused by chromosome non-disjunction, chromosome loss or intranucleic replication, and chromosome breakage as will as chromosome rearrangement, occuring in early cleavage of the zygote.

Y-linked inheritance

- Male to male transmission
- Only male are affected

Mitochondria disease

- **Heteroplasmic: Mitochondria DNAs are mixture of wide type and mutant DNAs.**
- **Maternal inheritance.**
- **Replication advantage of defected mitochondria DNA, homoplasmic.**
- **Later onset, progressive, and threshold.**