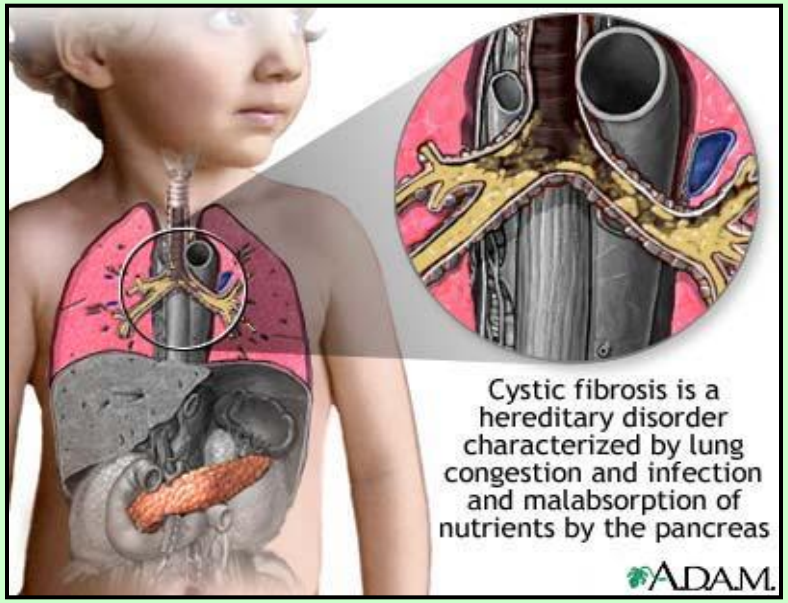
Cystic fibrosis (CF) - inherited autosomal recessive disorder

incidence of 1 in 3 000 live births

carrier frequency of 1 in 25

CF affects roughly 70 000 worldwide

Hallmarks of CF

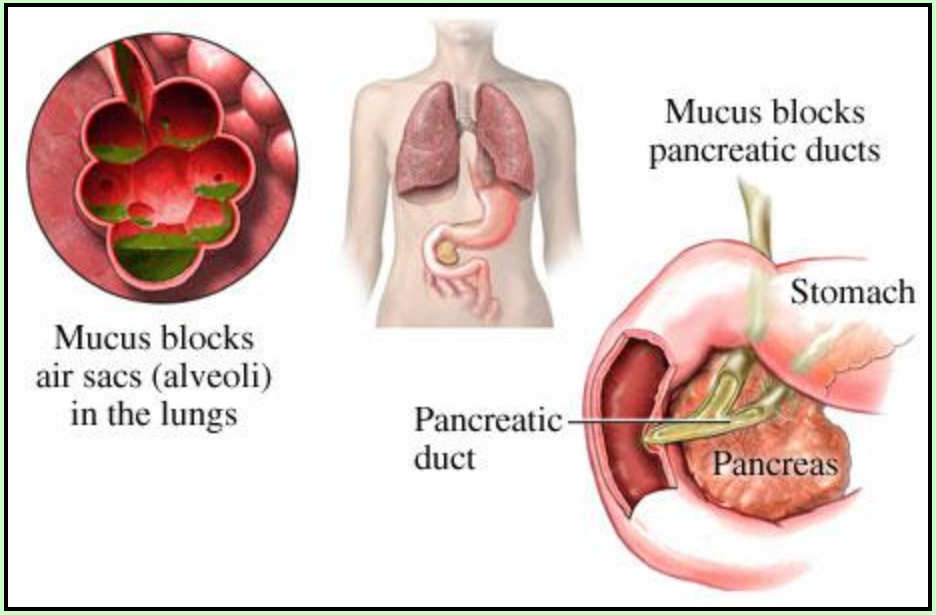


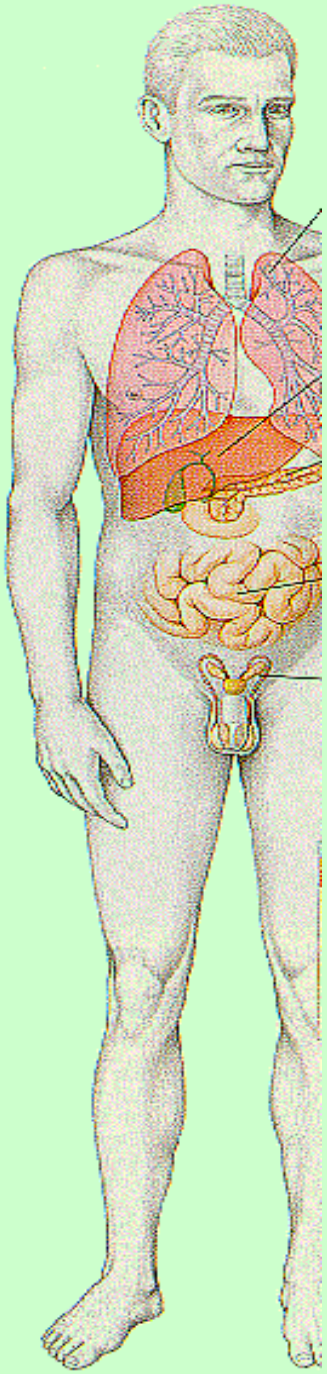
- Very salty-tasting skin
- Appetite, but poor growth & weight gain
- Coughing, wheezing & shortness of breath
- Lung infections, e.g. pneumonia/bronchitis

Clinical Aspects

Cystic fibrosis affects the entire body

- Lungs and sinuses
- GI, liver and pancreas
- Endocrine system
- Reproductive system





Organs Affected by Cystic Fibrosis

AIRWEAYS: Clogging and infection of bronchial passages impede breathing. The infection progressively destroy the lungs.

LIVER: Plugging of small bile ducts impedes digestion and discrupts liver function in perhaps 5% of patients

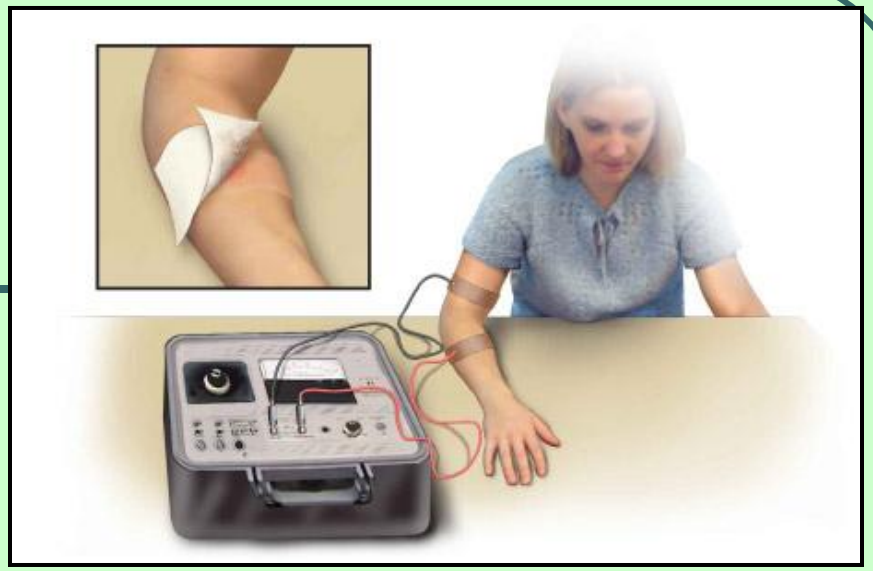
PANCREAS: Oclusion of ducts prevents the pancreas from delivering critical digestive enzymes to the bowel in 65% of patients. Diabetes can result as well.

SMALL INTESTINE: Obstruction of the gut by thick stool necessitates surgerry in about 10% of newborns

REPRODUCTIVE TRACT: Absence of fine ducts, such as the vas deferans, renders 95% of males infertile. Occasionally, women are made infertile by a dense plug of mucus that blocks sperm from entering the uterus.

SKIN: Malfunctioning of sweat glands causes perspiration to contain excessive salt (NaCl)

The Sweat Test



- Measures the concentration of chloride and sodium that is excreted in sweat.
- Two reliable positive results on two separate days is diagnostic for CF.
- Clinical presentation, family history and patient age must be considered to interpret the results.

CFTR gene (cystic fibrosis transmembrane conductance regulator)

Location: 7q31.2

Over 1,000 mutations in CFTR have been found

ΔF508 accounts for just 70% of CF cases

Panel 1: **Frequencies of *CFTR* mutations***

***CFTR* mutation**	**Allele frequency (%)**	***CFTR* mutation**	**Allele frequency**
ΔF508	69·4%	2789+5G→A	0·3%
Unknown	15·7%	R1162X	0·3%
G542X	2·3%	G85E	0·3%
G551D	2·2%	R560T	0·2%
ΔI507	1·6%	R334W	0·2%
W1282X	1·4%	3659ΔC	0·2%
N1303K	1·2%	A455E	0·1%
R553X	0·9%	711+1G→T	0·1%
621+1G→T	0·8%	1898+1G→A	0·1%
R117H	0·7%	2184ΔA	0·1%
3849+10 kbC→T	0·7%	S549N	0·1%
1717–lG→A	0·5%	1078ΔT	0·03%
R347P	0·3%		

*n=17 853.

The ΔF508 Mutation

A 3 base pair deletion called ΔF508 is the most common mutation causing cystic fibrosis

The mutation results in the deletion of a single amino acid (Phe) at position 508.

In Normal CFTR:

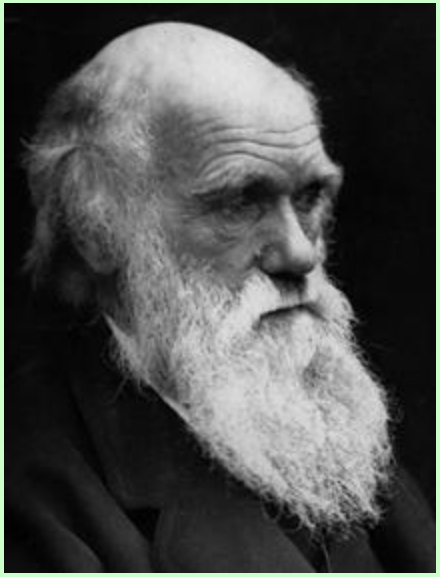
Nucleotide	AAT	ATC	ATC	TTT	GGT	GTT	TCC
Amino Acid	Asn	Ile	Ile	Phe	Gly	Val	Ser
	505			508			511

In ΔF508 CFTR:

Nucleotide	AAT	ATC	ATC	GGT	GTT	TCC
Amino Acid	Asn	Ile	Ile	Gly	Val	Ser
	505					

Benefits of ΔF508

The ΔF508 mutation most likely occurred over 50,000 years ago in Northern Europe.

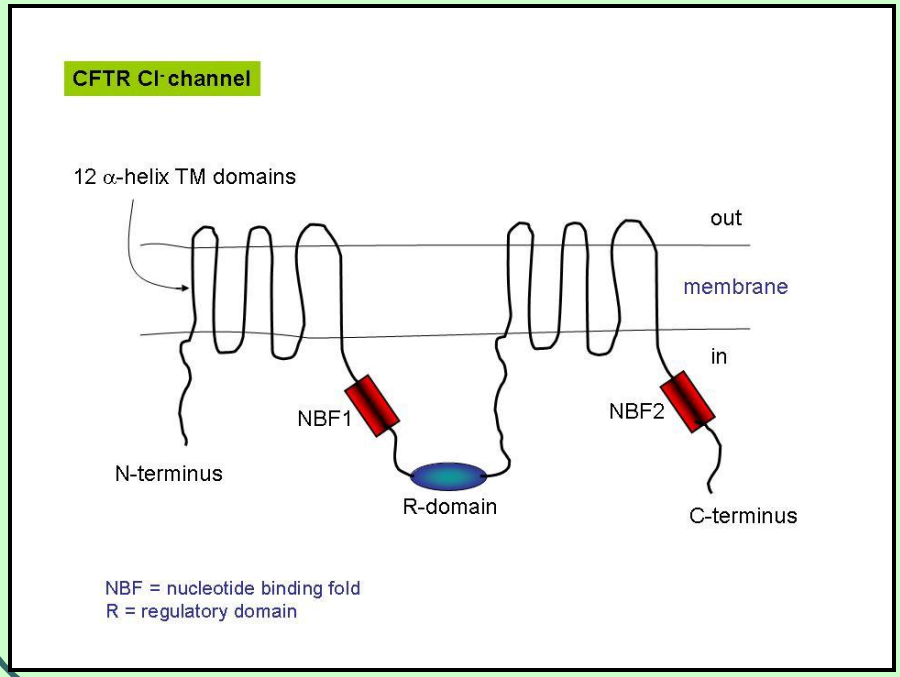


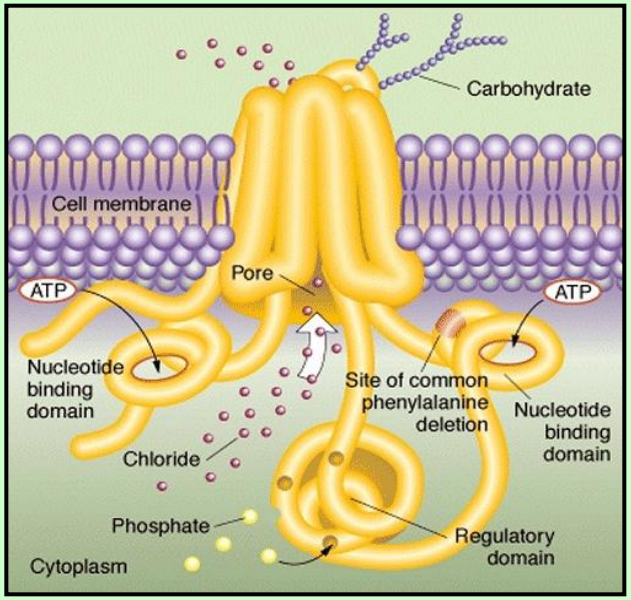
Individuals with two copies of ΔF508 get cystic fibrosis and often cannot reproduce.

Having one copy of ΔF508 reduces water loss during cholera, greatly increasing the chance of survival.

The Function of CFTR

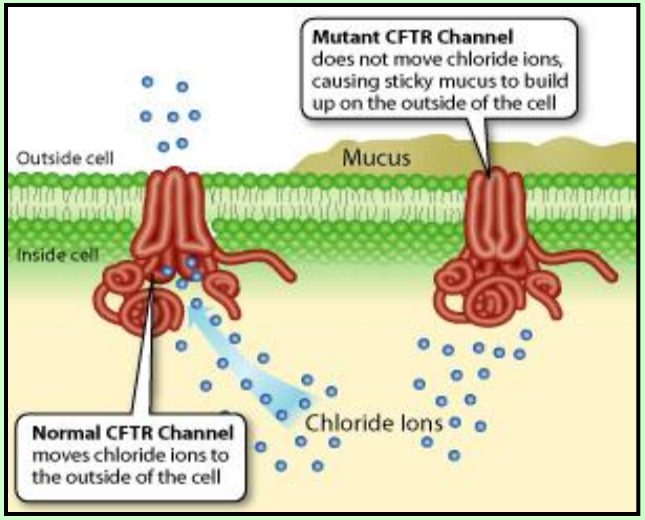
CFTR encodes a 170 kDa, membrane-based protein with an active transport function



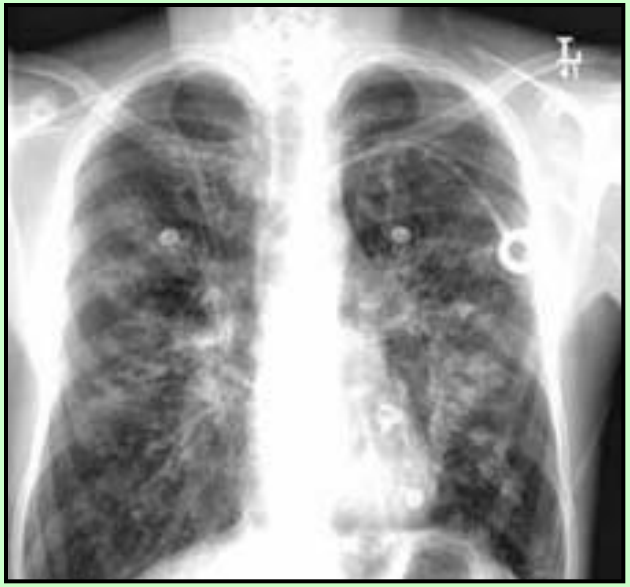


From Mutation to Disease

The mutant form of CFTR prevents chloride transport, causing mucus build-up



Mucus clogs the airways and disrupts the function of the pancreas & intestines.



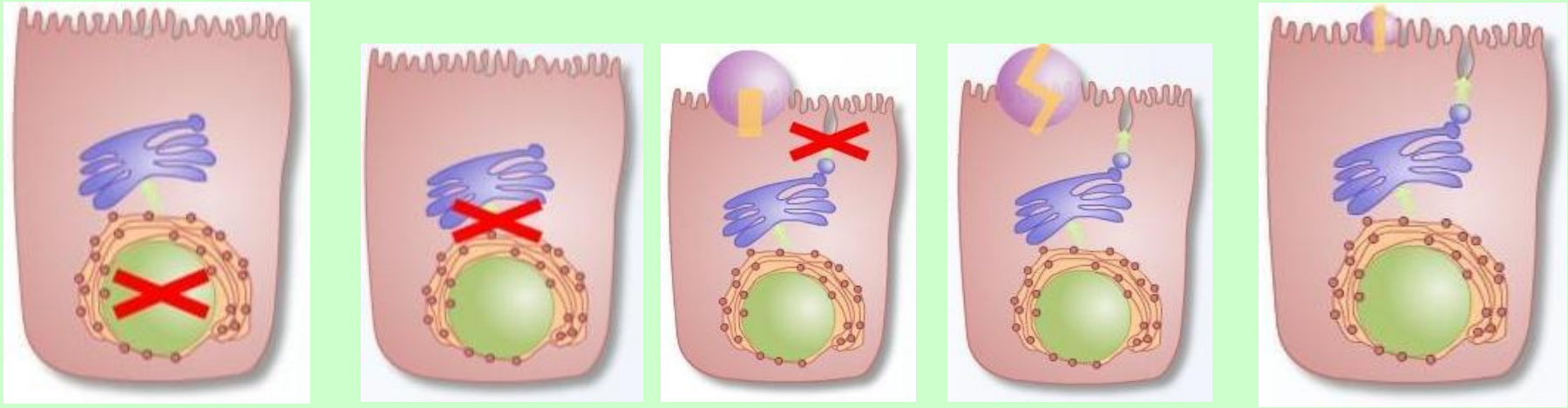
5 Classes of CFTR Mutations

CF Mutations can be classified by the effect they have on the CFTR protein.

Panel 2: **Functional classification of CFTR alleles**

Class	Functional effect of mutation	Allele
I	Defective protein production	G542X, R553X, W1282X, R1162X, 621–1G→T, 1717–1G→A, 1078ΔT, 3659ΔC
II	Defective protein processing	ΔF508, ΔI507, N1303K, S549N
III	Defective protein regulation	G551D, R560T
IV	Defective protein conductance	R117H, R334W, G85E, R347P
V	Reduced amounts of functioning CFTR protein	3849+10KbC→T, 2789+5G→A, A455E
Unknown		711+1G→T, 2184DA, 1898+1G→A

5 Classes of CFTR Mutations



I	II	III	IV	V
Defective Production	Defective Processing	Defective Regulation	Defective Conductance	Reduced Amounts

Probability of producing a child with CF:

IF: Both parents have CF THEN: 100% chance child will have CF.

IF: One parent has CF, the other is *not* a carrier THEN:

0% chance child will have CF (barring the very unlikely event of spontaneous mutation);

100% chance child will be a carrier.

IF: One parent has CF, the other is a carrier THEN:

50% chance that child will have CF;

50% chance that child will be a carrier.

IF: Both parents are carriers THEN:

25% chance that child will have CF;

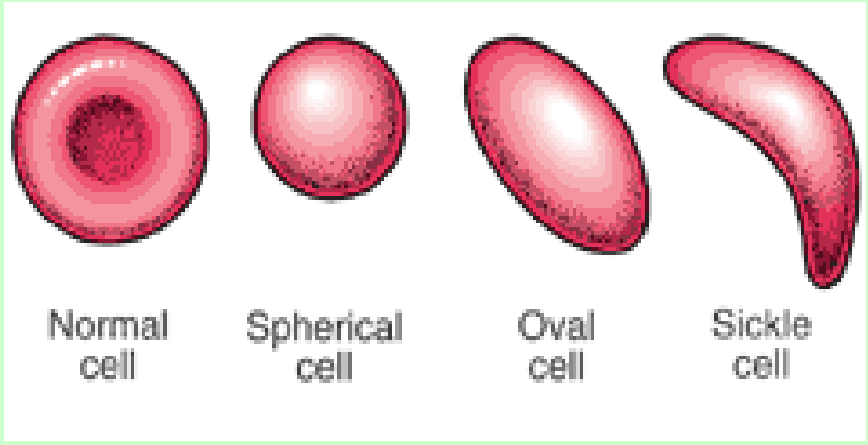
50% chance that child will be a carrier;

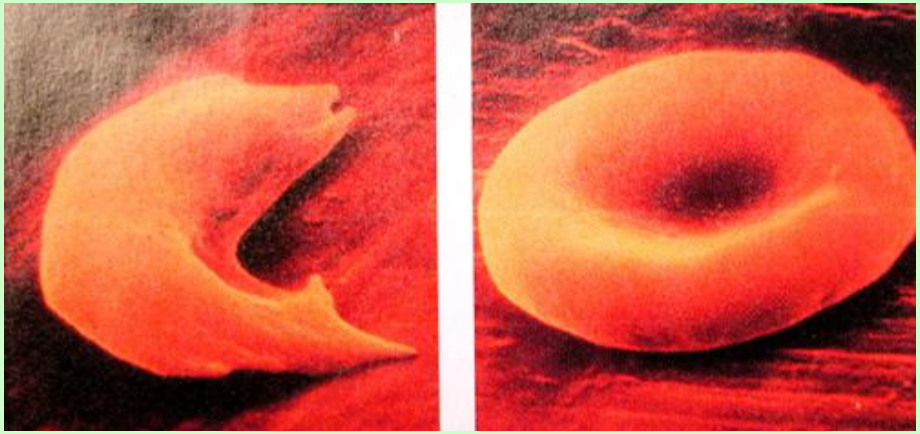
25% chance that child will not have CF or be a carrier.

Sickle Cell Anemia

autosomal recessive inheritance

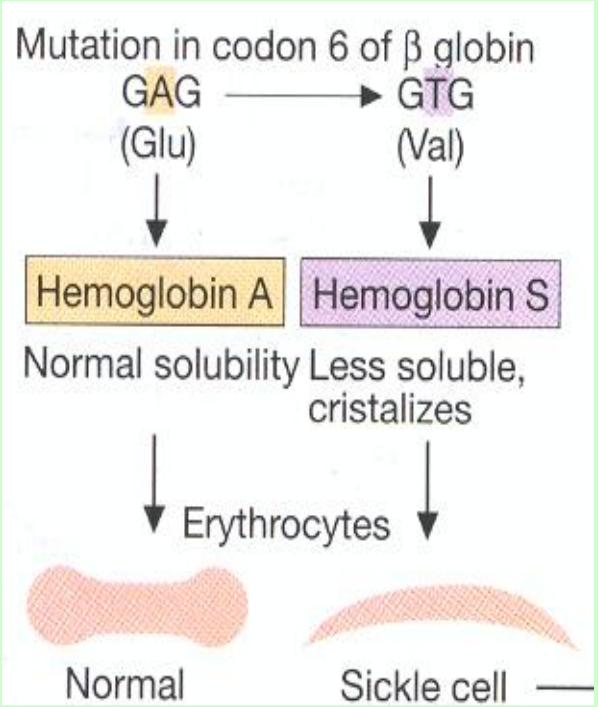
Sickle Cell Anemia

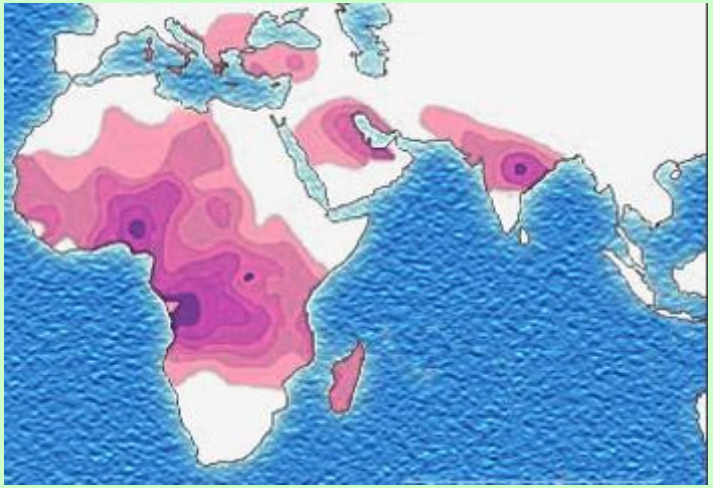




- mutation in the Hemoglobin Beta Gene which can be found in the chromosome 11
- abnormally shapes red blood cells.

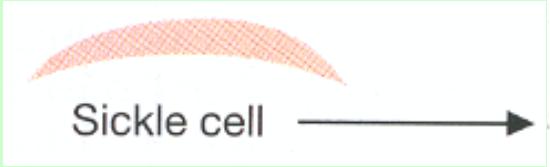
- substitution of the second nucleotide base of codon 6, adenin (A) to thymine (T) changes the codon GAG for glutamic acid to the codon GTG for valine

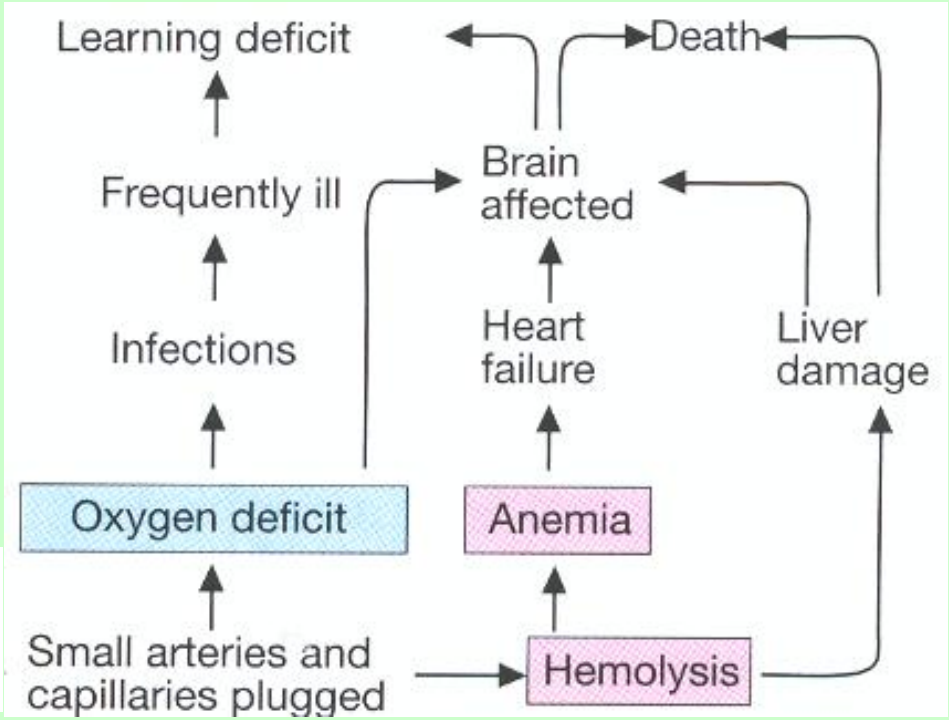




Sickle cells

- Unlike normal erythrocytes, sickle cells are unable to pass through small arteries and capillaries. These become clogged and cause local oxygen deficiency in the tisues, followed by infection. Defective erythrocytes are destroyed (hemolysis). The result is chronic anemia and its numerous sequelae such as heart failure, liver damage and infection





Hemophilia A

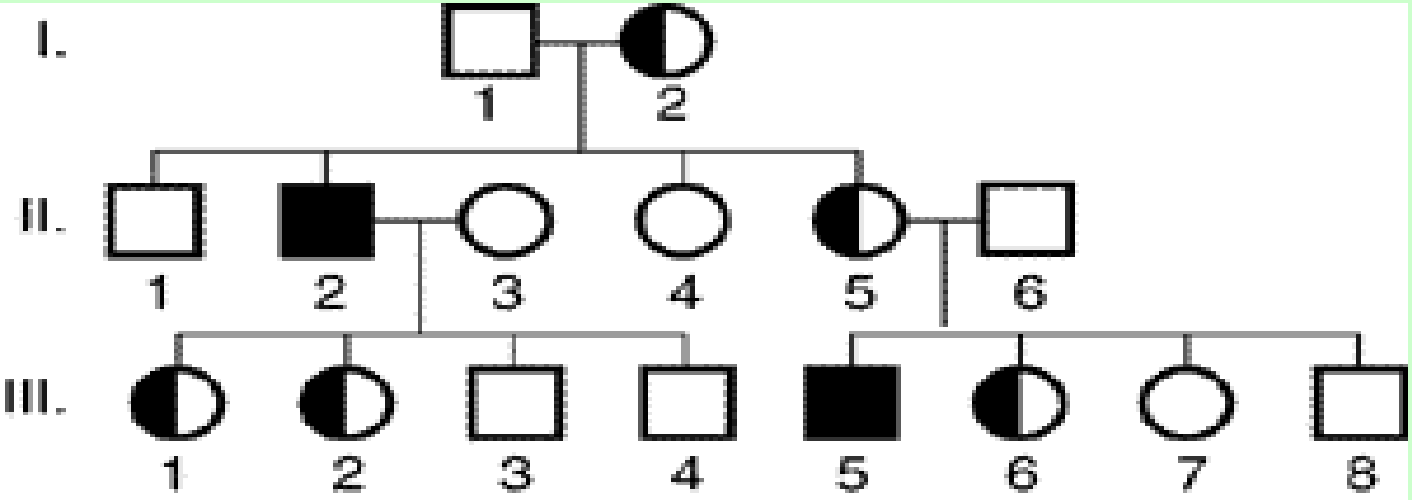
X linked recessive hereditary disorder

incidence about 1 in 5 000 males

Hemophilia A

- 2 types of hemophilia: A and B
- Hemophilia A: X linked recessive hereditary disorder
- Hemophilia A results from the deficiency of blood coagulation factor VIII, which function as a cofactor in the activation of factor X to factor Xa during the intermediate phase of the coagulation cascade

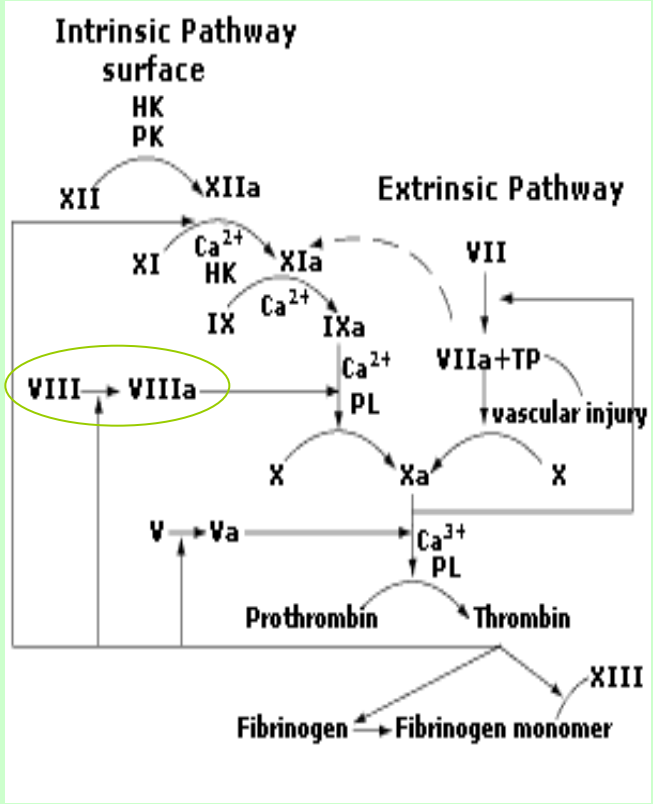
Genetics

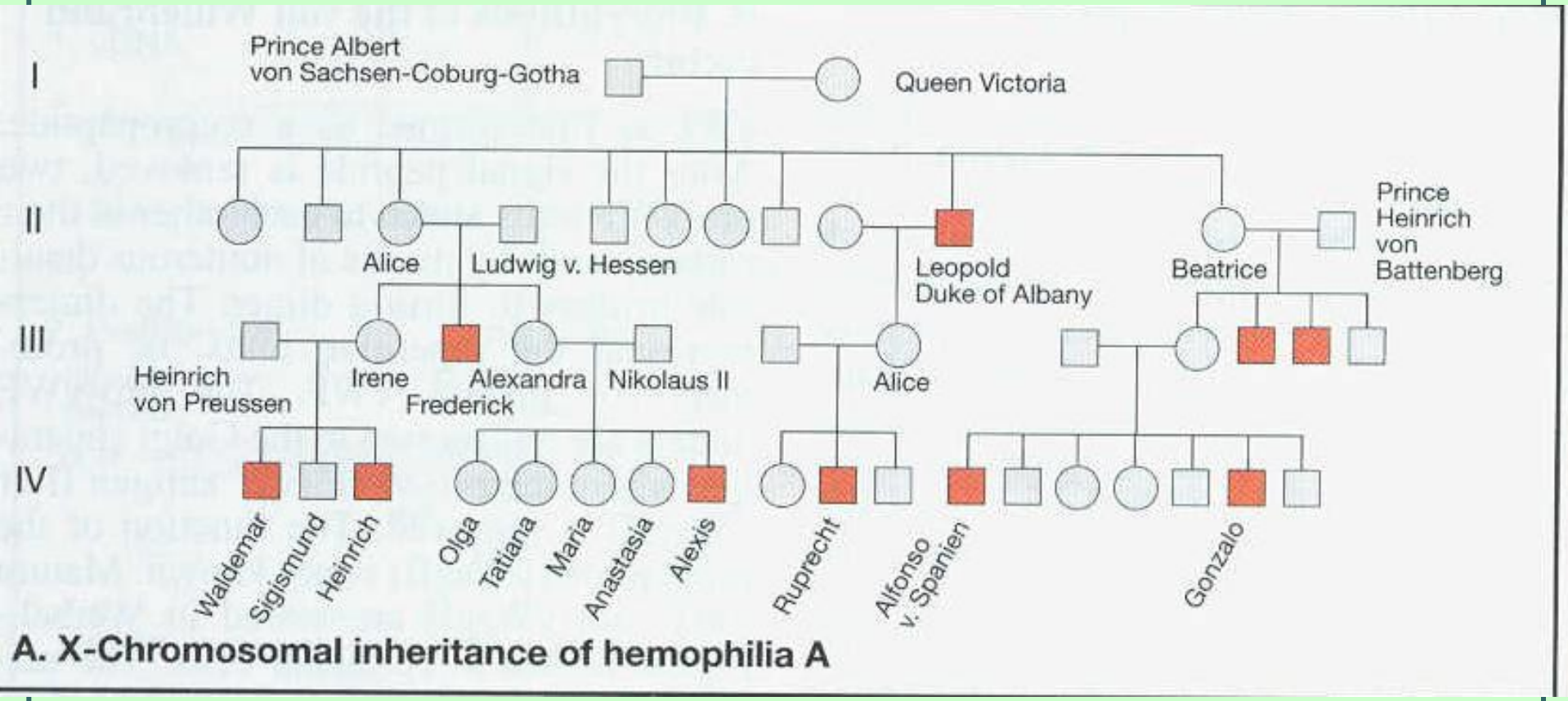


- Transmitted by females, suffered by males
- The female carrier transmits the disorder to half their sons and the carrier state to half her dtrs
- The affected male does not transmit the disease to his sons but all his dtrs are all carriers (transmission of defected X)

Genetics

- Factor VIII gene - Xq28, one of the largest genes -186kb, 26 exons. Its large size predisposes it to mutations
- In Hemophilia A there is no uniform abnormality. There are deletions, insertions, and mutations
- Aprox 40% of severe hemophilia A is caused by a major inversion in the gene- the breakpoint is situated within intron 22





A. X-Chromosomal inheritance of hemophilia A

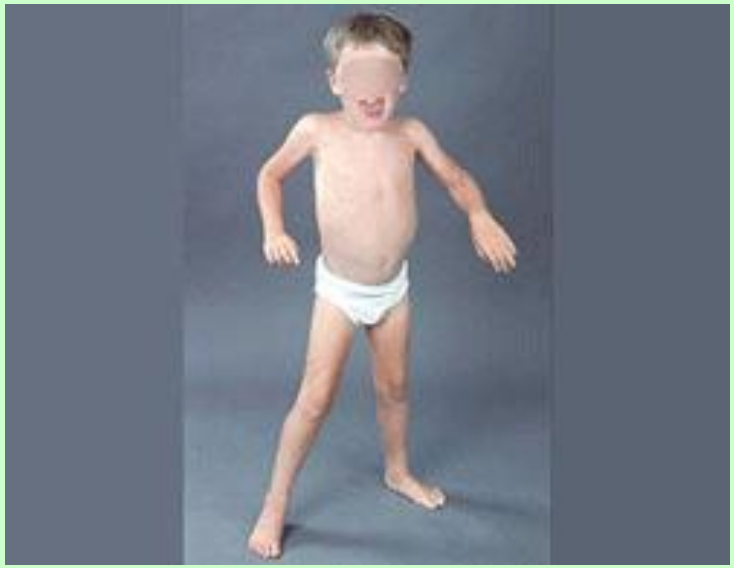
Duchenne Muscular Dystrophy

X – recesive

Occuring in 1 in 3000 males

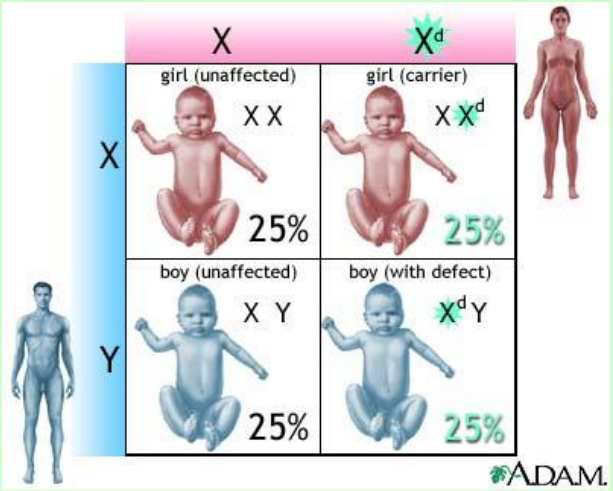
Duchenne Muscular Dystrophy

Occuring in 1 in 3000 males
X – recesive



Duchenne Muscular Dystrophy

- Females carry the DMD gene on the X chromosome.
  - Females are carriers and have a 50% chance of transmitting the disease in each pregnancy.
    - Sons who inherit the mutation will have the disease.
    - Daughters that inherit the mutation will be carriers.
- The DMD gene is located on the Xp 21 band of the X chromosome



- Dystrofin gene: locus Xp21
- 2,4 MB (1% of X chromosome)
- 79 exons
- The most frequent mutation:
  - –Deletion of 1and more exons (65%)
  - –Frameshift mutations
  - – 1/3 patients has *de novo* mutation

Clinical Features - Phenotype of DMD

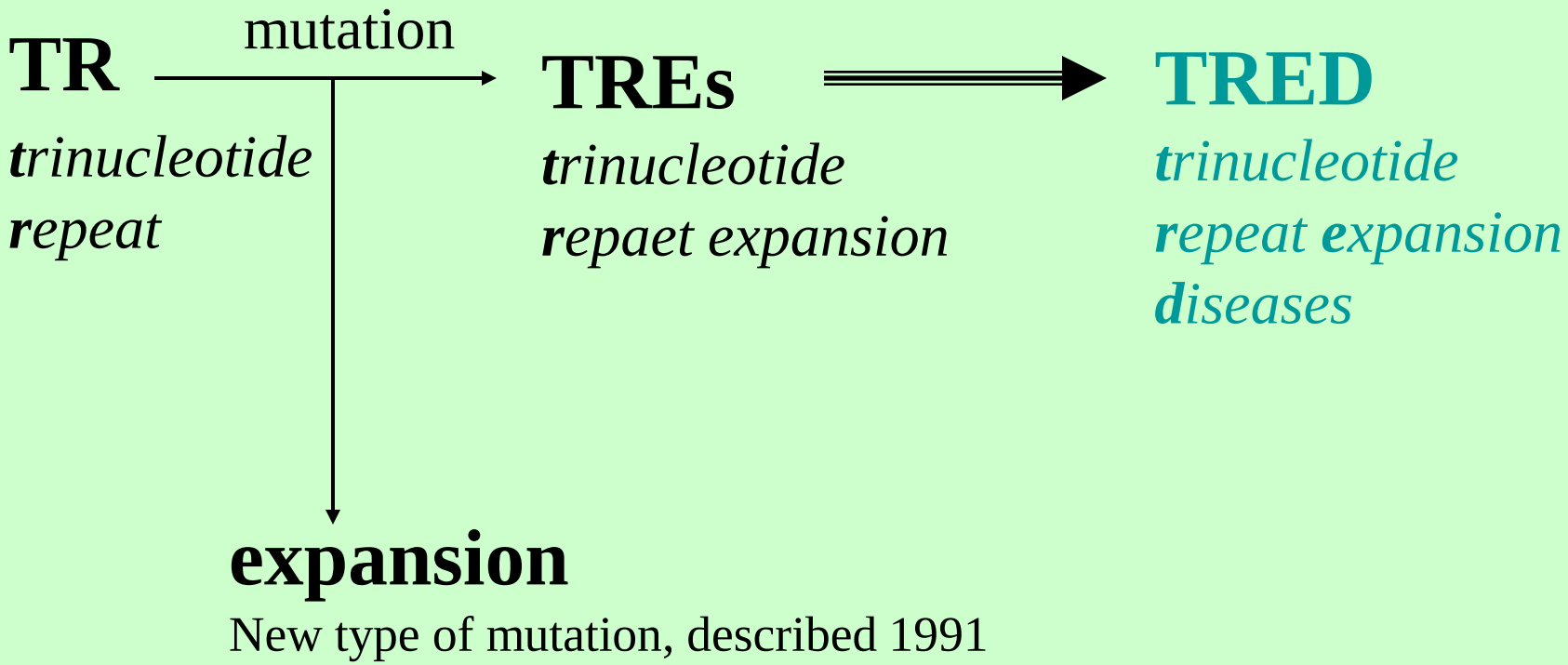
- Delays in early childhood stages involving muscle use
- Learning difficulties in 5% of patients.
- Speech problems in 3% of patients.
- Leg and calf pain.
- IQ’s usually below 75 points.
- Increase in bone fractures due to the decrease in bone density.
- Wheelchair bound by 12 years of age.
- Cardiomyopathy at 14 to 18 years.
- Few patients live beyond 30 years of age.
    - **Reparatory problems and cardiomyopathy leading to congestive heart failure are the usual cause of death.**

DMD Gene and Dystrofin - Function

- The DMD gene encodes for the protein dystrofin, found in muscle cells and some neurons.
  - Dystrofhin provides strength to muscle cells by linking the internal cytoskeleton to the surface membrane.
  - Without this structural support, the cell membrane becomes permeable. As components from outside the cell are allowed to enter the internal pressure of the cell increases until the cell bursts and dies.

Allelic Variants

Disease	Mutation	Effect of Mutation	Phenotype
Duchenne Muscular Dystrophy	Very Large Deletions caused by: Stop mutations Splicing mutations Deletions Duplications	Severely Functionally Impaired Dystrophin Protein	As Discussed In Prior Slides
Becker Muscular Dystrophy	Deletion or Duplication That Change In-Frame Exons	Creates A Protein That Is Partially Functional	Same As But Less Sever Then DMD But Onset At Greater Then 7 Years Old
DMD Related Dilated Cardiomyopathy	Effects The Cardiac Muscle Promoter and The First Exon	No Dystrophin Transcriptions Being Carried Out In Cardiac Muscle	Tachycardia (Fat Heart Beat) Leads To Congestive Hear Failure
Limb-Girdle Muscular Dystrophy	In Gene That Encodes Scarcoglycans and Other Proteins of Muscle Cells	Decrease In Scarcoglycans Proteins	Pelvic and Shoulder Girdle Can Look Like DMD or BMD


TR
mutation
TREs
TRED
trinucleotide
repeat
trinucleotide
repaet expansion
trinucleotide
repeat expansion
diseases
expansion
New type of mutation, described 1991

Trinucleotide repeat disorders

- caused by an unusual form of mutation called trinucleotide repeat expansion (TNRE)
  - The term refers to the phenomenon that a sequence of 3 nucleotides can increase from one generation to the next
- These diseases include
  - Huntington disease (HD)
  - Fragile X syndrome (FRAXA)

- Certain regions of the chromosome contain trinucleotide sequences repeated in tandem
  - In normal individuals, these sequences are transmitted from parent to offspring without mutation
  - However, in persons with TRNE disorders, the length of a trinucleotide repeat increases above a certain critical size
    - It also becomes prone to frequent expansion
    - This phenomenon is shown here with the trinucleotide repeat CAG

CAGCAGCAGCAGCAGCAGCAGCAGCAGCAG

***n* = 11**

CAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAGCAG

***n* = 18**

- In some cases, the expansion is within the coding sequence of the gene
  - Typically the trinucleotide expansion is CAG (glutamine)
  - Therefore, the encoded protein will contain long tracks of glutamine
    - This causes the proteins to aggregate with each other
    - This aggregation is correlated with the progression of the disease

- In other cases, the expansions are located in noncoding regions of genes
  - These expansions are hypothesized to cause abnormal changes in RNA structure
    - Thereby producing disease symptoms

Triplet Repeat Disorders

Table 12.7

Triplet Repeat Disorders

Disorder	OMIM	mRNA Repeat	Normal Number of Copies	Disease Number of Copies	Signs and Symptoms (Phenotype)
Fragile X syndrome	309550	CGG or CCG	6–50	200–2,000	Mental retardation, large testicles, long face
Friedreich ataxia	229300	GAA	6–29	200–900	Loss of coordination and certain reflexes, spine curvature, knee and ankle jerks
Haw River syndrome	140340	CAG	7–25	49–75	Loss of coordination, uncontrollable movements, dementia
Huntington disease	143100	CAG	10–34	40–121	Personality changes, uncontrollable movements, dementia
Jacobsen syndrome	147791	CGG	11	100–1,000	Poor growth, abnormal face, slow movement
Myotonic dystrophy type I	160900	CTG	5–37	80–1,000	Progressive muscle weakness; heart, brain, and hormone abnormalities
Myotonic dystrophy type II	602668	CCTG	<10	>100	Progressive muscle weakness; heart, brain, and hormone abnormalities
Spinal and bulbar muscular atrophy	313200	CAG	14–32	40–55	Muscle weakness and wasting in adulthood
Spinocerebellar ataxia (5 types)	271245	CAG	4–44	40–130	Loss of coordination