Autosomal Dominant and Autosomal Recessive Disorders

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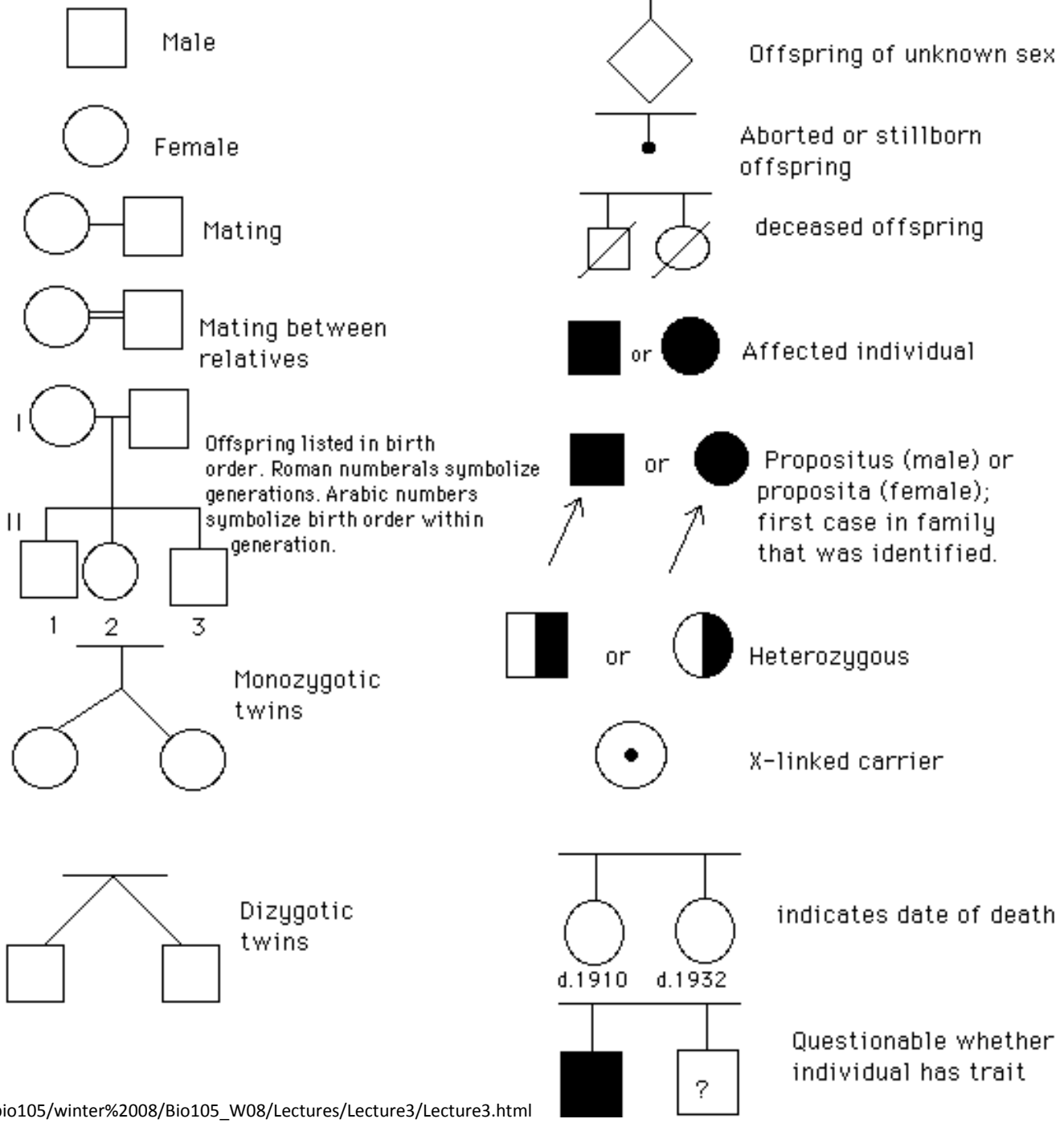
18/09/2015

Introduction

- Reminders on how to read a pedigree
- Consepts in autosomal dominant inheritance
- Autosomal dominant disorders
- Consepts in autosomal recessive inheritance
- Autosomal recessive disorders

Symbols in Pedigrees


Male
Female
Mating
Mating between relatives
I
II
1
2
3
Offspring listed in birth order. Roman numberals symbolize generations. Arabic numbers symbolize birth order within generation.
Monozygotic twins
Dizygotic twins
Offspring of unknown sex
Aborted or stillborn offspring
deceased offspring
or
Affected individual
or
Propositus (male) or proposita (female); first case in family that was identified.
or
Heterozygous
X-linked carrier
d.1910
d.1932
indicates date of death
?
Questionable whether individual has trait

Autosomal Dominant Inheritance

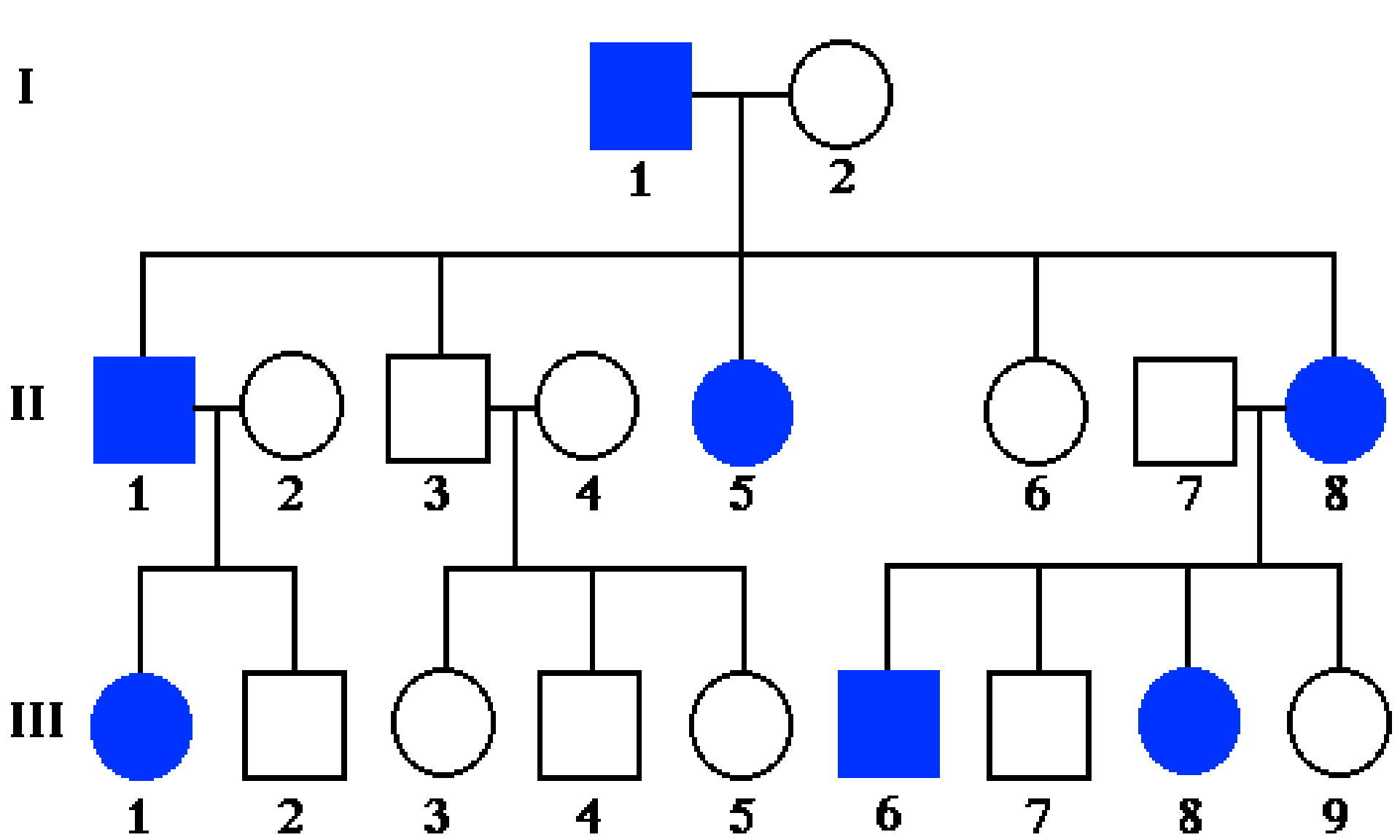
- Individuals have at least one affected parent
- Affected individuals have 50% chance of transmitting the dominant trait
- There are affected individuals in every generation in large families and transmission is vertical in pedigree.
- The frequency of males and females being affected is similar
- Two affected individuals may have unaffected offsprings.

Familial Hypercholesterolemia

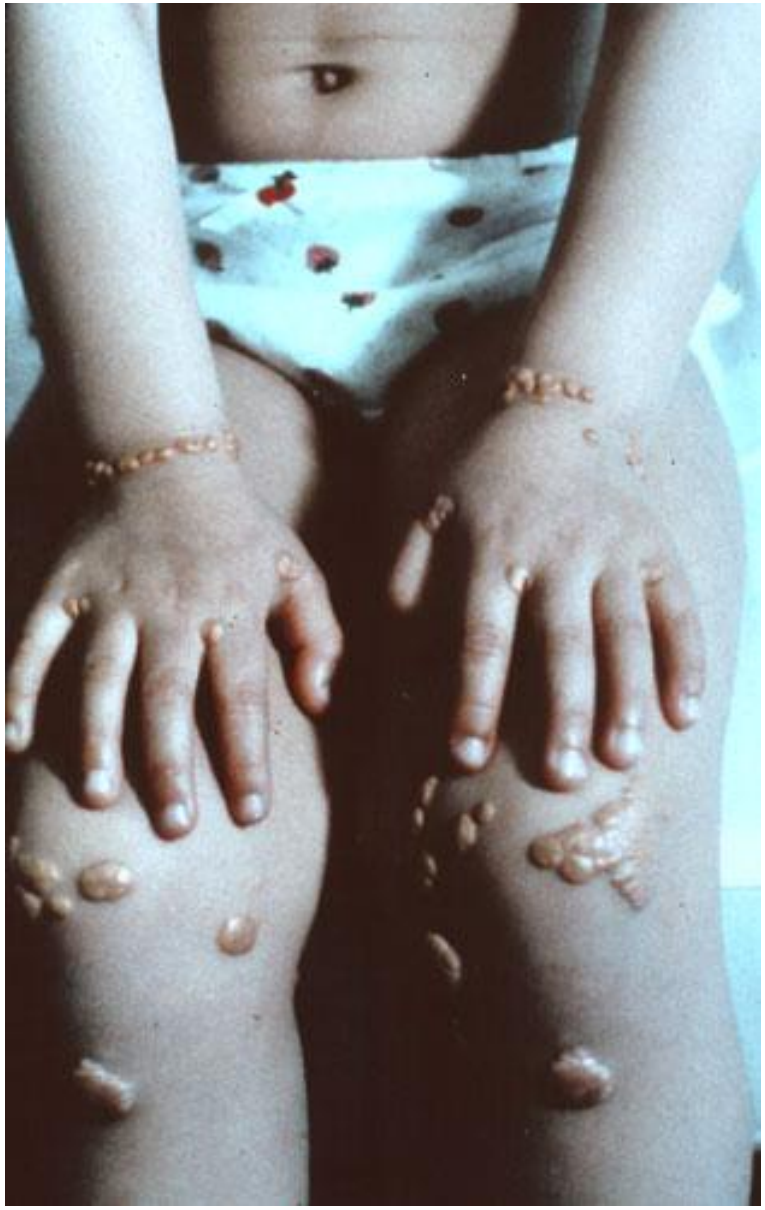
- Autosomal Dominant
- Prevalence 1 in 500 in UK
- High cholesterol levels- specifically LDL
- Formation of xanothomas (fatty deposits)
- Treatment towards conventional cholesterol management usually does not work efficiently because of the mutations
- May lead to cardiovascular disease at early age

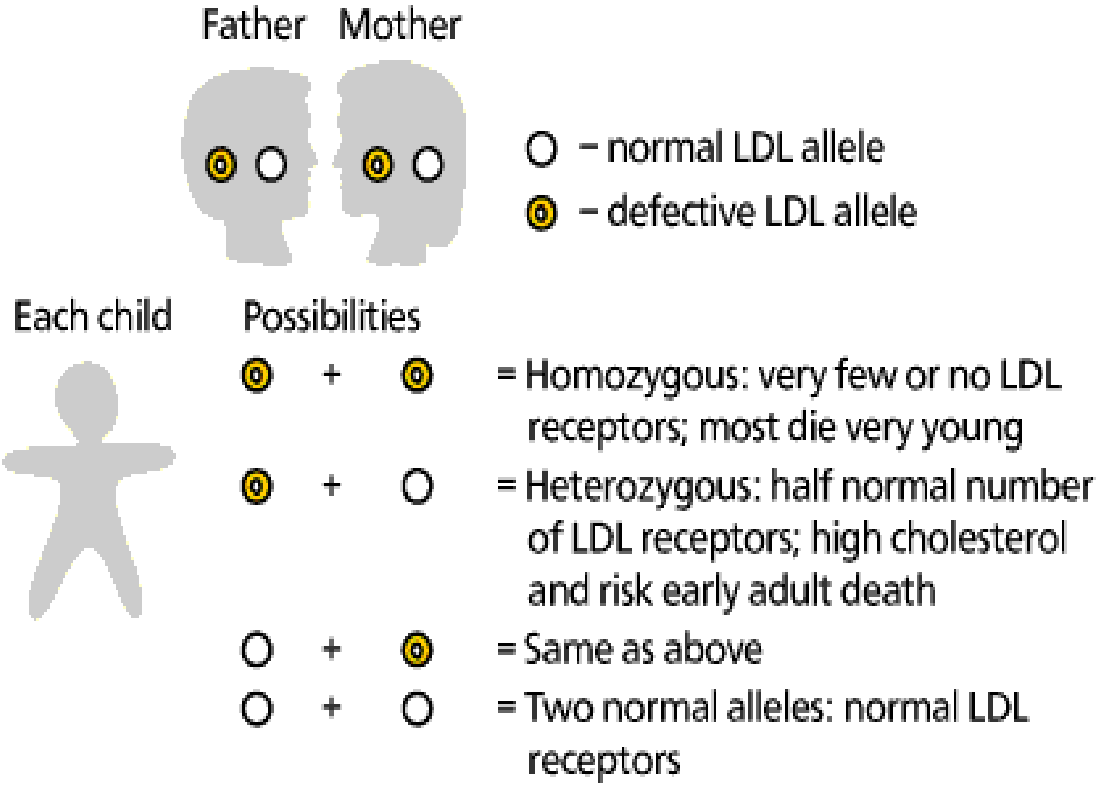
Familial Hypercholesterolemia

- Mutations in
  - LDLR on chr 19
  - ApoB on chr2 (mostly R3500Q)
  - PCSK9 on chr 1
- Mutations mostly result in either reduced LDL receptors and efficiency or LDL receptor ligands
- Thus the rate of LDL conversion is slowed resulting with the phenotype



Pedigree 1. An idealized pedigree of a family with hypercholesterolemia, an autosomal dominant disease where the heterozygote has a reduced number of functional low density lipoprotein receptors.





Obtained from National Human Genome Research Institute.

Huntington's Disease

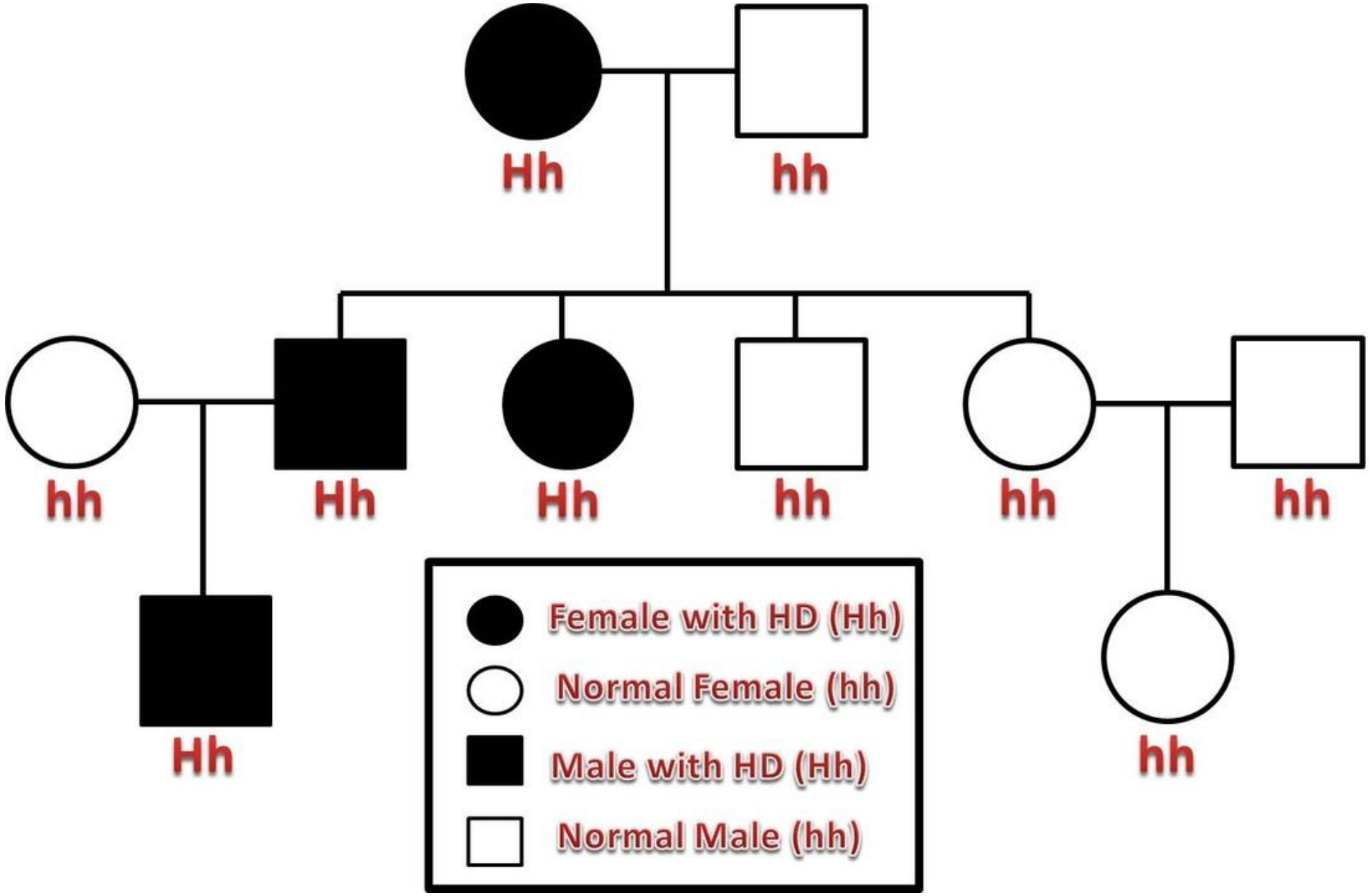
- Neurodegenerative disorder
- Cognition problems
- Lack of coordination
- Jerky body movements and decline in mental abilities
- Physical abilities gradually worsen
- Dementia, physical injury due to falls

Huntington's Disease

- Triplet repeat disorder
- Prevelance 1 in 10 000 in the world
- HTT gene on chr 4
- HTT contains CAG repeats
- CAG repeats over 28 are unstable during replication
- CAG repeat expansion results in Huntington's Disease

Huntington's Disease

Repeat count	Classification	Disease status	Risk to offspring
<26	Normal	Will not be affected	None
27–35	Intermediate	Will not be affected	Elevated but <<50%
36–39	Reduced Penetrance	May or may not be affected	50%
40+	Full Penetrance	Will be affected	50%
60<	Full penetrance	Will be affected severely	50%

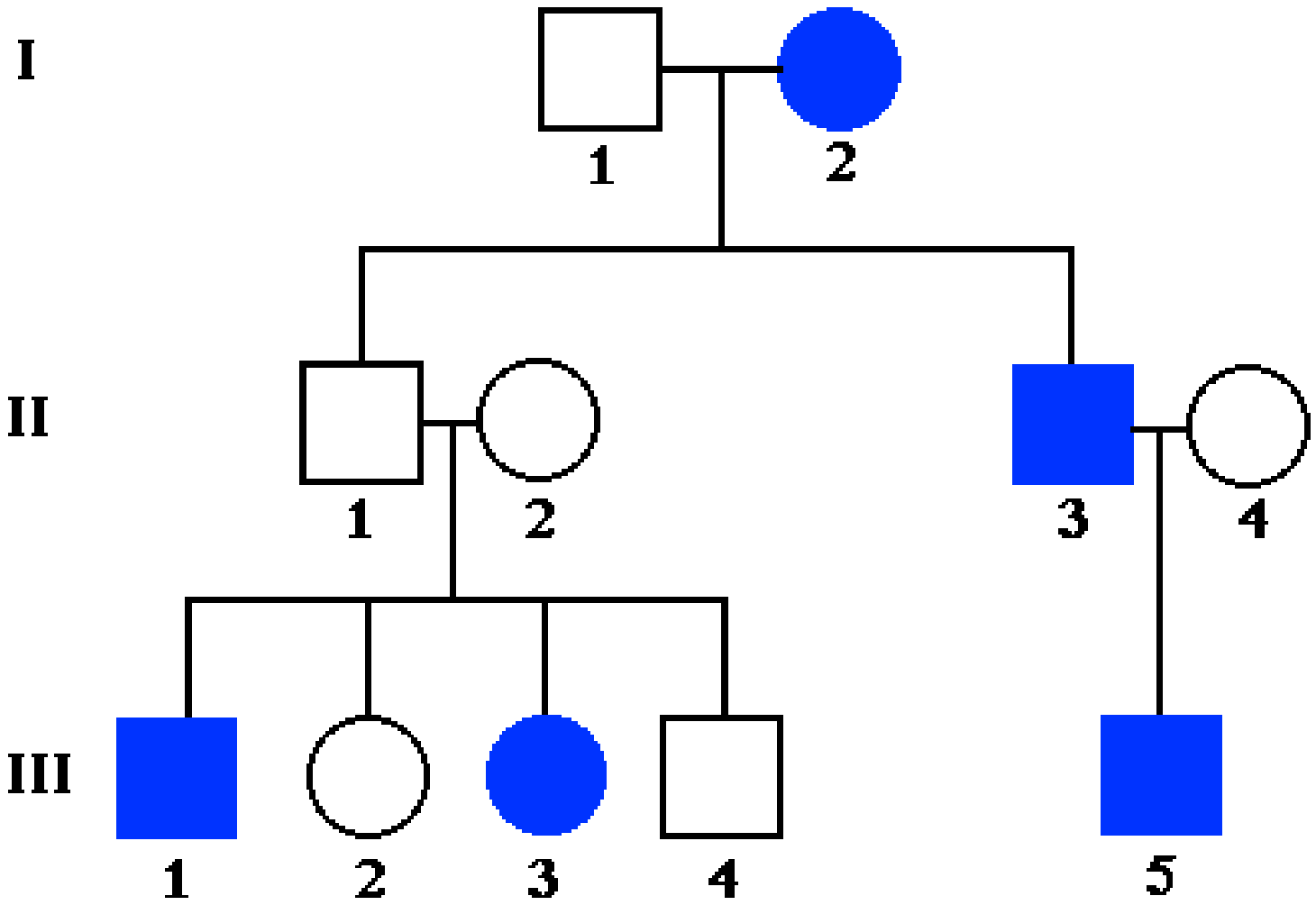


Huntington's Disease

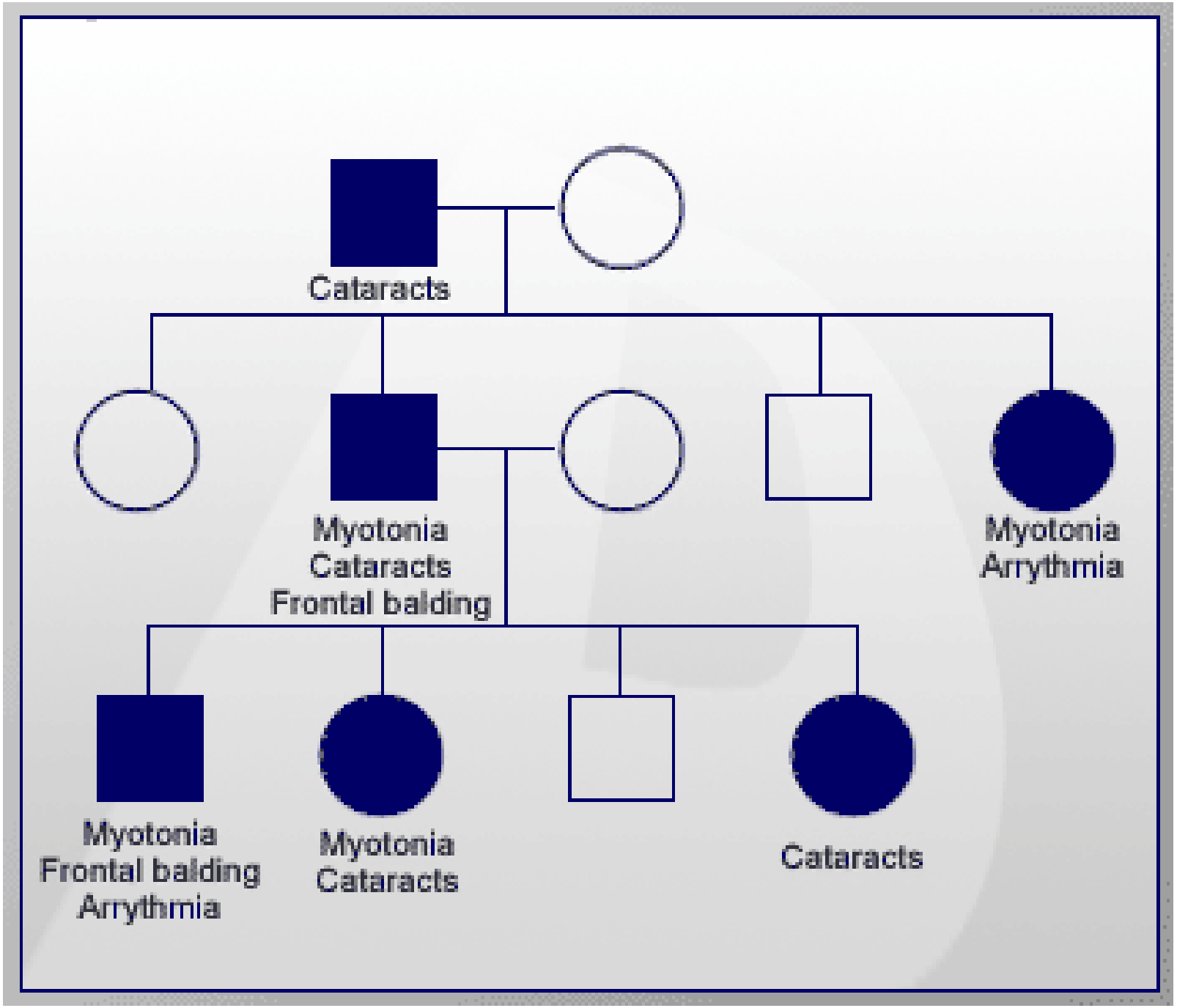
- Genetic anticipation
  - symptoms of a **genetic** disorder become apparent at an earlier age as it is passed on to the next generation. e.g Huntington's Disease
- The symptoms progress faster in every generation in families with Huntington's Disease because of genetic anticipation

Variable Expressivity vs Incomplete Penetrancce

- Each individual with a autosomal dominant trait may express all of the symptoms, or only a few. This is called **variable expressivity**.
- The individual with an autosomal dominant trait either expresses the disease phenotype or he/she doesn't. This is called **incomplete penetrance**
- Variable expressivity and incomplete penetrance are only associated with autosomal dominant inheritance. These concepts are not relevant when autosomal recessive traits are considered.



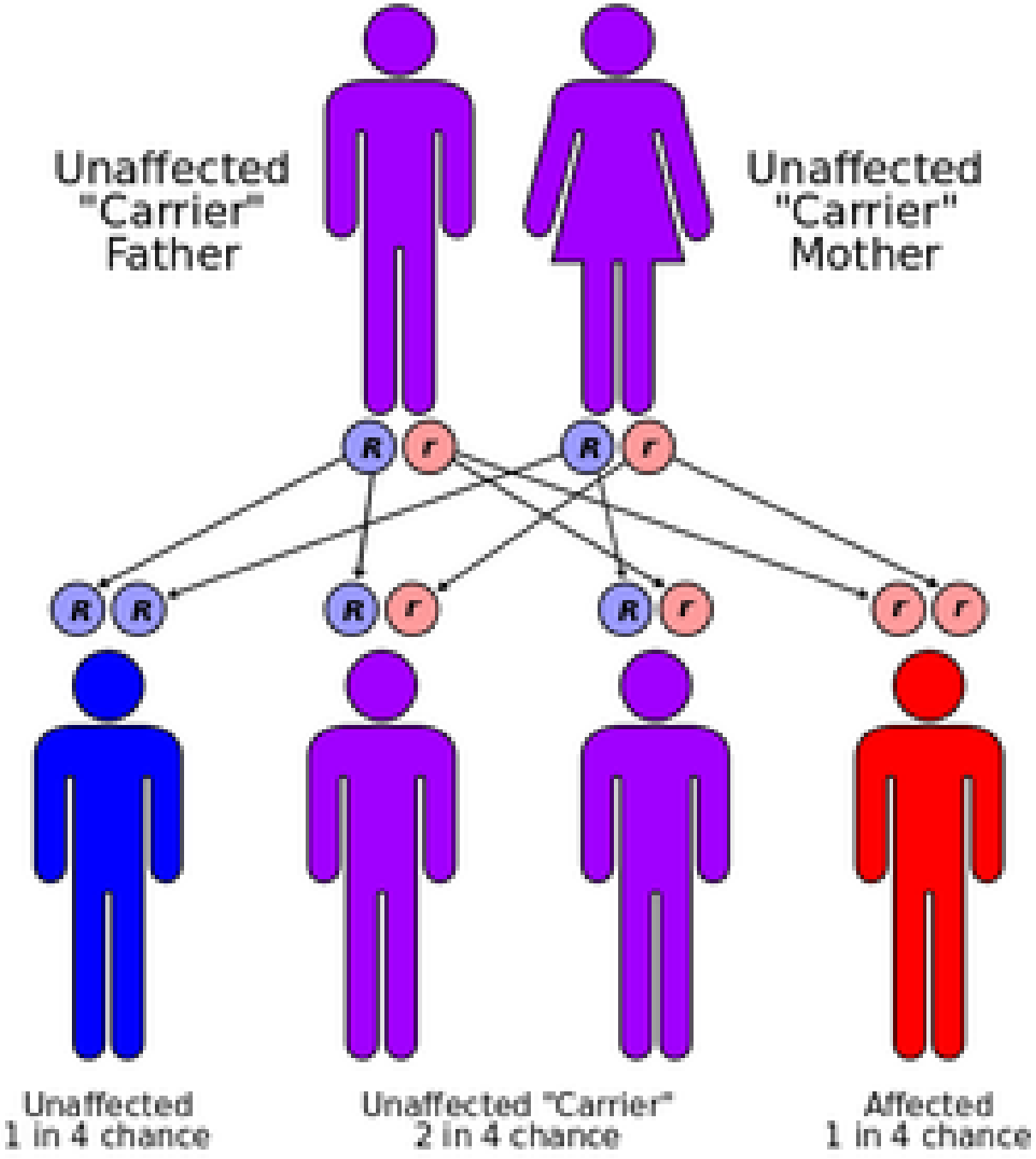
Pedigree 2. An idealized pedigree demonstrating the effects of incomplete penetrance.



http://hihg.med.miami.edu/code/http/modules/education/Design/Print.asp?CourseNum=1&LessonNum=4

Autosomal Recessive Inheritance

- Males and females are affected
- Affected individuals may not have affected parents. However both parents must be carriers or affected for an individual to be affected
- There is 25% chance of being affected if the parents are carriers
- The risk of being carrier should be accounted in autosomal recessive traits
- People with the condition are usually in one sibship in one generation
- Consanguity increases the risk becuase of shared alleles in the family


Unaffected
"Carrier"
Father
Unaffected
"Carrier"
Mother
R
r
R
r
R R
R r
R r
r r
Unaffected
1 in 4 chance
Unaffected "Carrier"
2 in 4 chance
Affected
1 in 4 chance

Cystic Fibrosis

- Progressive damage to respiratory system and chronic digestive system promlems
- The features and severity is highly variable among patients depending on the mutations
- Great variety of mutations
- Inherited in an autosomal recessive manner
- Treatment in different ways: mutation specific treatments are available

All mutations and their classes

All mutations

Current name	New name	Class	N	*(%)*
DF508	p.Phe508del	II	7516	*(90.6)*
G551D	p.Gly551Asp	III	466	*(5.6)*
R117H	p.Arg117His	IV	336	*(4.1)*
G542X	p.Gly542X	I	295	*(3.6)*
621+1G->T	c.489+1G>T	I	193	*(2.3)*
N1303K	p.Asn1303Lys	II	113	*(1.4)*
1717-1G->A	c.1585-1G>A	I	108	*(1.3)*
1898+1G->A	c.1766+1G>A	I	104	*(1.3)*
R560T	p.Arg560Thr	III	82	*(1.0)*
DI507	p.Ile507del	II	82	*(1.0)*
3659delC	c.3528delC	II	76	*(0.9)*
R553X	p.Arg553X	I	73	*(0.9)*
3849+10kbC->T	c.3717+10kbC>T	V	62	*(0.8)*
G85E	p.Gly85Glu	IV	57	*(0.7)*
E60X	p.Glu60X	I	53	*(0.6)*
D1152H	p.Asp1152His	IV	51	*(0.6)*
Q493X	p.Gln493X	I	50	*(0.6)*
W1282X	p.Trp1282X	I	42	*(0.5)*
1078delT	c.948delT	II	35	*(0.4)*
2184delA	c.2052delA	II	32	*(0.4)*
2789+5G->A	c.2657+5G>A	V	28	*(0.3)*
V520F	p.Val520Phe	III	27	*(0.3)*
R347P	p.Arg347Pro	IV	22	*(0.3)*
R1162X	p.Arg1162X	I	21	*(0.3)*
A455E	p.Ala455Glu	V	21	*(0.3)*
S549N	p.Ser549Asn	II	19	*(0.2)*
R347H	p.Arg347His	IV	14	*(0.2)*
R1158X	p.Arg1158X	I	12	*(0.1)*
711+1G->T	c.579+1G>T	I	11	*(0.1)*
3120+1G->A	c.2988+1G>A	I	11	*(0.1)*
R334W	p.Arg334Trp	IV	9	*(0.1)*
1161delC	c.1029delC	I	7	*(0.1)*
I148T	p.Ile148Thr	V	7	*(0.1)*

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1717-1G->A	c.1585-1G>A	I	108	*(1.3)*
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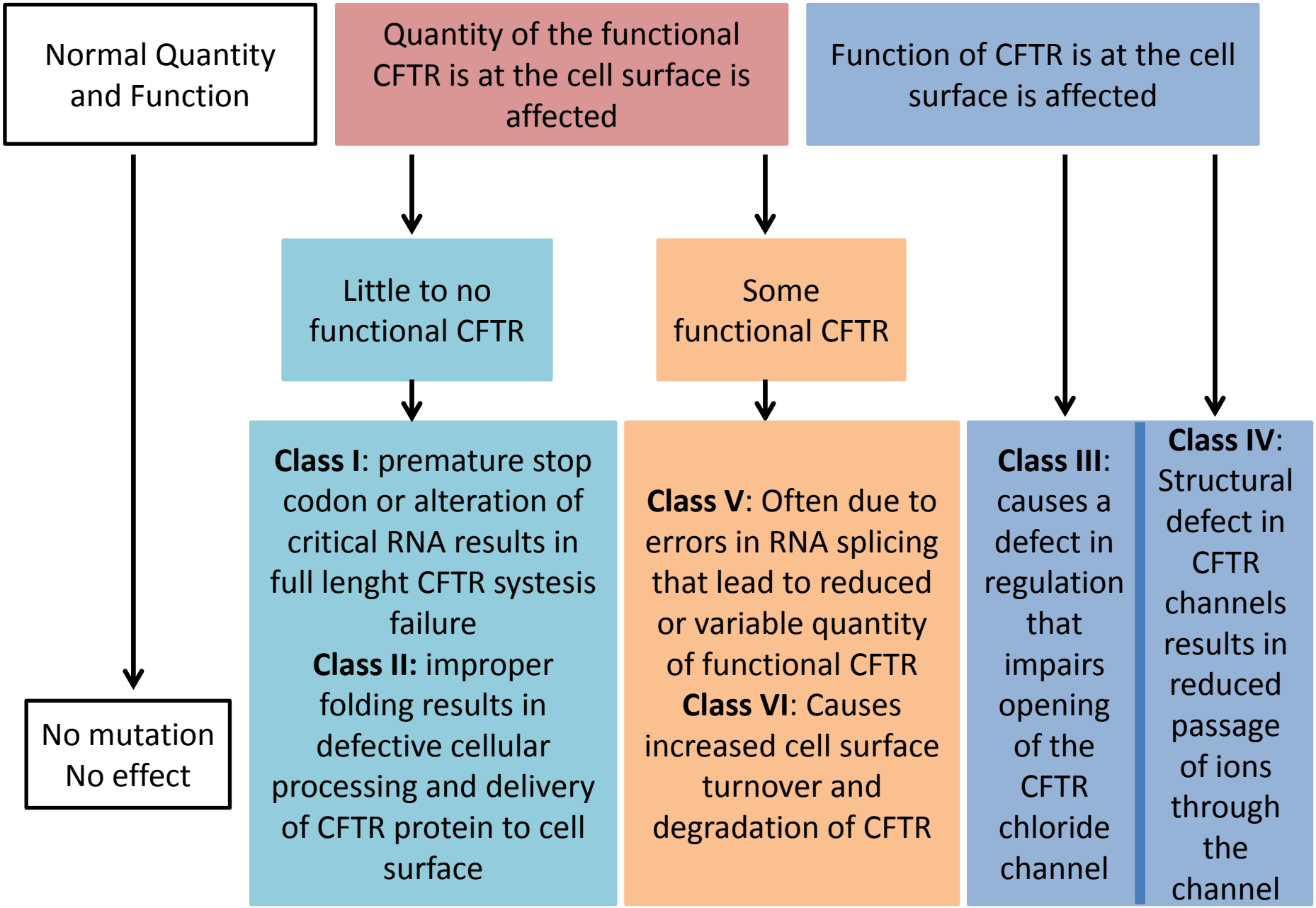
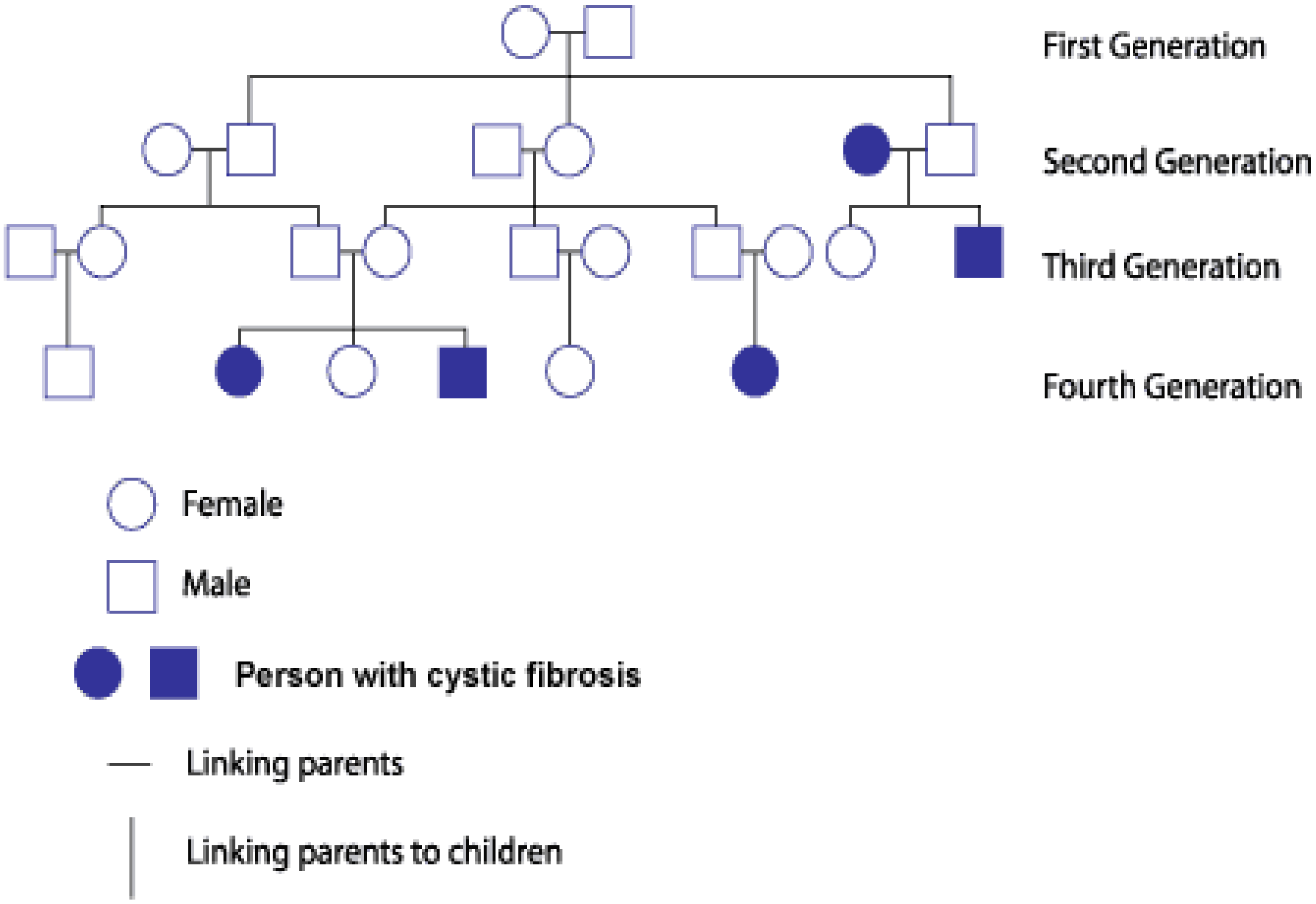
R560T	p.Arg560Thr	III	82	*(1.0)*
DI507	p.Ile507del	II	82	*(1.0)*

Cystic Fibrosis Mutations and Their Functional Effects





https://thednafiles.wordpress.com/2008/04/17/cystic-fibrosis-and-gene-therapy/

Treatment

- Often with antibiotics to tackle the excess amount of bacteria in the lungs
- Physiotherapy to open up luns
- Bronchiodilators
- Mutation specific treatment
  - Ivacaftor for p.Gly551Asp
  - Gentamicin for p.Phe508del and other class I mutations

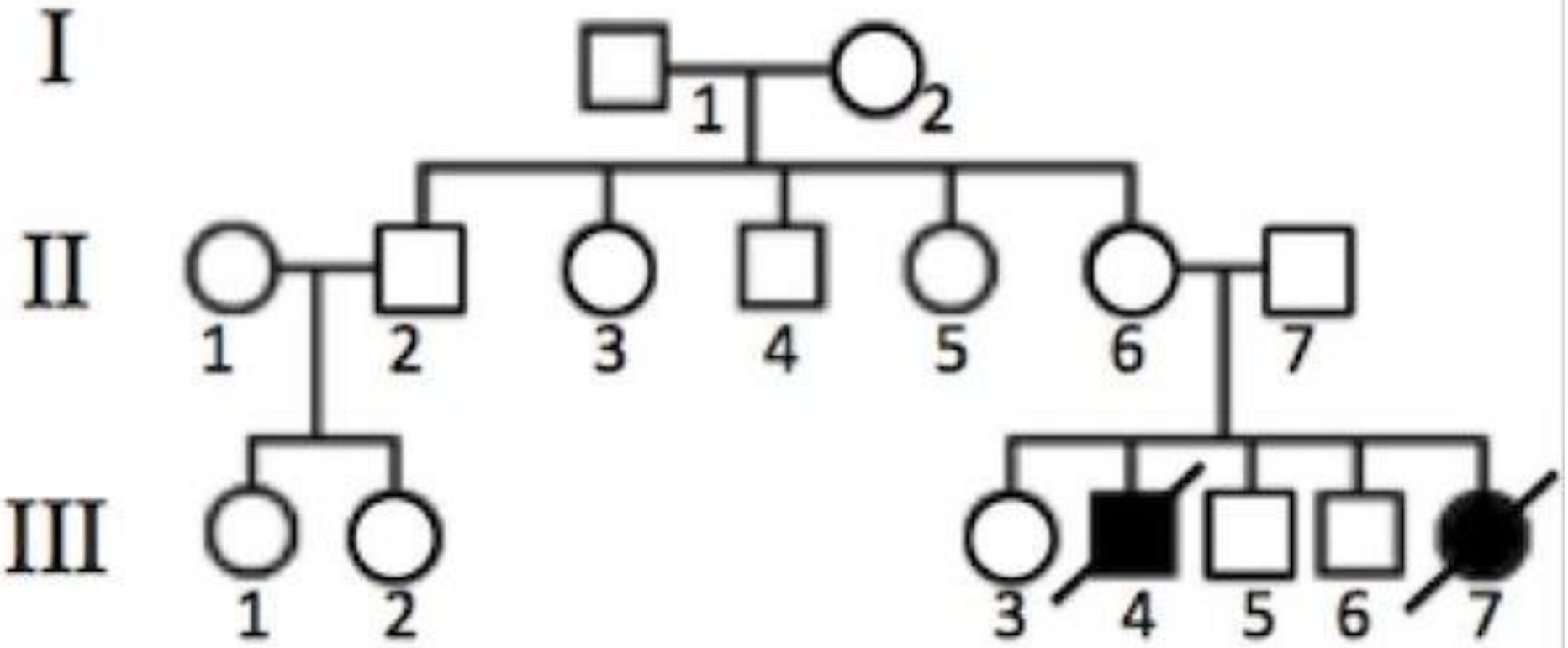
Tay Sachs Disease

- Autosomal recessive
- Progressive neurodegenerative disease
- Build up undigested fat in brain cells
- Usually fatal by age 2 or 3
- Presented by intellectual disability, paralysis, dementia and blindness
- HEXA gene mutations
- 78 mutations across the gene causing TSD (mosly base substitutions)

Tay Sachs Disease

- Insufficient activity of hexosaminidase A, a vital enzyme found in lysosomes
- Glycolipids can not be broken down
- Diagnosis with enzyme assay
- There is no cure for the disease
- Prevention through prenatal diagnosis, preimplantation genetics and mate selection reduces the incidence of the disease

Tay Sachs Disease Family

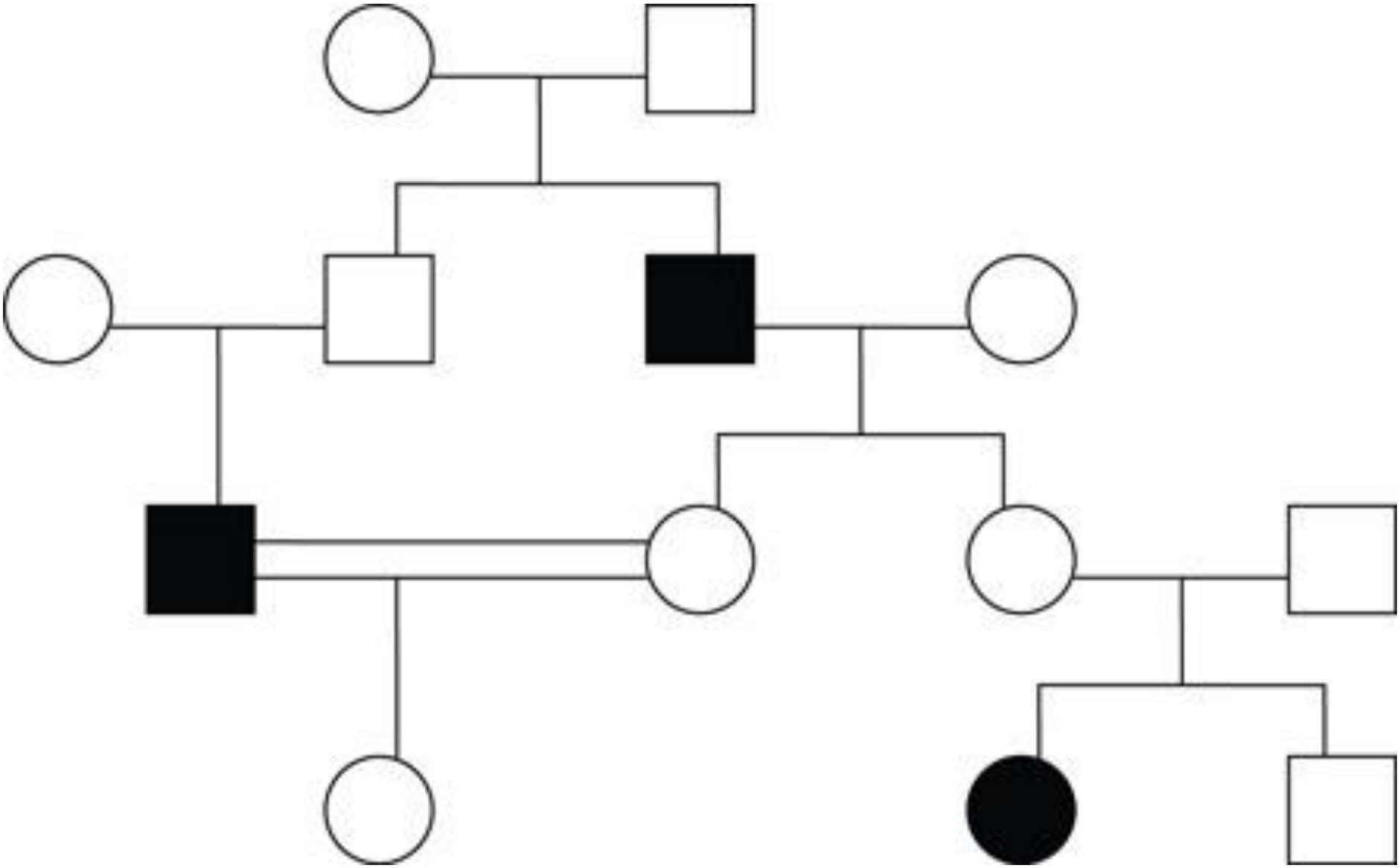


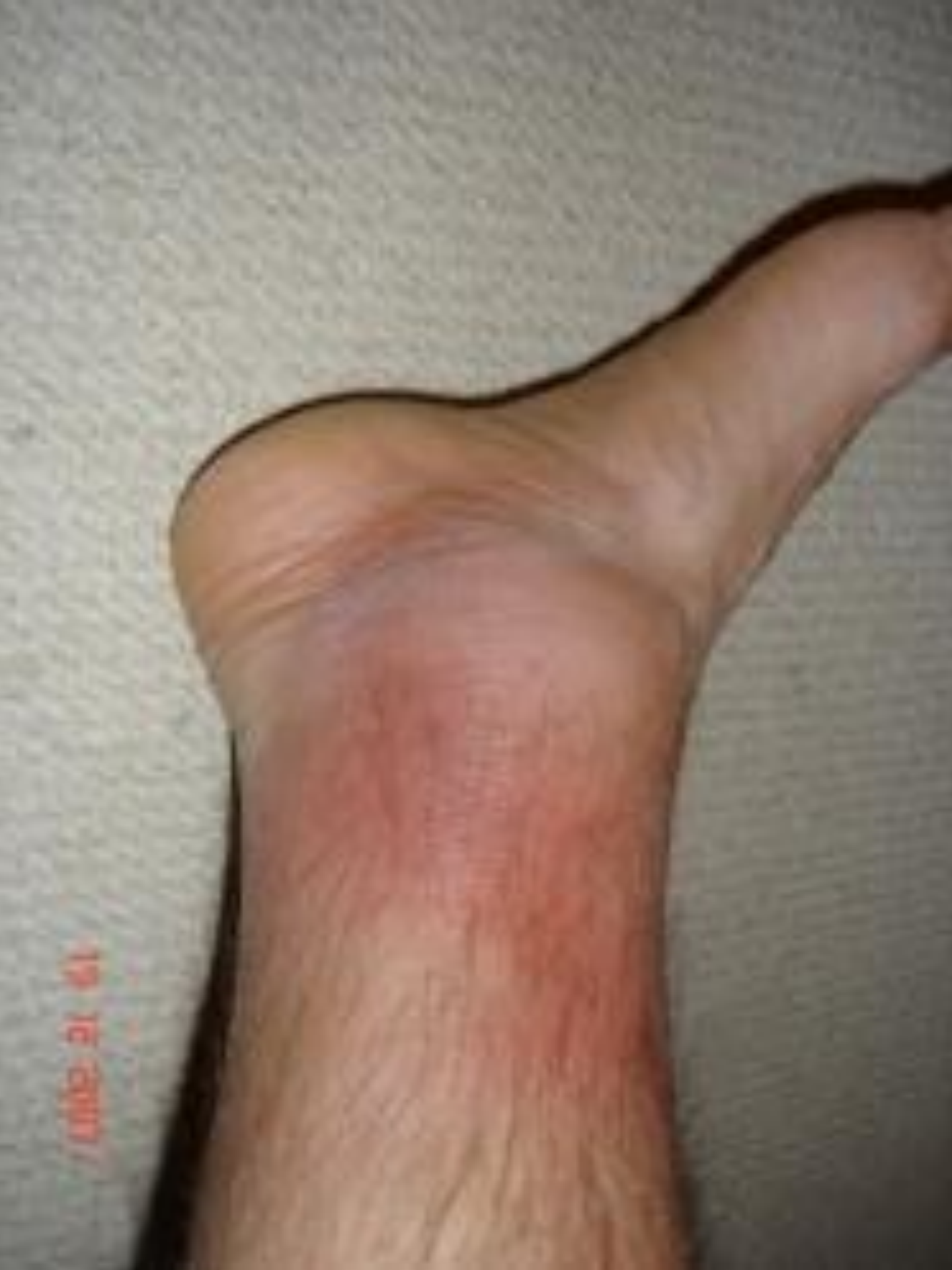
Familial Mediterranean Fever

- Autosomal recessive and autosomal dominant forms
- MEFV gene at 16p13.3
- Some mutations result in autosomal dominant inheritance whereas others (mostly) result in autosomal recessive inheritance. This is due to haploinsufficiency.
- Dominant form is milder compared with recessive form of the disease

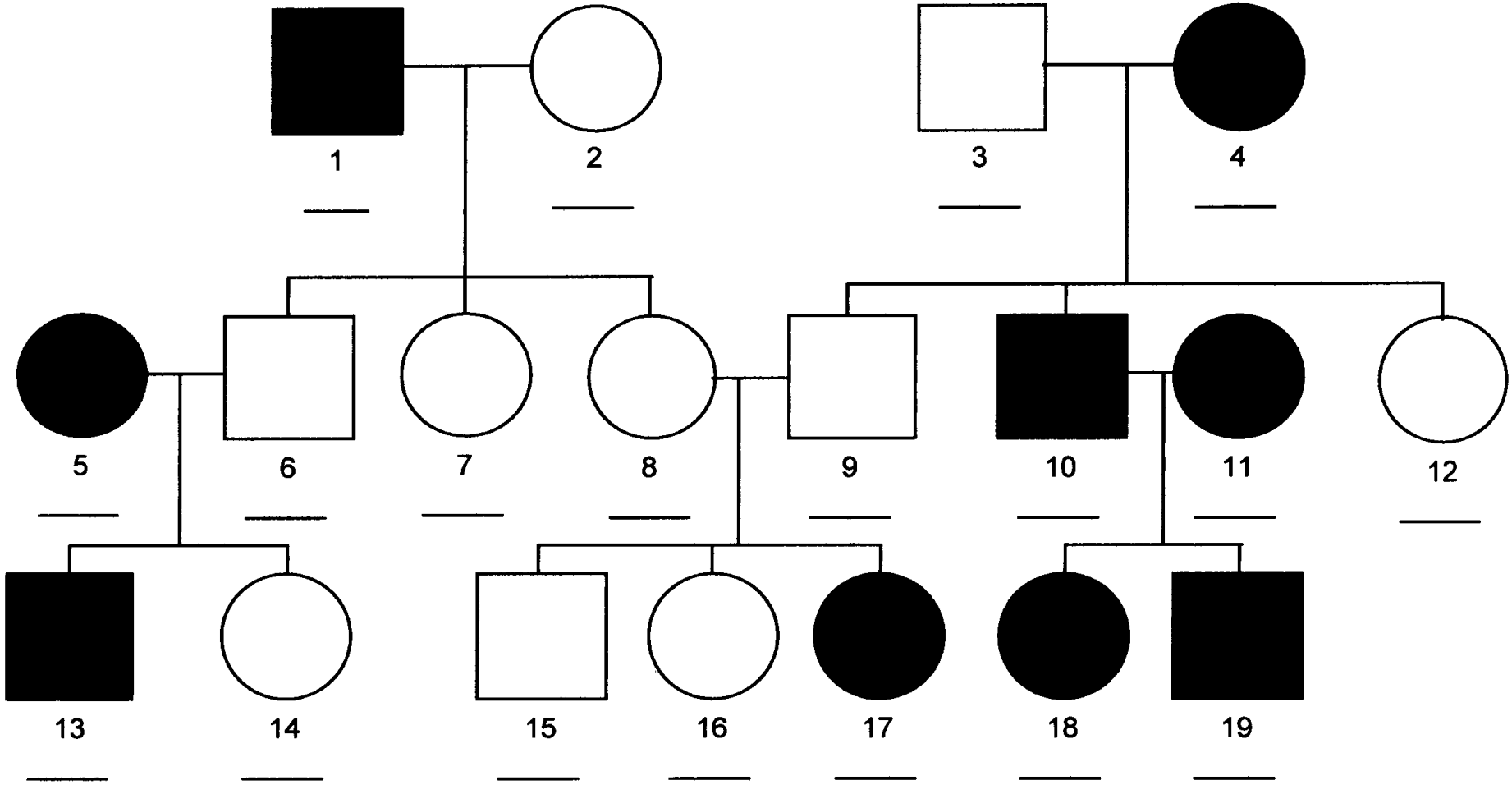
Familial Mediterranean Fever

- Recurrent attacks of fever
- Inflamation and pain
- Amyloidosis with renal failure
- Disease presents early in life, often childhood
- It is a manageable disease
- Use of cholchecine reduces painful attacks, amyloidosis in FMF

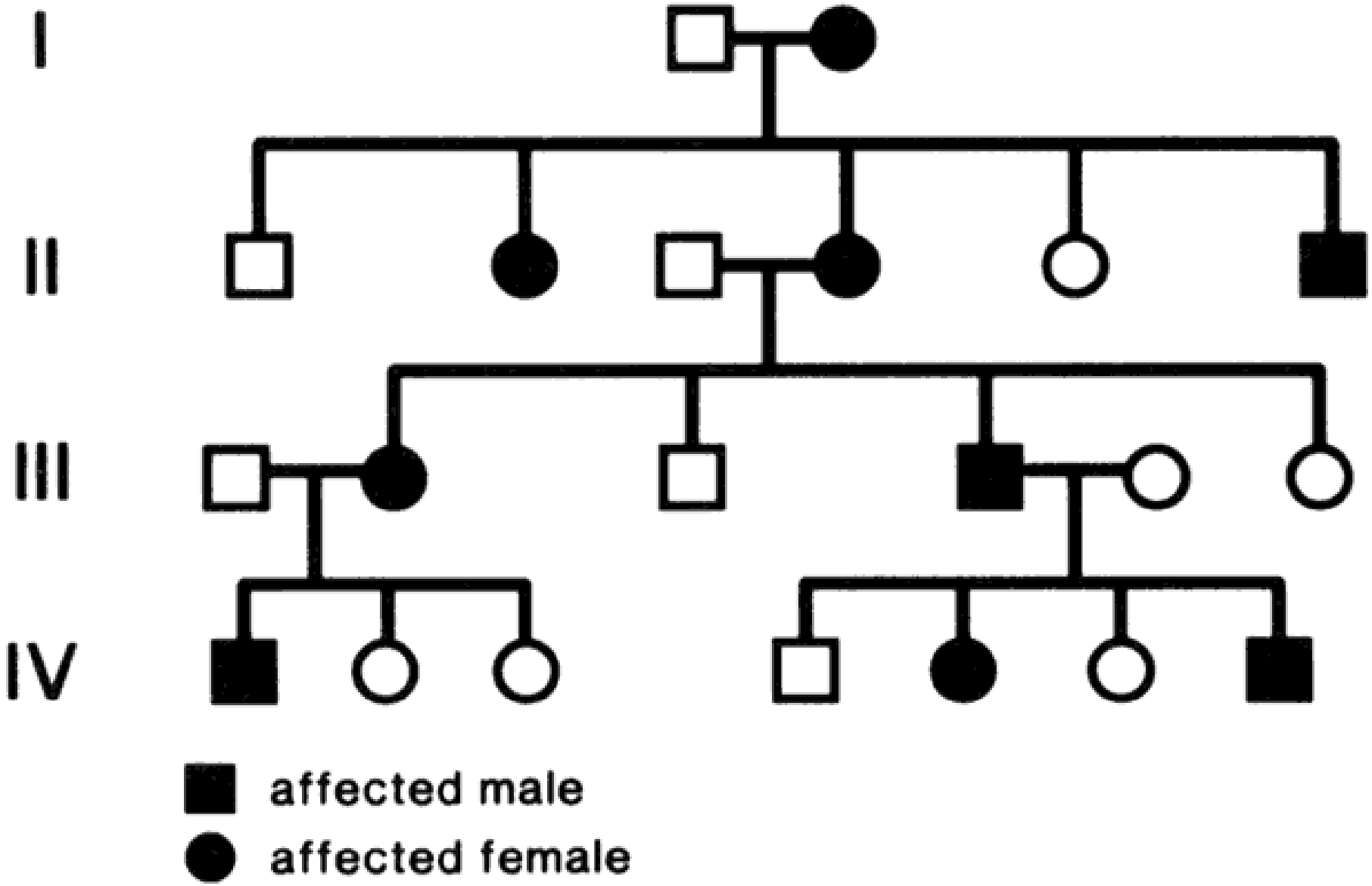




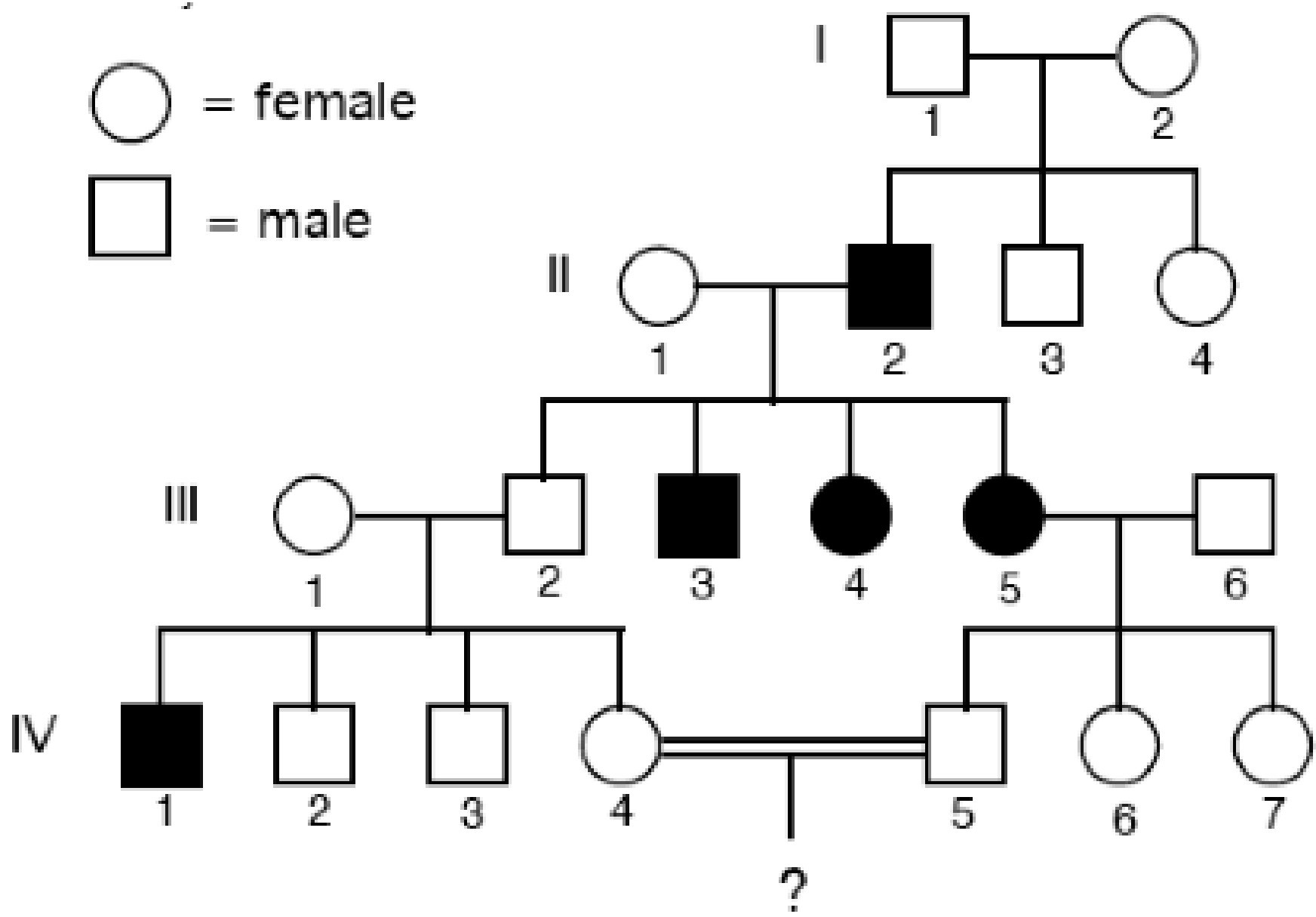
Pedigree 1



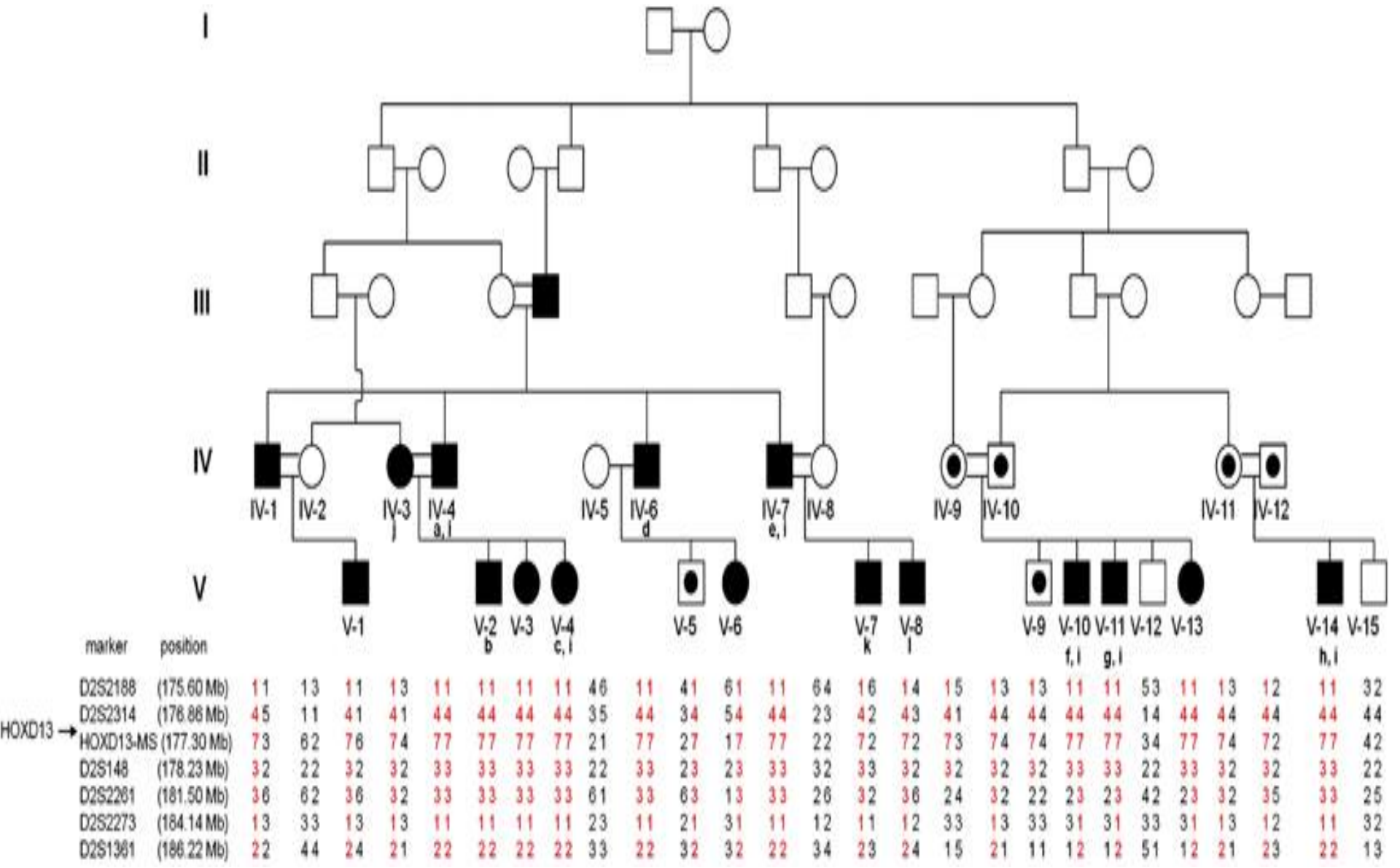
Pedigree 2



Pedigree 3



Pedigree 4


I
II
III
IV
V
IV-1
IV-2
IV-3
j
IV-4
a, j
IV-5
IV-6
d
IV-7
e, l
IV-8
IV-9
IV-10
IV-11
IV-12
V-1
V-2
b
V-3
V-4
c, l
V-5
V-6
V-7
k
V-8
l
V-9
V-10
f, l
V-11
g, l
V-12
V-13
V-14
h, l
V-15
marker
position
HOXD13
D2S2188 (175.60 Mb) 11 13 11 13 11 11 11 11 46 11 41 61 11 64 16 14 15 13 13 11 11 53 11 13 12 11 32
D2S2314 (176.86 Mb) 45 11 41 41 44 44 44 44 35 44 34 54 44 23 42 43 41 44 44 44 44 14 44 44 44 44 44
HOXD13-MS (177.30 Mb) 73 62 76 74 77 77 77 77 21 77 27 17 77 22 72 72 73 74 74 77 77 34 77 74 72 77 42
D2S148 (178.23 Mb) 32 22 32 32 33 33 33 33 22 33 23 23 33 32 33 32 32 32 32 33 33 22 33 32 32 33 22
D2S2261 (181.50 Mb) 36 62 36 32 33 33 33 33 61 33 63 13 33 26 32 36 24 32 22 23 23 42 23 32 35 33 25
D2S2273 (184.14 Mb) 13 33 13 13 11 11 11 11 23 11 21 31 11 12 11 12 33 13 33 31 31 33 31 13 12 11 32
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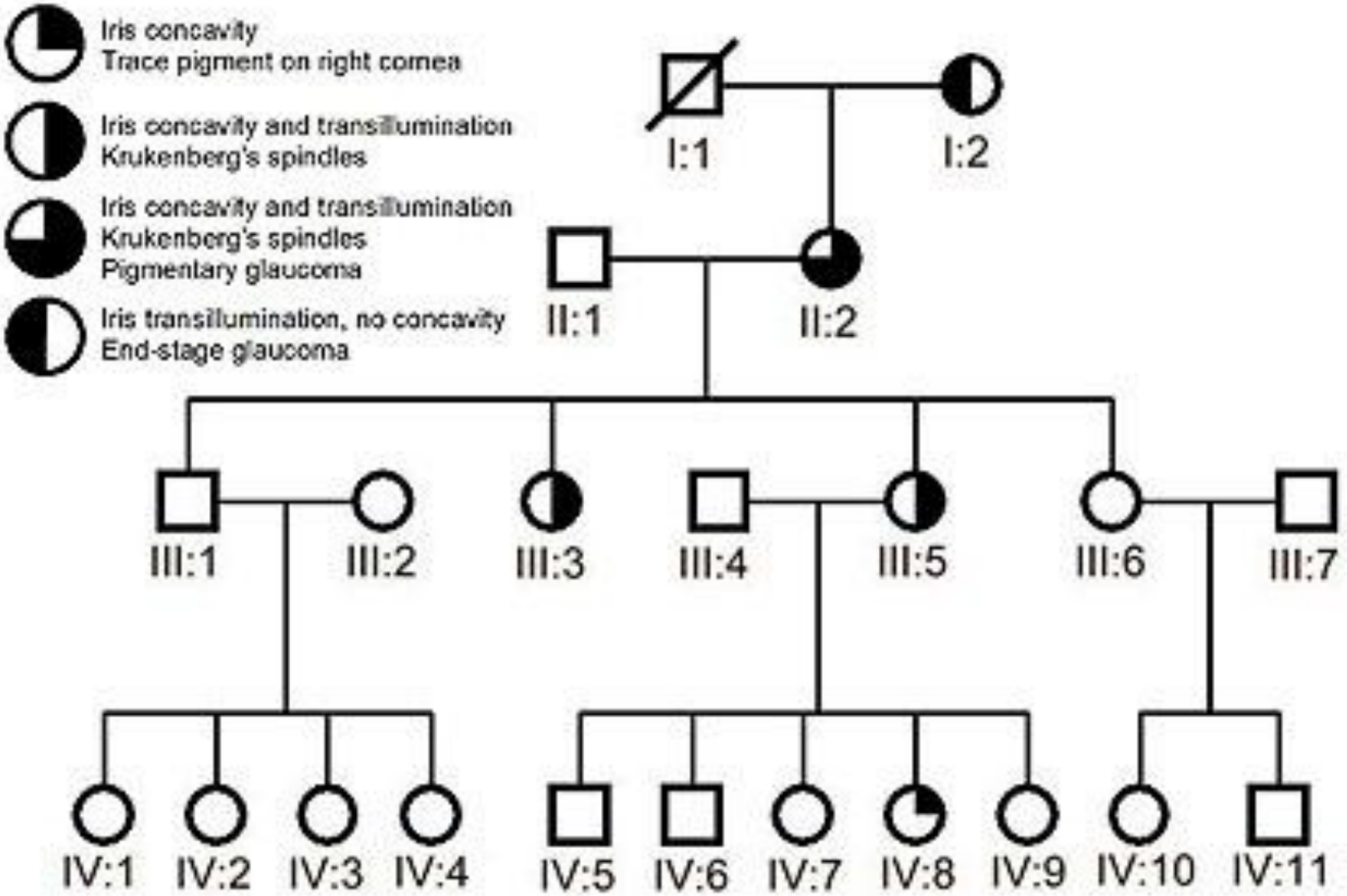
Pedigree 5


Iris concavity
Trace pigment on right cornea
Iris concavity and transillumination
Krukenberg's spindles
Iris concavity and transillumination
Krukenberg's spindles
Pigmentary glaucoma
Iris transillumination, no concavity
End-stage glaucoma
I:1
I:2
II:1
II:2
III:1
III:2
III:3
III:4
III:5
III:6
III:7
IV:1
IV:2
IV:3
IV:4
IV:5
IV:6
IV:7
IV:8
IV:9
IV:10
IV:11

Summary

- Autosomal dominant vs autosomal recessive inheritance patterns are different
- Variable expressivity, incomplete penetrance and haploinsufficiency are considered in autosomal dominant inheritance
- Carrier status should be considered in autosomal recessive inheritance
- Disease severity does not depent on recessiveness or dominance
- The risk of passing disease is different in different inheritance patterns