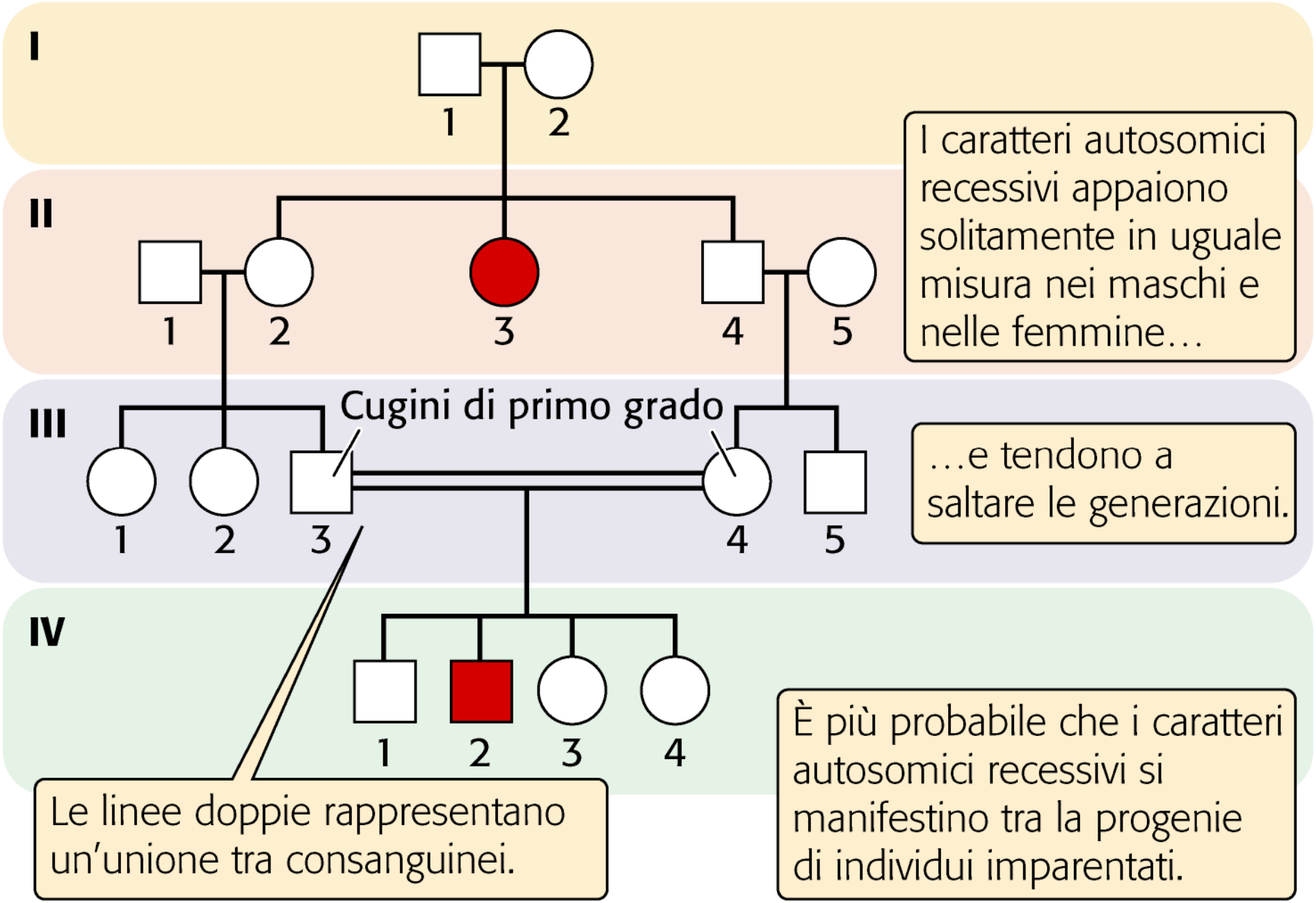
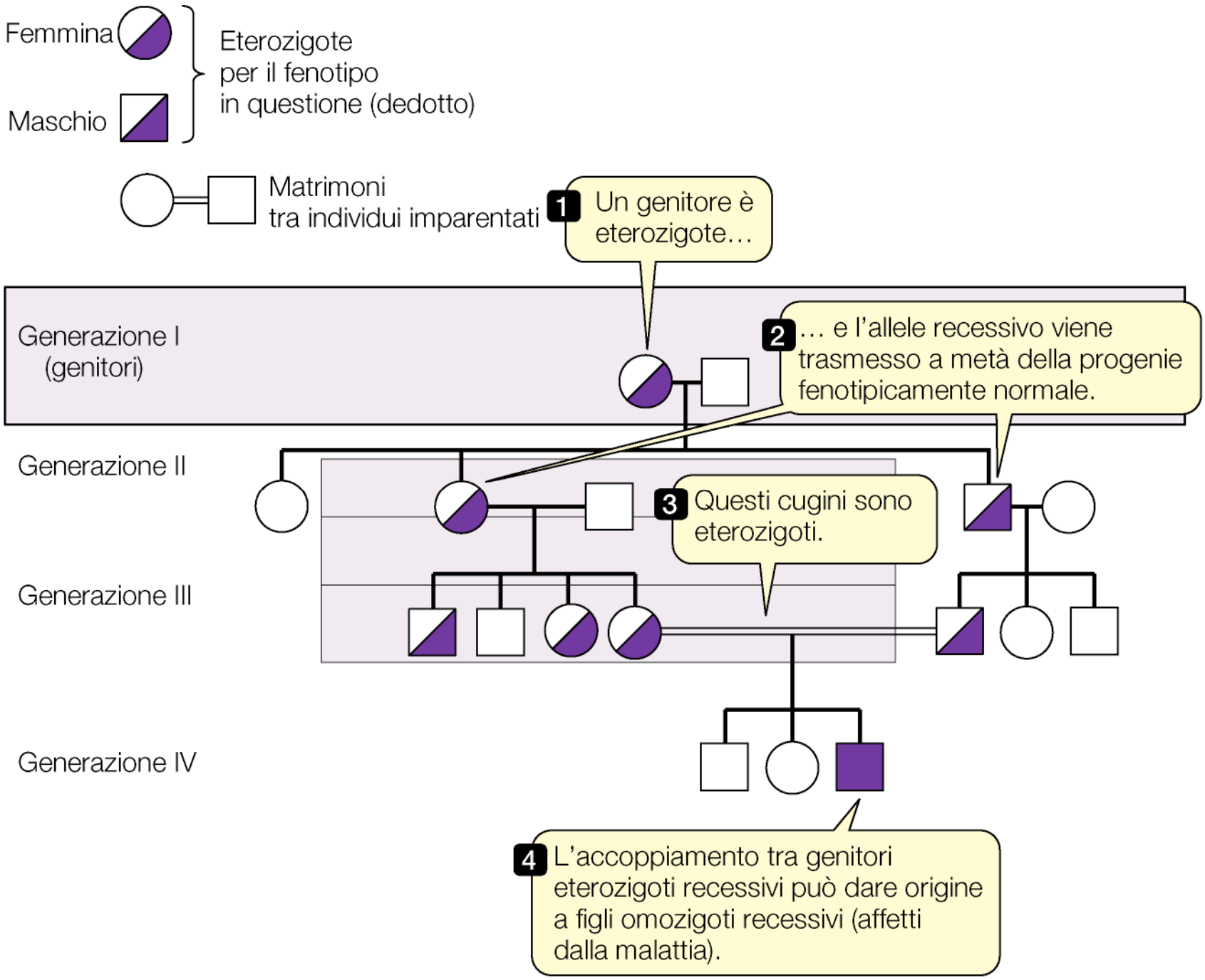
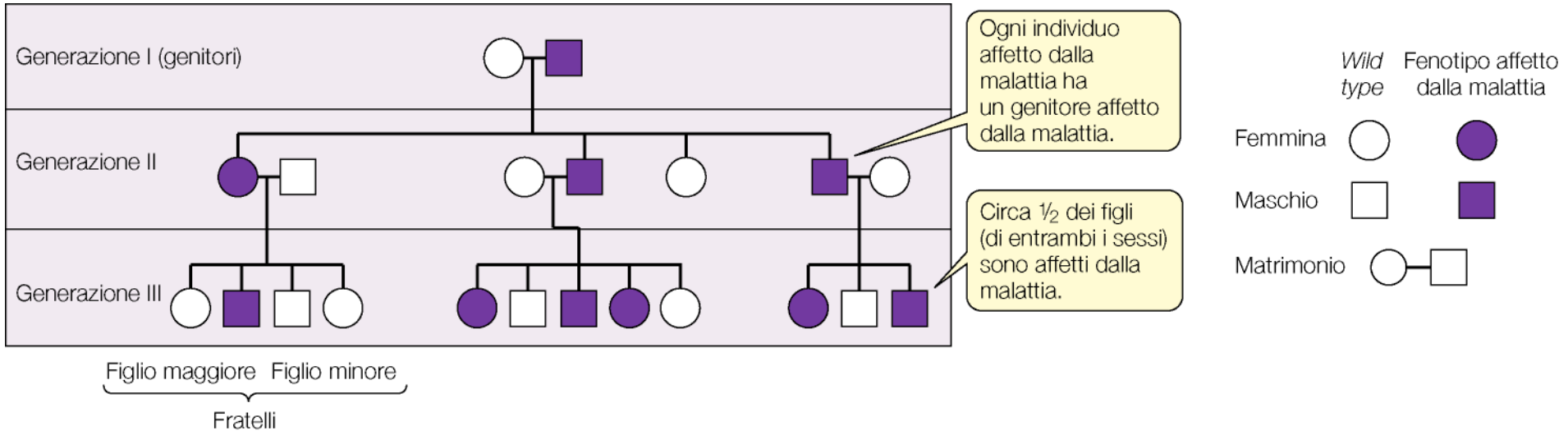
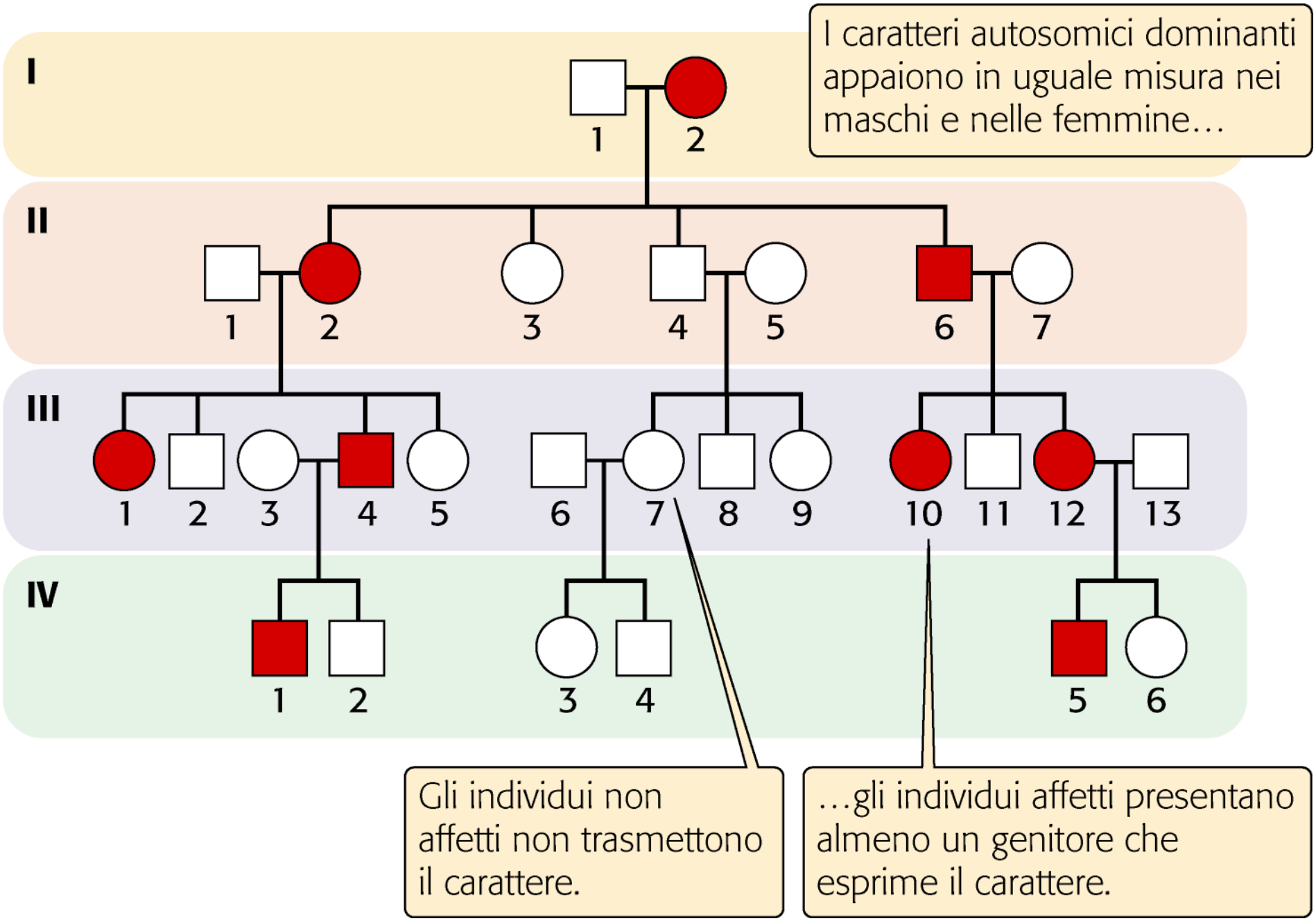
Modalità di Eredità

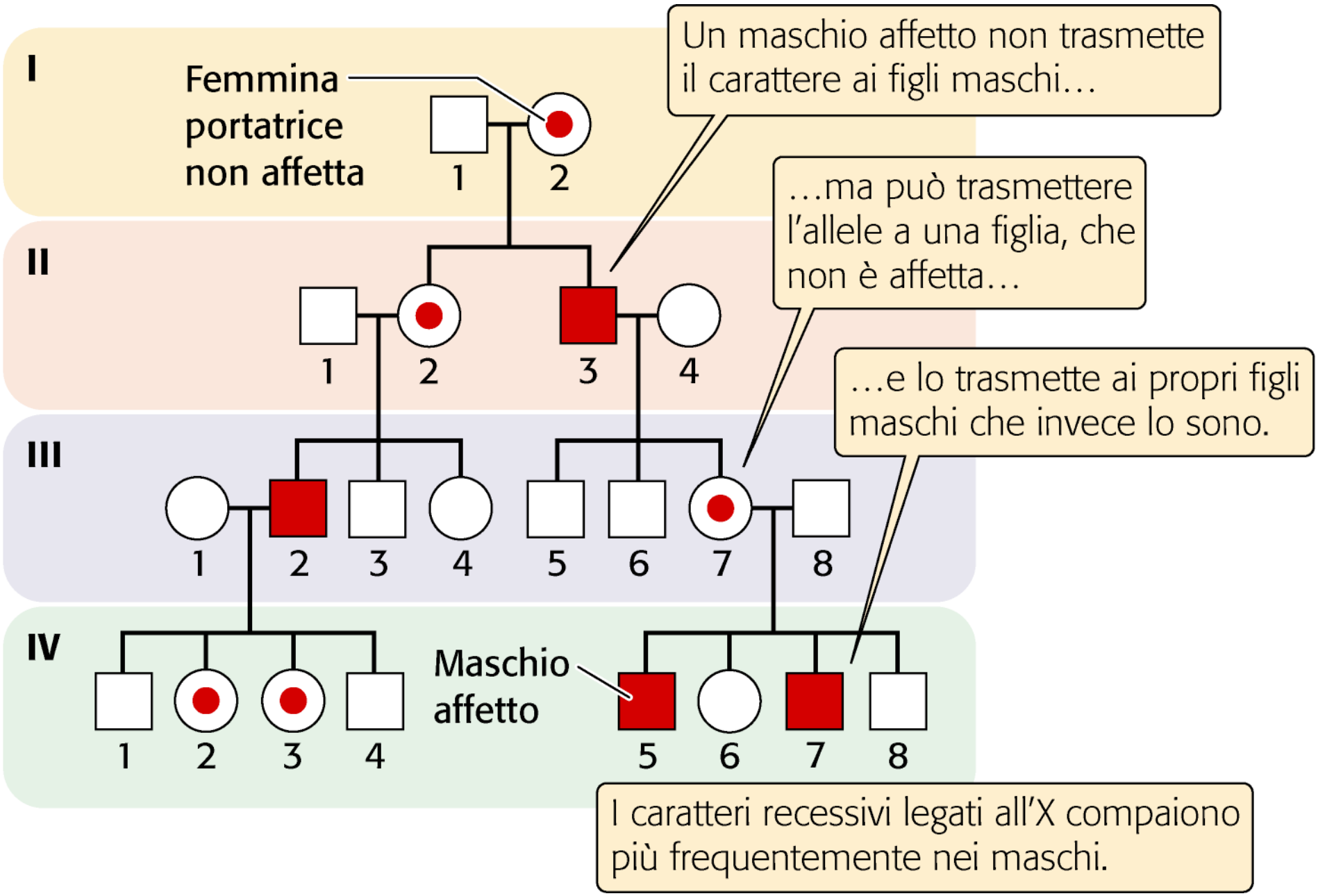
- **Eredità Autosomica Recessiva**
- **Eredità Autosomica Dominante**
- **Eredità Legata al Cromosoma X Recessiva**
- **Eredità Legata al Cromosoma X Dominante**
- **Eredità Legata al Cromosoma Y**
- **Eredità Mitocondriale**

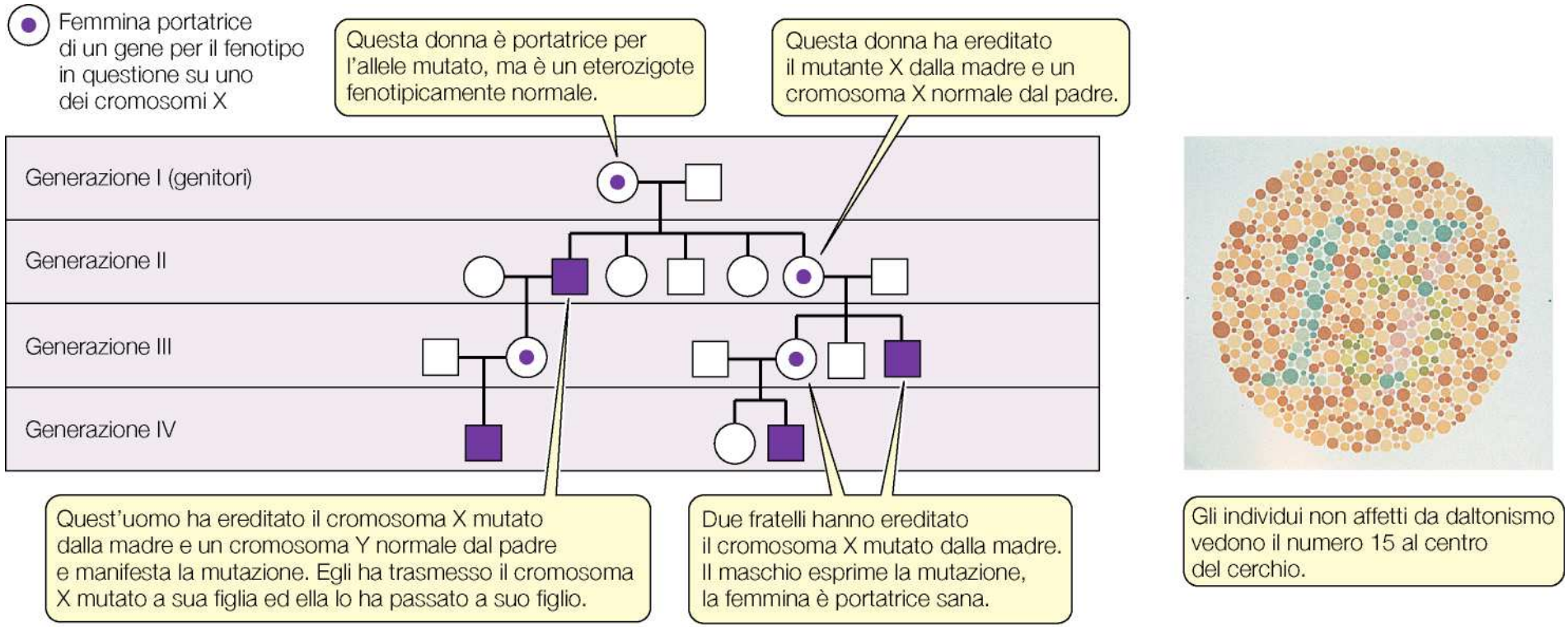

I
1
2
II
1
2
3
4
5
III
Cugini di primo grado
1
2
3
4
5
IV
1
2
3
4
I caratteri autosomici recessivi appaiono solitamente in uguale misura nei maschi e nelle femmine…
…e tendono a saltare le generazioni.
È più probabile che i caratteri autosomici recessivi si manifestino tra la progenie di individui imparentati.
Le linee doppie rappresentano un'unione tra consanguinei.


Femmina
Maschio
Eterozigote per il fenotipo in questione (dedotto)
Matrimoni tra individui imparentati
1 Un genitore è eterozigote…
2 … e l'allele recessivo viene trasmesso a metà della progenie fenotipicamente normale.
3 Questi cugini sono eterozigoti.
4 L'accoppiamento tra genitori eterozigoti recessivi può dare origine a figli omozigoti recessivi (affetti dalla malattia).
Generazione I (genitori)
Generazione II
Generazione III
Generazione IV

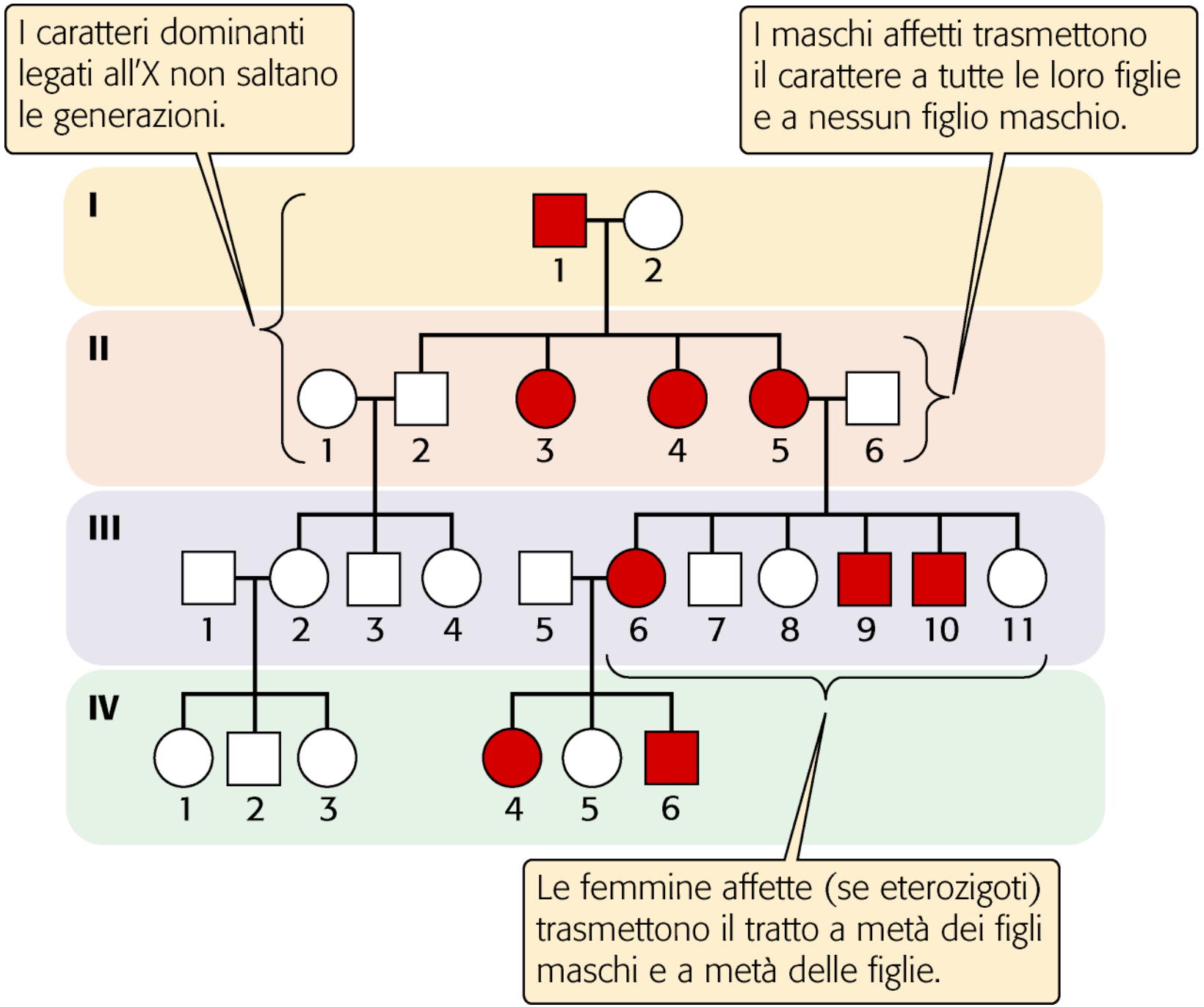

Generazione I (genitori)
Generazione II
Generazione III
Ogni individuo affetto dalla malattia ha un genitore affetto dalla malattia.
Circa ½ dei figli (di entrambi i sessi) sono affetti dalla malattia.
Figlio maggiore
Figlio minore
Fratelli
Wild type
Fenotipo affetto dalla malattia
Femmina
Maschio
Matrimonio


I caratteri autosomici dominanti appaiono in uguale misura nei maschi e nelle femmine…
I
II
III
IV
1 2
1 2 3 4 5 6 7
1 2 3 4 5 6 7 8 9 10 11 12 13
1 2 3 4 5 6
Gli individui non affetti non trasmettono il carattere.
…gli individui affetti presentano almeno un genitore che esprime il carattere.

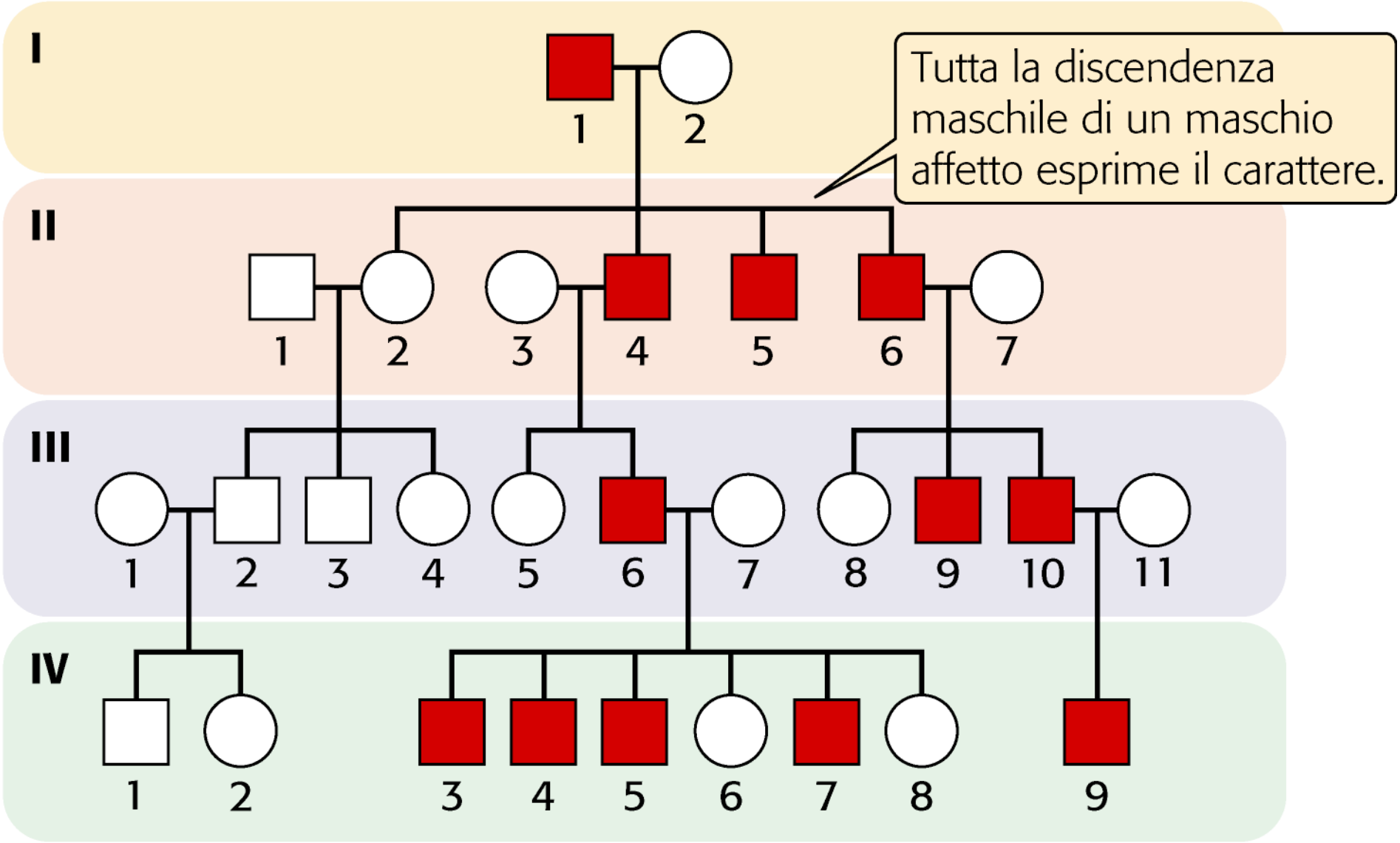

I
II
III
IV
Femmina portatrice non affetta
Maschio affetto
1
2
3
4
5
6
7
8
Un maschio affetto non trasmette il carattere ai figli maschi…
…ma può trasmettere l'allele a una figlia, che non è affetta…
…e lo trasmette ai propri figli maschi che invece lo sono.
I caratteri recessivi legati all'X compaiono più frequentemente nei maschi.

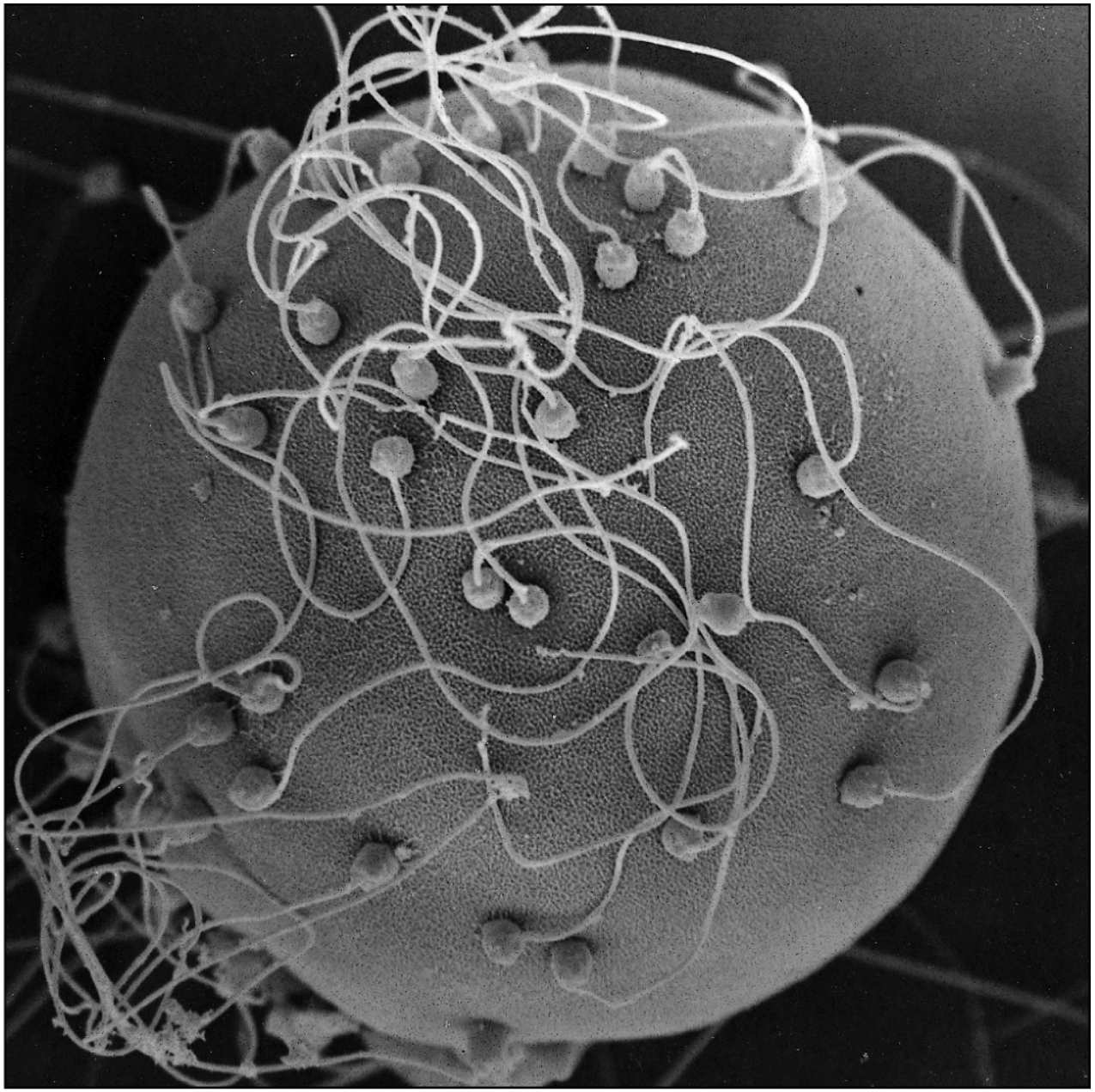


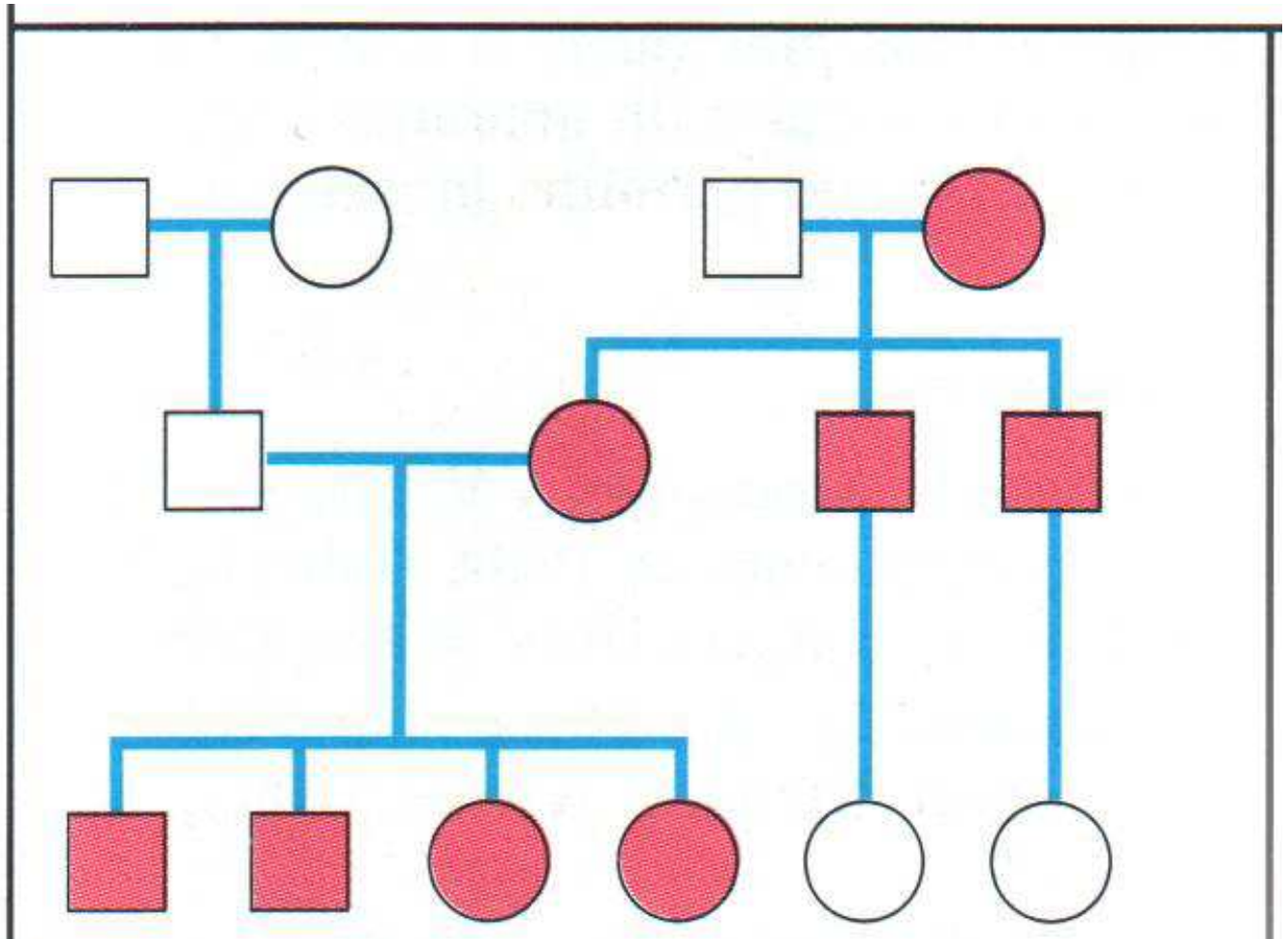
Gli individui non affetti da daltonismo vedono il numero 15 al centro del cerchio.


I caratteri dominanti legati all'X non saltano le generazioni.
I maschi affetti trasmettono il carattere a tutte le loro figlie e a nessun figlio maschio.
I
II
III
IV
1 2
1 2 3 4 5 6
1 2 3 4 5 6 7 8 9 10 11
1 2 3
4 5 6
Le femmine affette (se eterozigoti) trasmettono il tratto a metà dei figli maschi e a metà delle figlie.

I caratteri legati all'Y compaiono solo nei maschi.




50 µm



B. Maternal inheritance of a mitochondrial disease

Box 4.1: Characteristics of the Mendelian patterns of inheritance.

Autosomal dominant inheritance (*Figure 4.2A*):

an affected person usually has at least one affected parent (for exceptions see *Figure 4.4*);

affects either sex;

transmitted by either sex;

a child of an affected x unaffected mating has a 50% chance of being affected (this assumes the affected person is heterozygous, which is usually true for rare conditions).

Autosomal recessive inheritance (*Figure 4.2B*):

affected people are usually born to unaffected parents;

parents of affected people are usually asymptomatic carriers;

there is an increased incidence of parental consanguinity;

affects either sex;

after the birth of an affected child, each subsequent child has a 25% chance of being affected (assuming both parents are phenotypically normal carriers).

X-linked recessive inheritance (*Figure 4.2C*):

affects mainly males;

affected males are usually born to unaffected parents; the mother is normally an asymptomatic carrier and may have affected male relatives;

females may be affected if the father is affected and the mother is a carrier, or occasionally as a result of nonrandom X-inactivation (*Section 4.2.2*);

there is no male-to-male transmission in the pedigree (but matings of an affected male and carrier female can give the *appearance* of male to male transmission, see *Figure 4.5G*).

X-linked dominant inheritance (*Figure 4.2D*):

affects either sex, but more females than males;

females are often more mildly and more variably affected than males;

the child of an affected female, regardless of its sex, has a 50% chance of being affected;

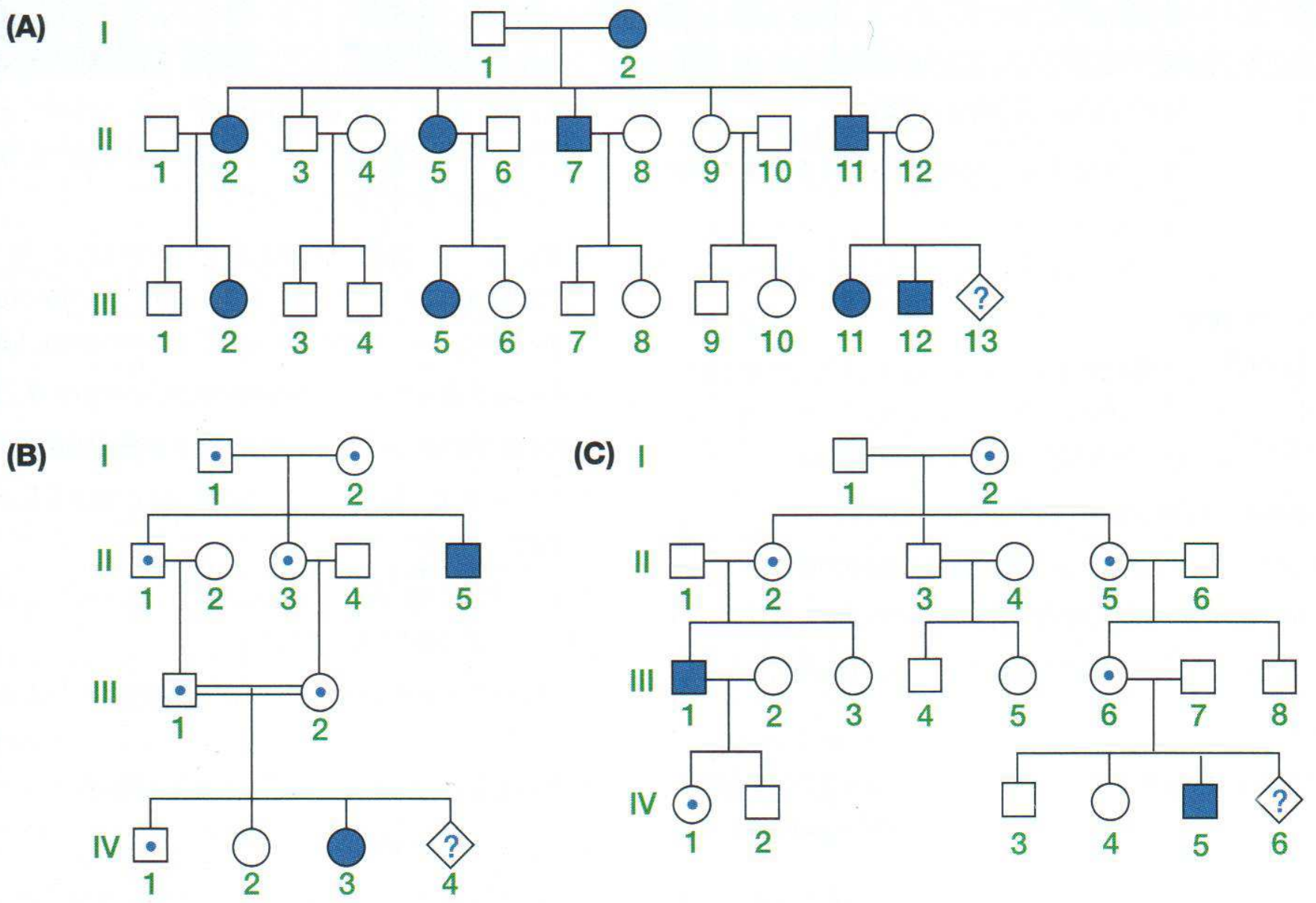
for an affected male, all his daughters but none of his sons are affected.

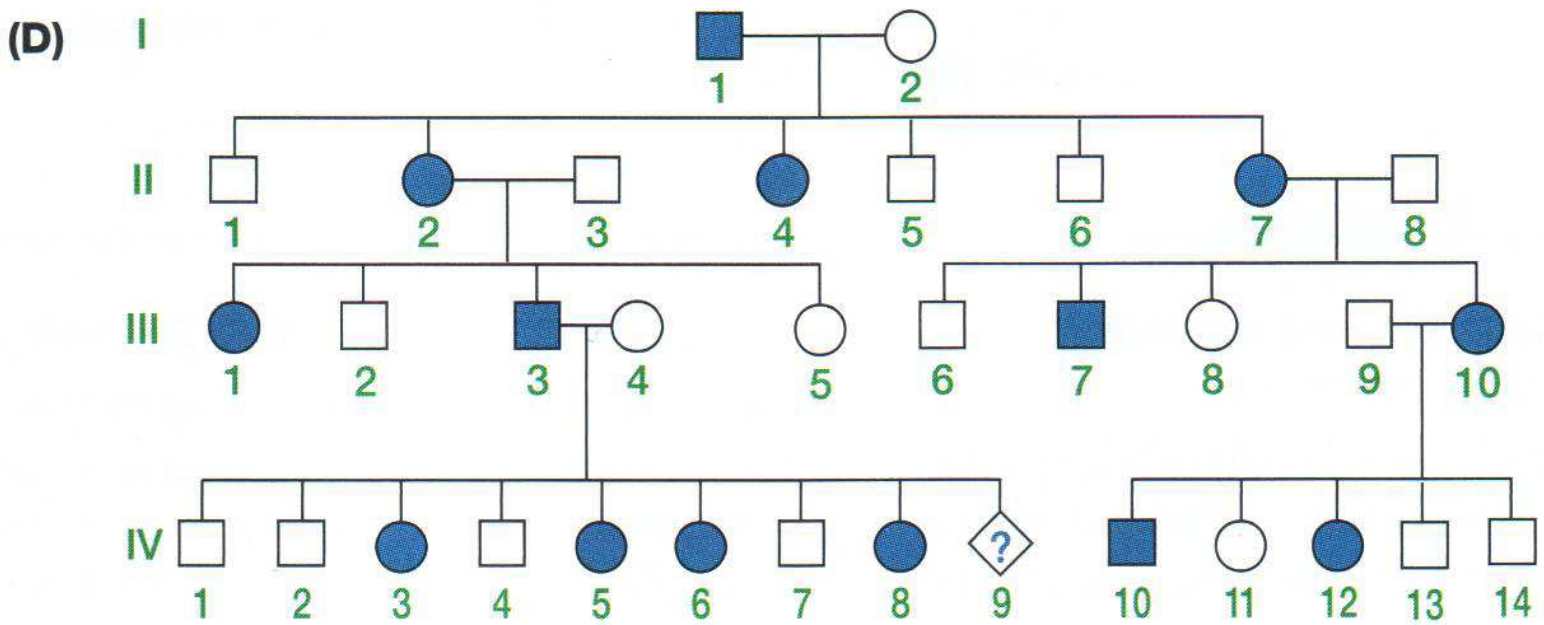
Y-linked inheritance (*Figure 4.2E*):

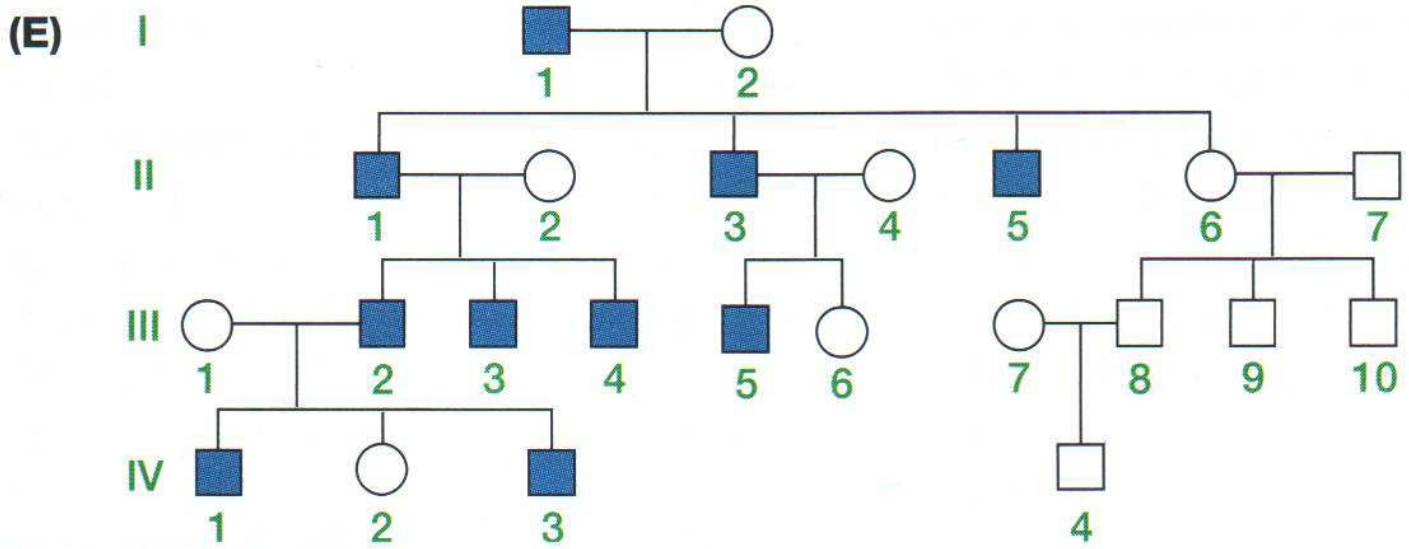
affects only males.

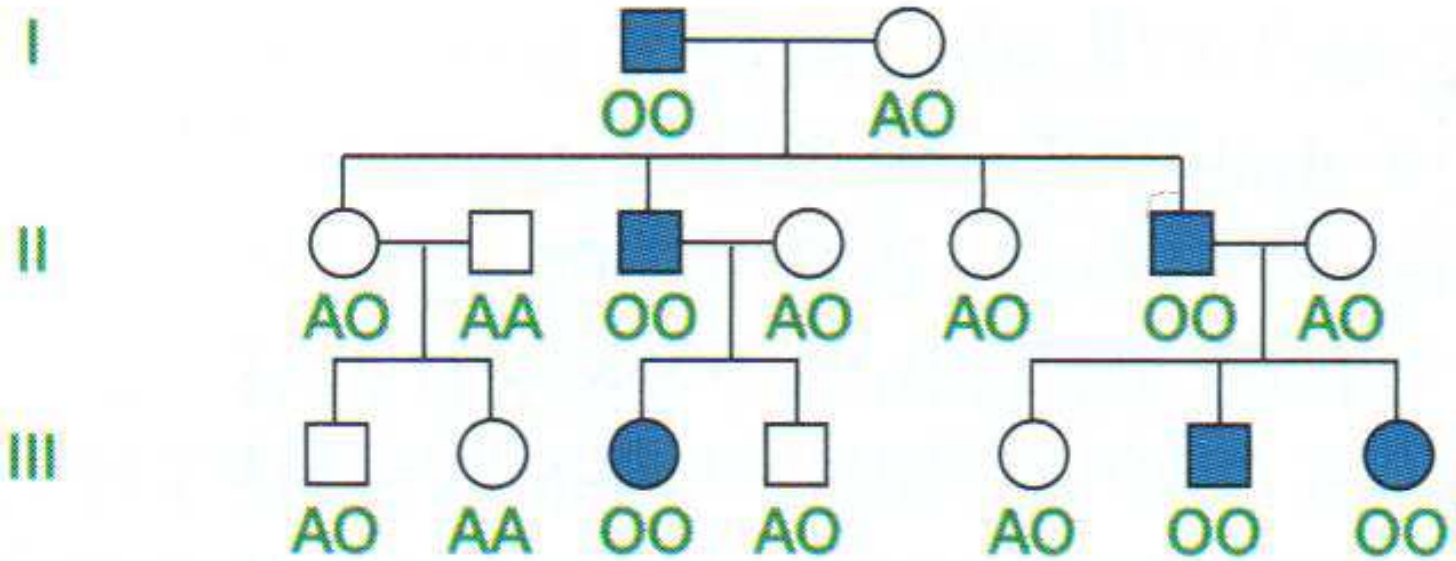
affected males always have an affected father (unless there is a new mutation).

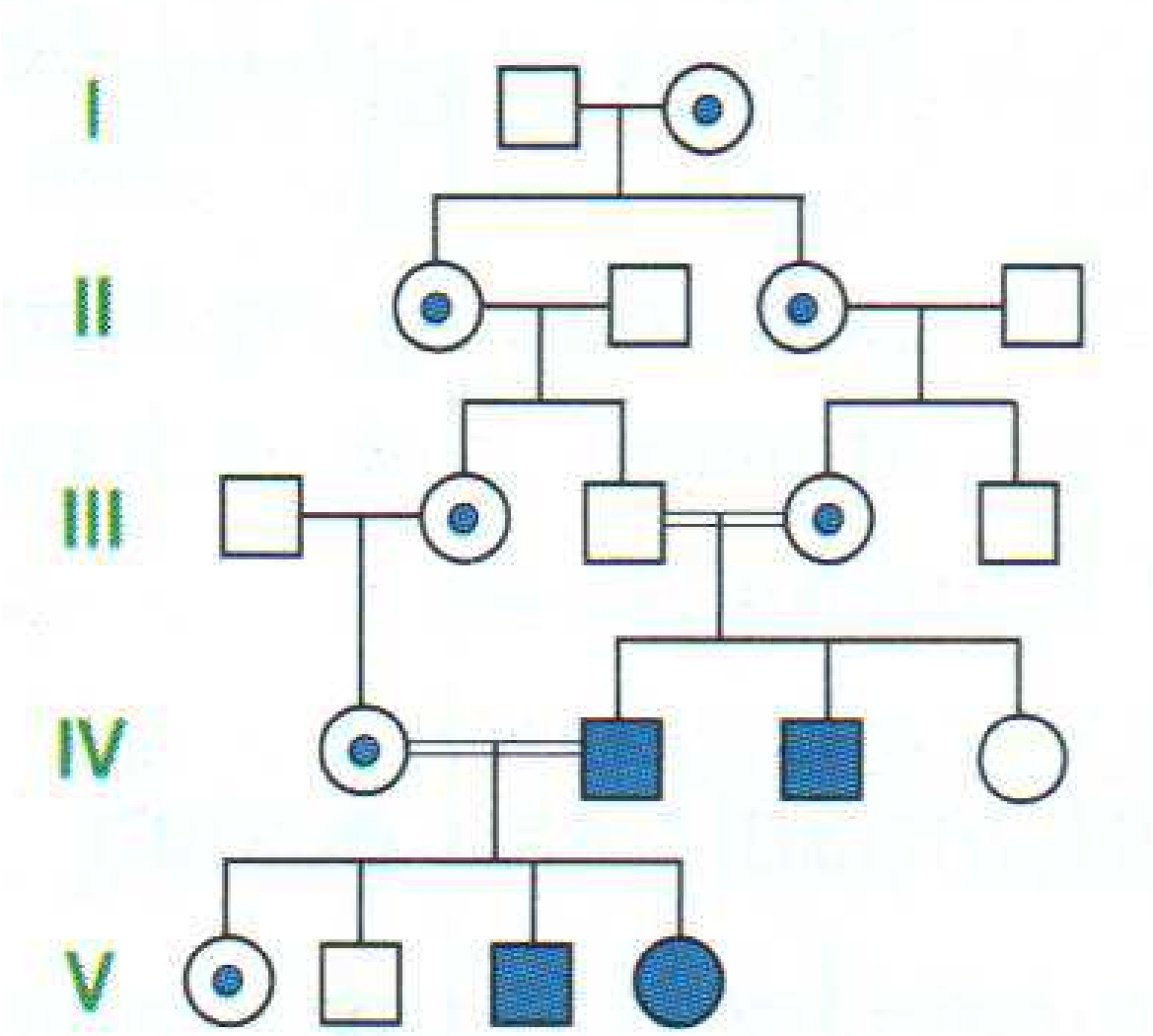
all sons of an affected man are affected.

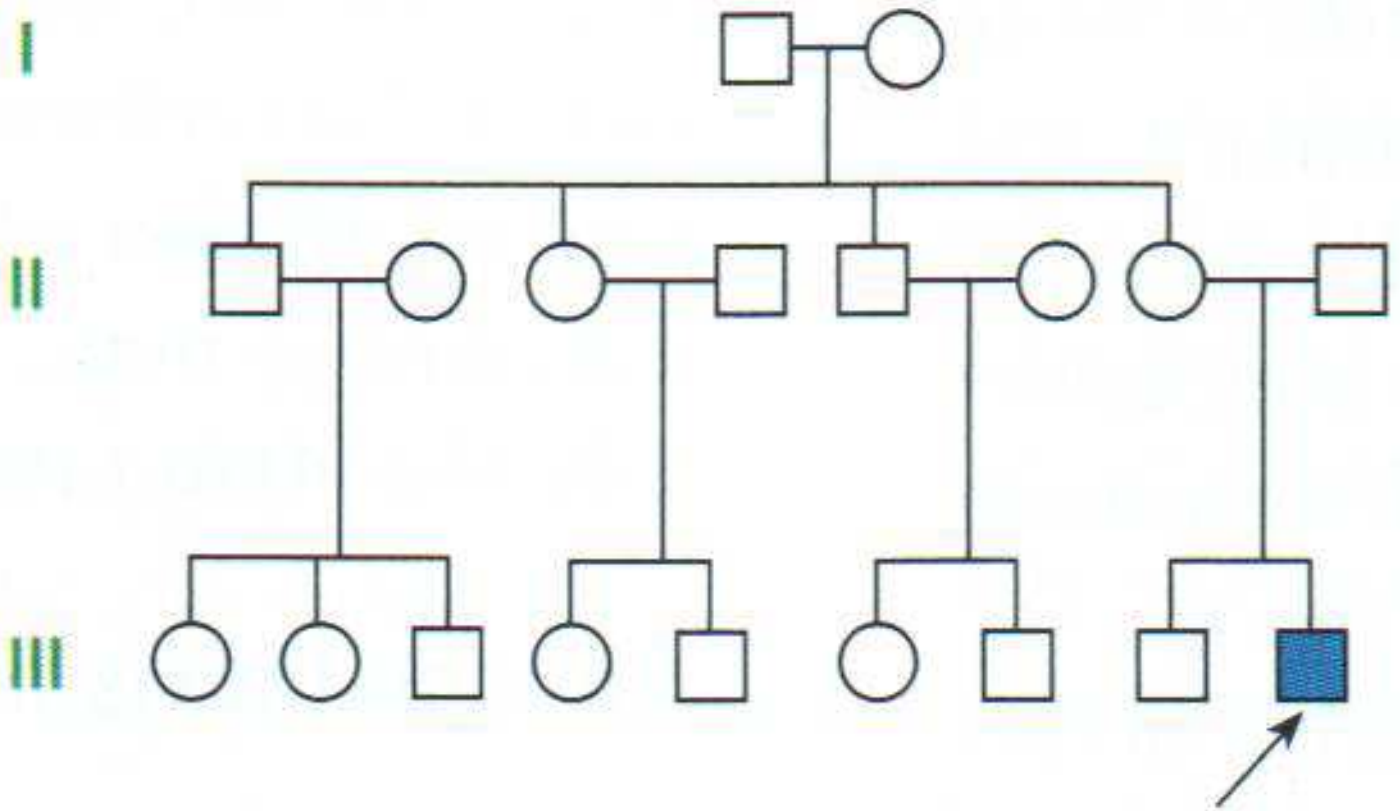

(A)
I
1
2
II
1
2
3
4
5
6
7
8
9
10
11
12
III
1
2
3
4
5
6
7
8
9
10
11
12
?
13
(B)
I
1
2
II
1
2
3
4
5
III
1
2
IV
1
2
3
?
4
(C)
I
1
2
II
1
2
3
4
5
6
III
1
2
3
4
5
6
7
8
IV
1
2
3
4
5
?
6

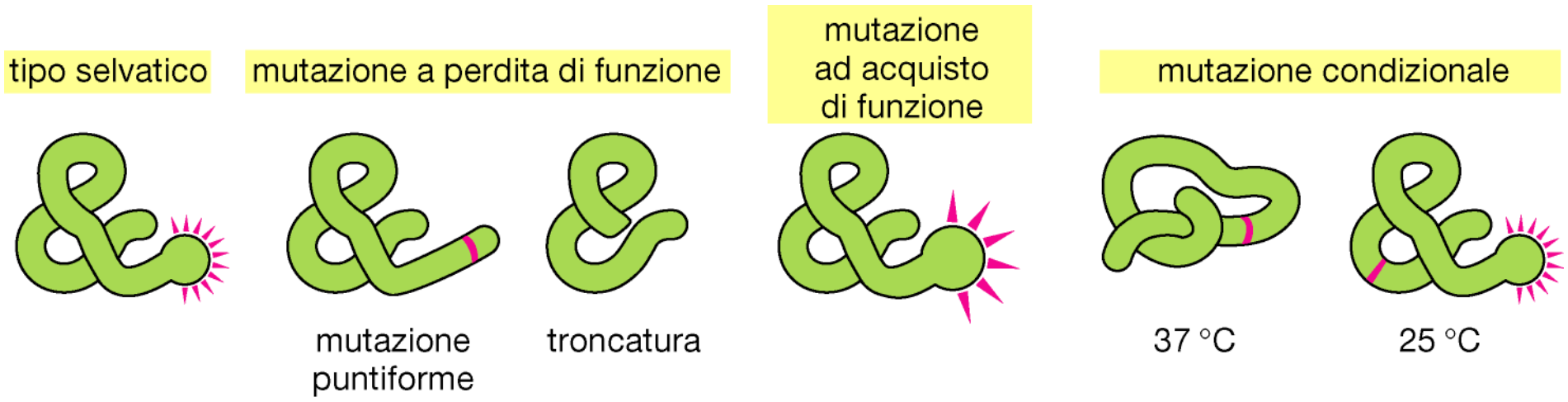

(D)
I
1
2
II
1
2
3
4
5
6
7
8
III
1
2
3
4
5
6
7
8
9
10
IV
1
2
3
4
5
6
7
8
9
?
10
11
12
13
14


(E)
I
1
2
II
1
2
3
4
5
6
7
III
1
2
3
4
5
6
7
8
9
10
IV
1
2
3
4


I
II
III
OO
AO
AO
AA
OO
AO
AO
OO
AO
AO
AA
OO
AO
AO
OO
OO


I
II
III
IV
V


I
II
III


tipo selvatico
mutazione a perdita di funzione
mutazione ad acquisto di funzione
mutazione condizionale
mutazione puntiforme
troncatura
37 °C
25 °C

Mutazioni che comportano perdita di funzione (loss-of-function mutations) sono di solito recessive.

Mutazioni che producono enzimi iperattivi, o attivi in circostanze inappropriate (gain-of-function mutations) sono di solito dominanti.

Il fenotipo dell’eterozigote indica se un particolare carattere è dominante o recessivo.

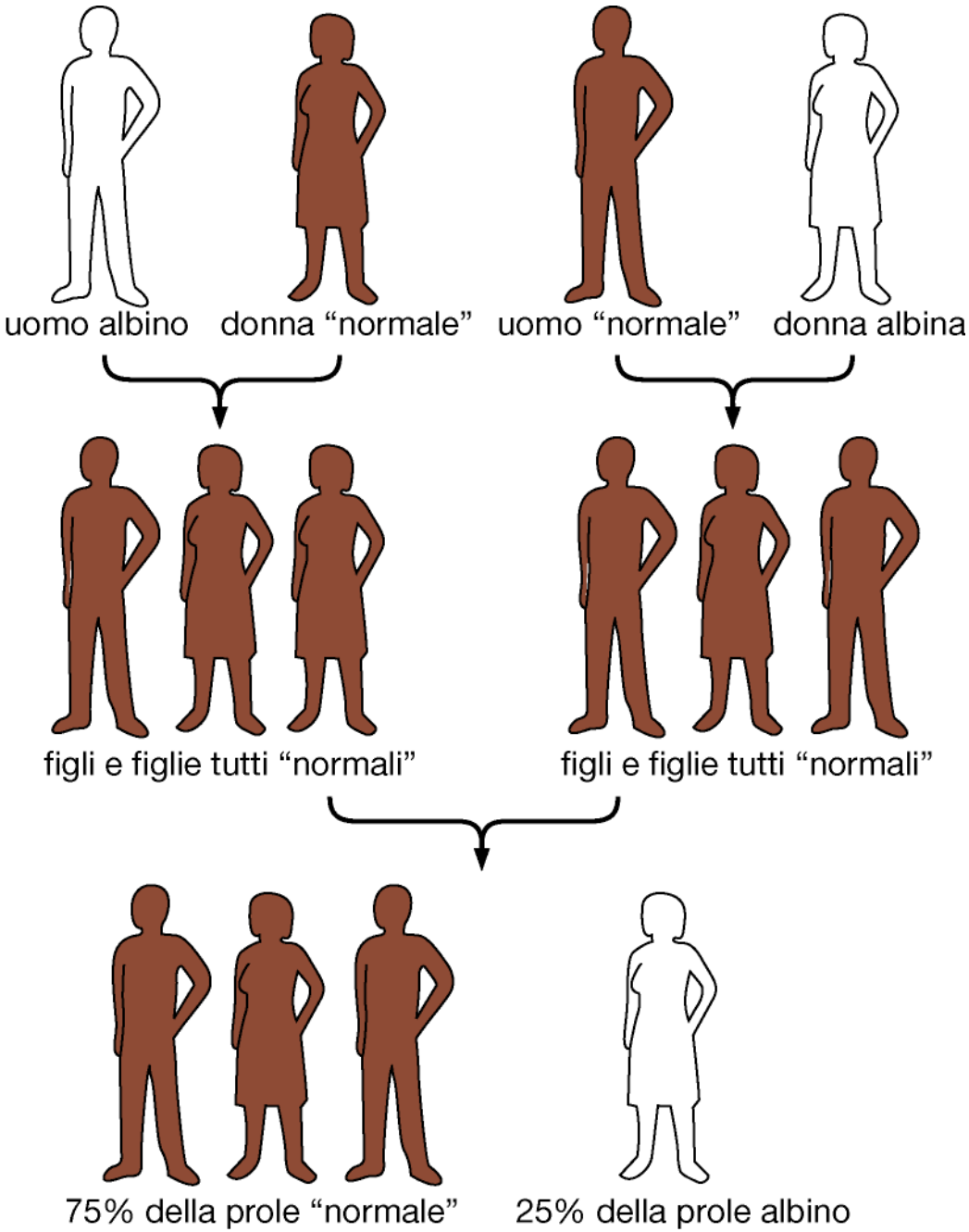

uomo albino
donna “normale”
uomo “normale”
donna albina
figli e figlie tutti “normali”
figli e figlie tutti “normali”
75% della prole “normale”
25% della prole albino

Figure 10.1

Phenylalanine-tyrosine metabolic pathways. Individuals with alkaptonuria cannot metabolize homogentisic acid (HA) to maleylacetoacetic acid, and HA accumulates. Individuals with PKU cannot metabolize phenylalanine to tyrosine, and phenylpyruvic acid accumulates. Individuals with albinism cannot synthesize much melanin from tyrosine.

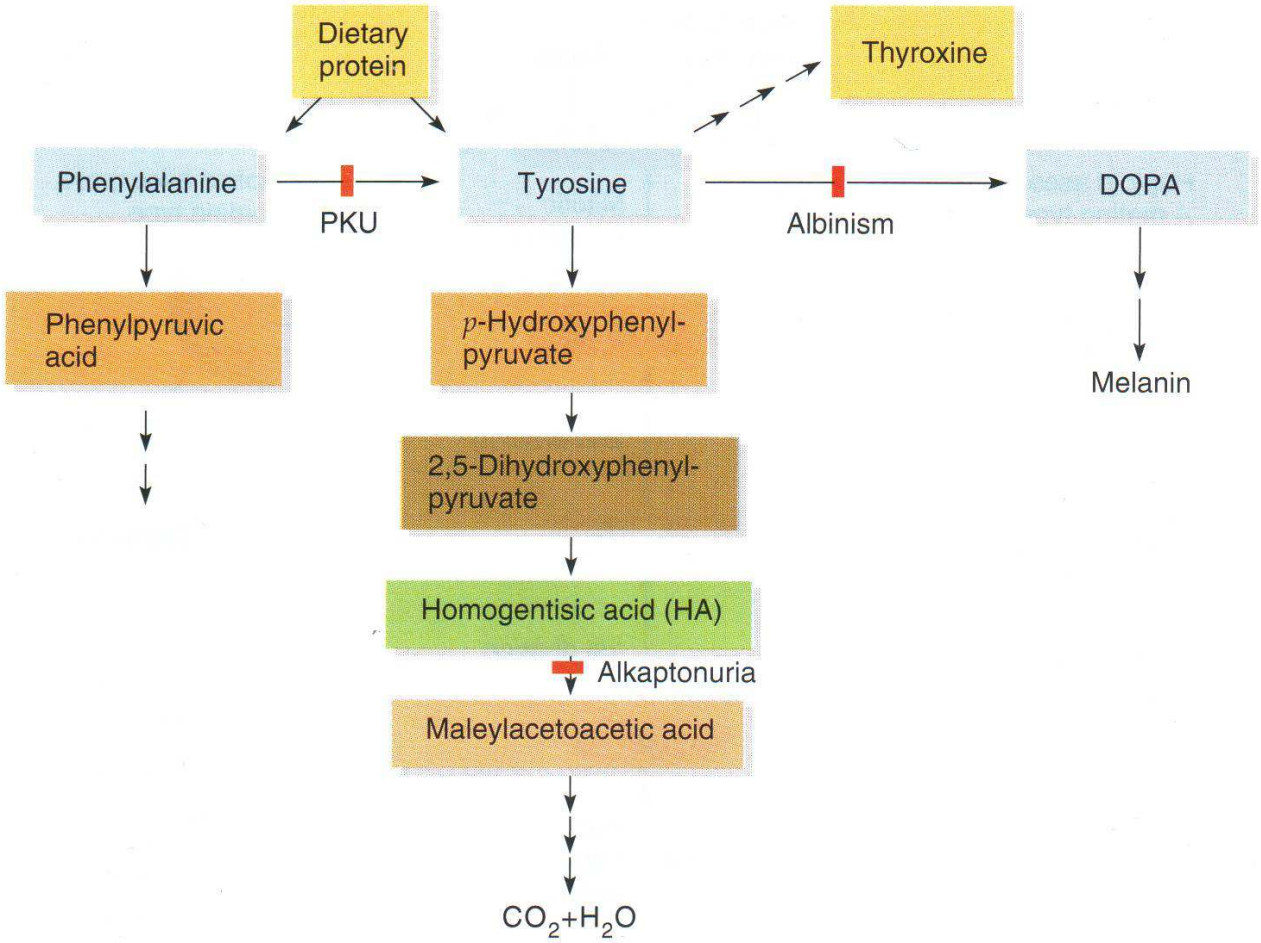


Table 16.1: Eleven ways to reduce or abolish the production of a functioning gene product

Change	Example
Delete:	
(i) the entire gene	Most α-thalassemia mutations (*Figure 16.3*)
(ii) part of the gene	60% of Duchenne muscular dystrophy (*Figure 16.2*)
Insert a sequence into the gene	Insertion of LINE-1 repetitive sequence (see Section 11.5.6) into *F8* gene in hemophilia A
Disrupt the gene structure:	
(i) by a translocation	X–autosome translocations in women with Duchenne muscular dystrophy (*Figure 14.10*)
(ii) by an inversion	Inversion in *F8* gene (*Figure 11.20*)
Prevent the promoter working:	
(i) by mutation	β-Globin g.-29A→G mutation (*Table 18.5*)
(ii) by methylation	*CDKN2A* gene in many tumors (Section 17.6.1)
Destabilize the mRNA:	
(i) polyadenylation site mutation	α-globin g.AATAAA→AATAGA mutation
(ii) by nonsense-mediated RNA decay	β-Globin p.Q39X
Prevent correct splicing (Section 11.4.3)	
(i) inactivate donor splice site	*PAX3* g.451+1G→T mutation (*Figure 16.1*)
(ii) inactivate acceptor splice site	*PAX3* g.452-2A→G mutation (*Figure 16.1*)
(iii) alter an exonic splicing enhancer	*SMN2* exon 7 g.C6T (Cartegni and Krainer 2002)
(iv) activate a cryptic splice site(maybe deep within an intron)	*LGMD2A* G624G (*Figure 11.12*)
	β-Globin IVS1–110G→A mutation (*Table 18.5*)
	CFTR 3849+10kb C→T (*Table 18.6*)
Introduce a frameshift in translation	*PAX3* g.874_875insG mutation (*Figure 16.1*)
Convert a codon into a stop codon	*PAX3* p.Q254X mutation (*Figure 16.1*)
Replace an essential amino acid	*PAX3* p.R271C mutation (*Figure 16.1*)
Prevent post-transcriptional processing	Cleavage-resistant collagen N-terminal propeptide in Ehlers Danlos VII syndrome (*Section 16.6.1*).
Prevent correct cellular localization of product	p.F508del mutation in cystic fibrosis