Genetic diseases & screening continued
Preimplantation Genetic Diagnosis & Genetic counseling

Huntington's Disease (HD) is inherited as an autosomal dominant trait

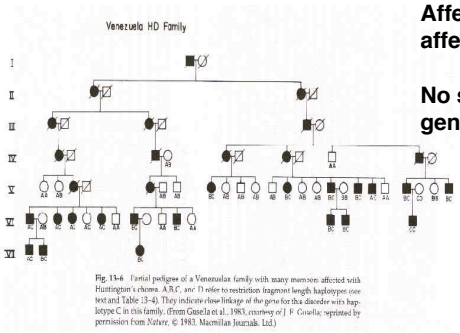


Fig. 13-6 Partial pedigree of a Venezuelan family with many members affected with Huntington's chorea. A,B,C, and D refer to restriction fragment length haplotypes (see text and Table 13-4). They indicate close linkage of the gene for the disorder with haplotype C in this family. (From Gusella et al., 1983, courtesy of J. F. Gusella; reprinted by permission from *Nature*, © 1983, Macmillan Journals, Ltd.)

Affected person has an affected parent

No skipping of generations

Huntington's disease (HD) is a late onset, progressive disorder of the central nervous system that affects 1 in 10,000 individuals in the U.S. The disorder usually begins to affect adults between the ages of 30-50 years old. Initial symptoms include irritability, clumsiness, depression and forgetfulness. These progress to more severe mental and physical impairment that leads to death.

Folksinger Woody Guthrie, who died of the disease, was first thought to be an alcoholic and later schizophrenic, before he was properly diagnosed.

Molecular basis for Huntington's disease

HD is caused by an increase in the number of repeats of three nucleotide bases, CAG, which translates into increases in the amino acid glutamine in the Huntington protein. The normal version of the HD gene has between 6 and 34 copies of CAG. The mutation which causes Huntington's increases the number of repeats to 37 or more. There appears to be a correlation between the number of CAG repeats and the age of disease onset. People with more than 60 repeat can develop HD before age 20. Most people with late adult onset HD have between 37 and 52 repeats.

Table 11.3 **Some Mutations with Expanded Trinucleotide Repeats**

Gene	Triplet Repeat	Normal Copy	Copy in Disease	MIM/OMIN Number
Spinal and bulbar muscular atrophy	CAG	12–34	40–62	313200
Spinocerebellar ataxia type 1	CAG	6–39	41–81	164400
Huntington disease	CAG	6–37	35–121	143100
Haw-River syndrome	CAG	7–34	54–70	140340
Machado-Joseph disease	CAG	13–36	68–79	109150
Fragile-X syndrome	CGG	5–52	230–72,000	309550
Myotomic dystrophy	CTG	5–37	50–72,000	160900
Friedreich ataxia	GAA	10–21	200–900	229300

A hypothetical case

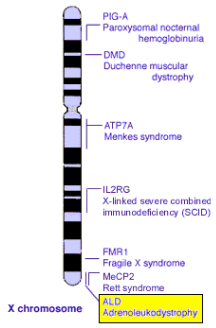
An airline pilot informs his doctor that his father has just died from HD. It is conceivable that HD could impair his functioning as a pilot.

Does the airline pilot have a duty to his passengers to have the PCR test?

Does the airline have the right to know?

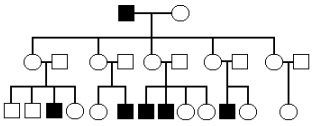
Does the physician have the right to inform the airline of his patient's father?

X-linked diseases



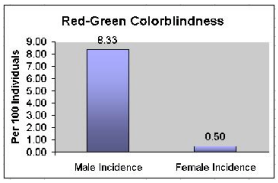
Positions of some genes associated with X-linked inherited diseases.

Colorblindness is an recessive X-linked trait.



Color-blindness: X-Linked Recessive

Grandfather to Grandson
Transmission thru a Female



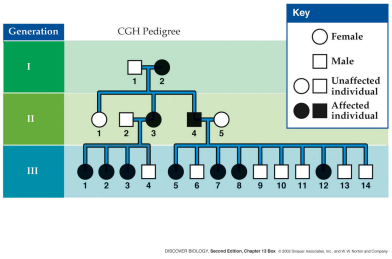
Trait usually expressed only in males.

Sons of carrier females have a 50% chance of being affected.

Affected males do not have affected children.

Trait skips generations.

Congenital Generalized Hypertrichosis is an X-linked dominant trait.



Daughters, but not sons, can inherit the trait from their fathers.

Daughters and sons can inherit the trait from their mothers.

The trait is present in each generation or is lost.

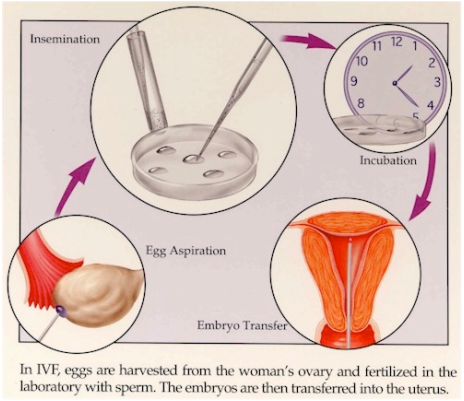
Congenital Generalized Hypertrichosis is one medical syndrome that could have contributed to the werewolf myth.

Scientists are interested in this atavistic syndrome as its understanding could shed light on how during our evolution we lost hair from parts of our body.

Shao-Lin martial arts master Su Kong Tai Djin.

Preimplantation Genetic Diagnosis

But first, *in vitro* fertilization (IVF)



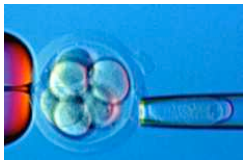
In IVF, eggs are harvested from the woman's ovary and fertilized in the laboratory with sperm. The embryos are then transferred into the uterus.

Who uses IVF?

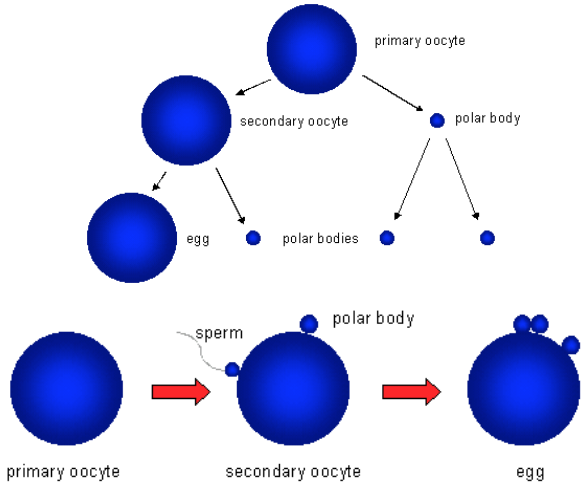
For couples that are infertile.

For couples at risk for having babies with chromosomal abnormalities and genetic diseases Preimplantation Genetic Diagnosis (PGD)

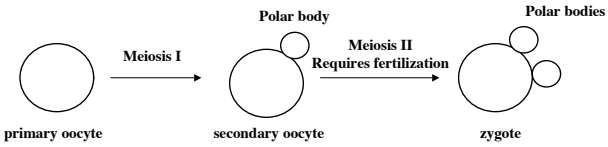
Blastomere Isolation



After IVF, 1-2 cells, known as blastomeres, can be removed from the 8-cell embryo without doing any harm. These can be tested by PCR, and embryos lacking disease alleles transferred into the uterus.

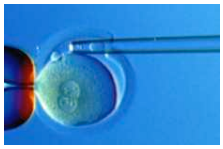


Polar Body Sampling



To test for abnormal chromosome content or disease gene carried by mother, DNA from first polar body (or both the first and second polar bodies) can be tested.

Removal of polar body



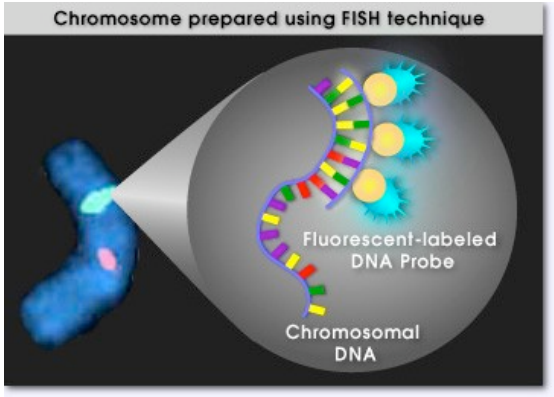
Preimplantation Genetic Diagnosis (PGD)

Two techniques used to test blastomeres or polar bodies

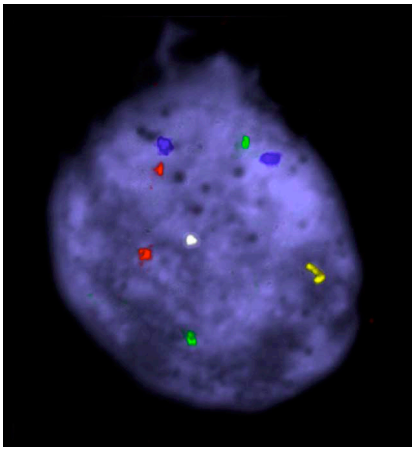
1. Fluorescence in situ hybridization (FISH)

2. Polymerase chain reaction (PCR)

FISH



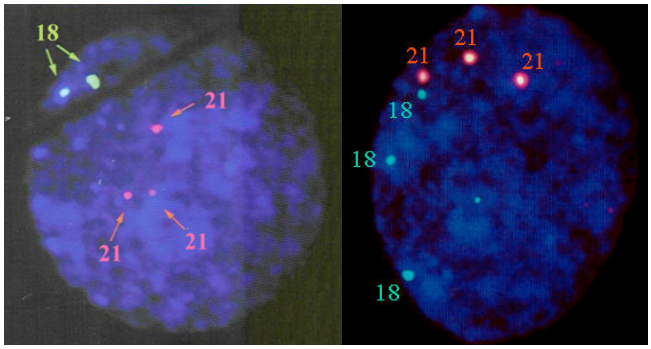
FISH of isolated blastomer



Color-chr.
Blue-18
Red-21
Green-13
Yellow-X
White-Y

FISH abnormal blastomeres

Trisomy 21 **Triploid**



Genetic Counseling

Family history
Order genetic tests
Evaluate results
Help understand and reach decisions

Who needs genetic counseling?

-Standard prenatal test abnormal
-Abnormal karyotype
-If either parent already has a child with inherited disease
-If either parent has close relative with inherited disease
-Three or more miscarriages or babies that die in infancy
-If woman is 35 or older
-Couple in at risk ethnic or racial group