

Table 9.1		Some Autosomal Disorders in Humans
Disorder	Major Symptoms	Incidence
<i>Recessive Disorders</i>		
Albinism	Lack of pigment in skin, hair, and eyes	$\frac{1}{22,000}$
Cystic fibrosis	Excess mucus in lungs, digestive tract, liver; increased susceptibility to infections; death in early childhood unless treated	$\frac{1}{1,800}$ European-Americans
Galactosemia	Accumulation of galactose in tissues; mental retardation; eye and liver damage	$\frac{1}{100,000}$
Phenylketonuria (PKU)	Accumulation of phenylalanine in blood; lack of normal skin pigment; mental retardation unless treated	$\frac{1}{10,000}$ in U.S. and Europe
Sickle-cell disease (homozygous)	Sickled red blood cells; damage to many tissues	$\frac{1}{500}$ African-Americans
Tay Sachs disease	Lipid accumulation in brain cells; mental deficiency; blindness; death in childhood	$\frac{1}{3,500}$ Ashkenazi Jews
<i>Dominant Disorders</i>		
Achondroplasia	Dwarfism	$\frac{1}{25,000}$
Alzheimer's disease (one type)	Mental deterioration; usually strikes late in life	Not known
Huntington's disease	Mental deterioration and uncontrollable movements; strikes in middle age	$\frac{1}{25,000}$
Hypercholesterolemia	Excess cholesterol in blood; heart disease	$\frac{1}{500}$

Albinism : tyrosinase deficiency.

Complete dominance of
pigmented phenotype
over
albino phenotype



Father

A/a

Son

a/a

14 May 2014 Last updated at 12:15 GMT

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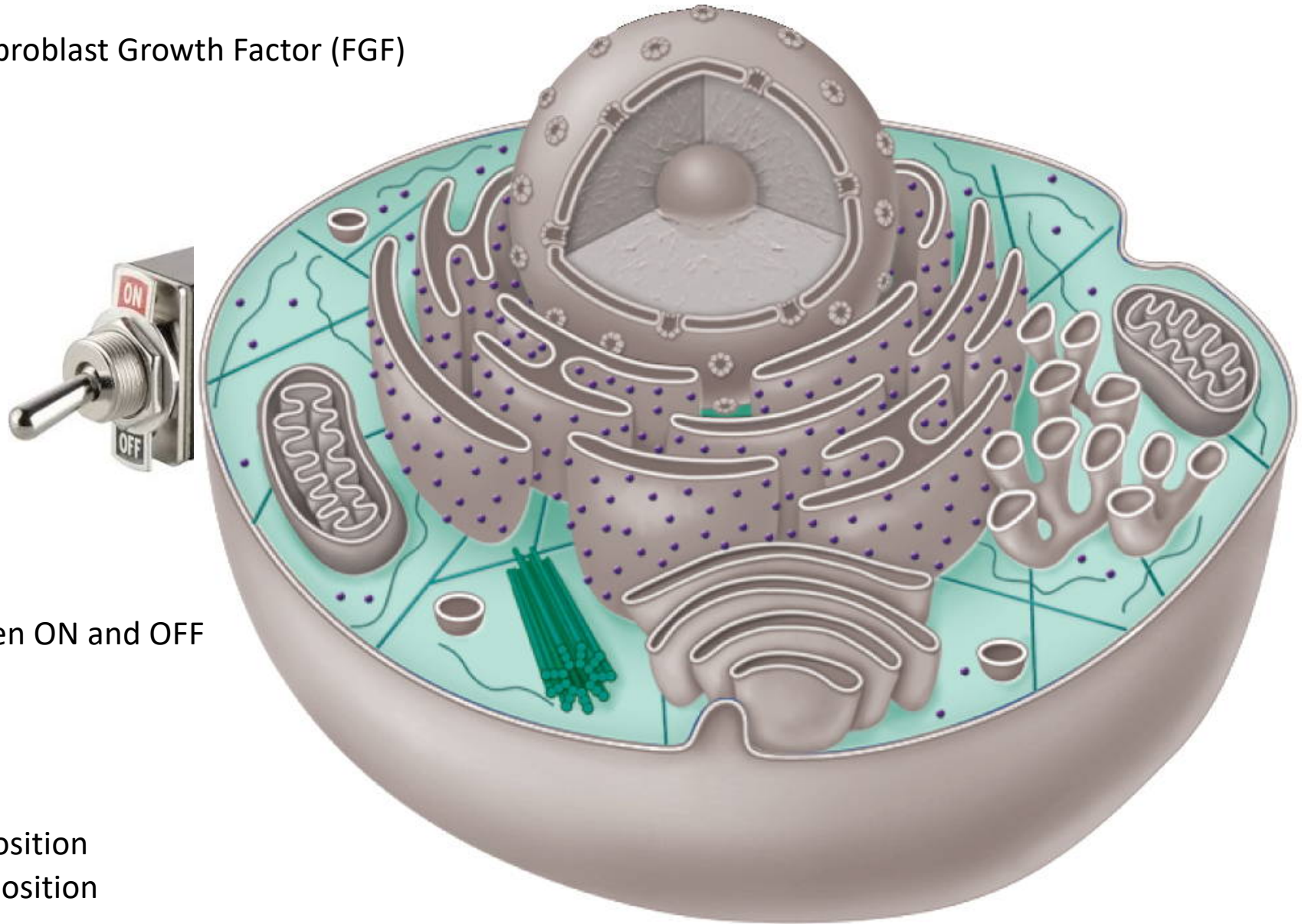


Tanzanian witch doctors arrested over albino killing



Albinos in Tanzania have become targets for body-snatchers seeking to sell them to witch doctors

Fibroblast Growth Factor (FGF)



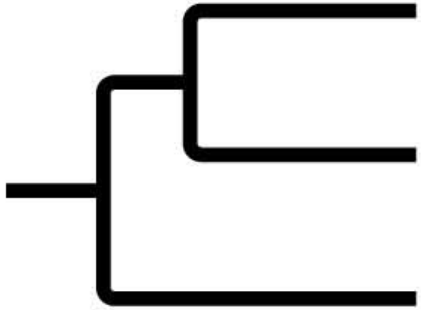
Normal FGFR3 :
can switch between ON and OFF

Mutated FGFR3 :
unable to switch

- blocked in ON position
- blocked in OFF position

MAJOR THEMES IN BIOLOGY

Evolution



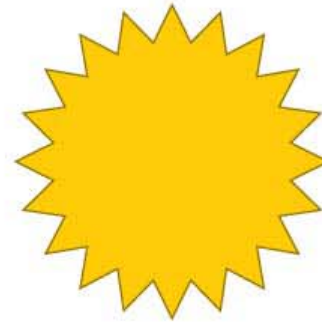
Structure/
Function



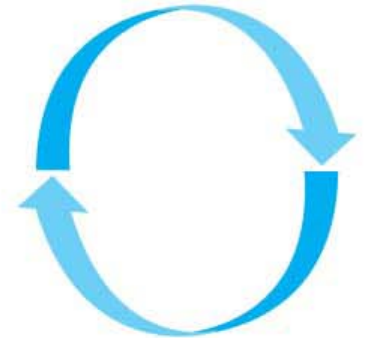
Information
Flow



Energy
Transformations



Interconnections
within Systems



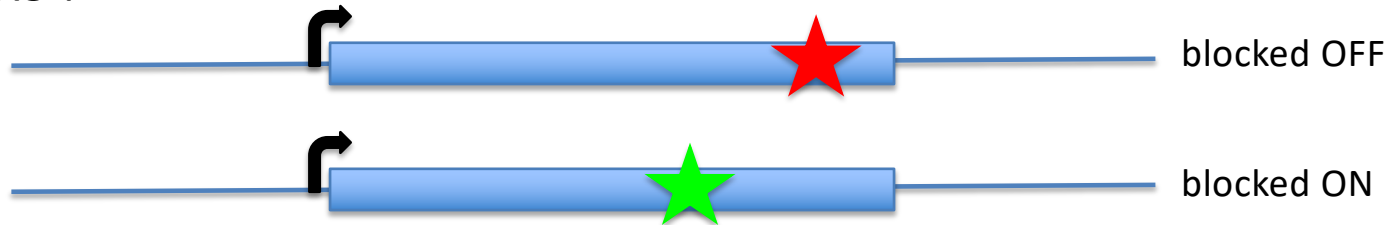
Achondroplasia is a disease of cell-to cell communication



Loss-of-function / Gain-of-function



FGFR3 :



Phenotype :

too
short

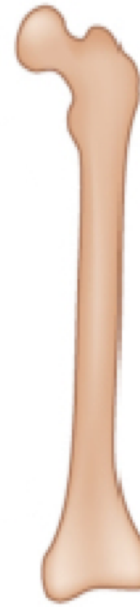


gain

right
size



too
long



loss



Examples of how mutations can generate recessive vs. dominant phenotypes

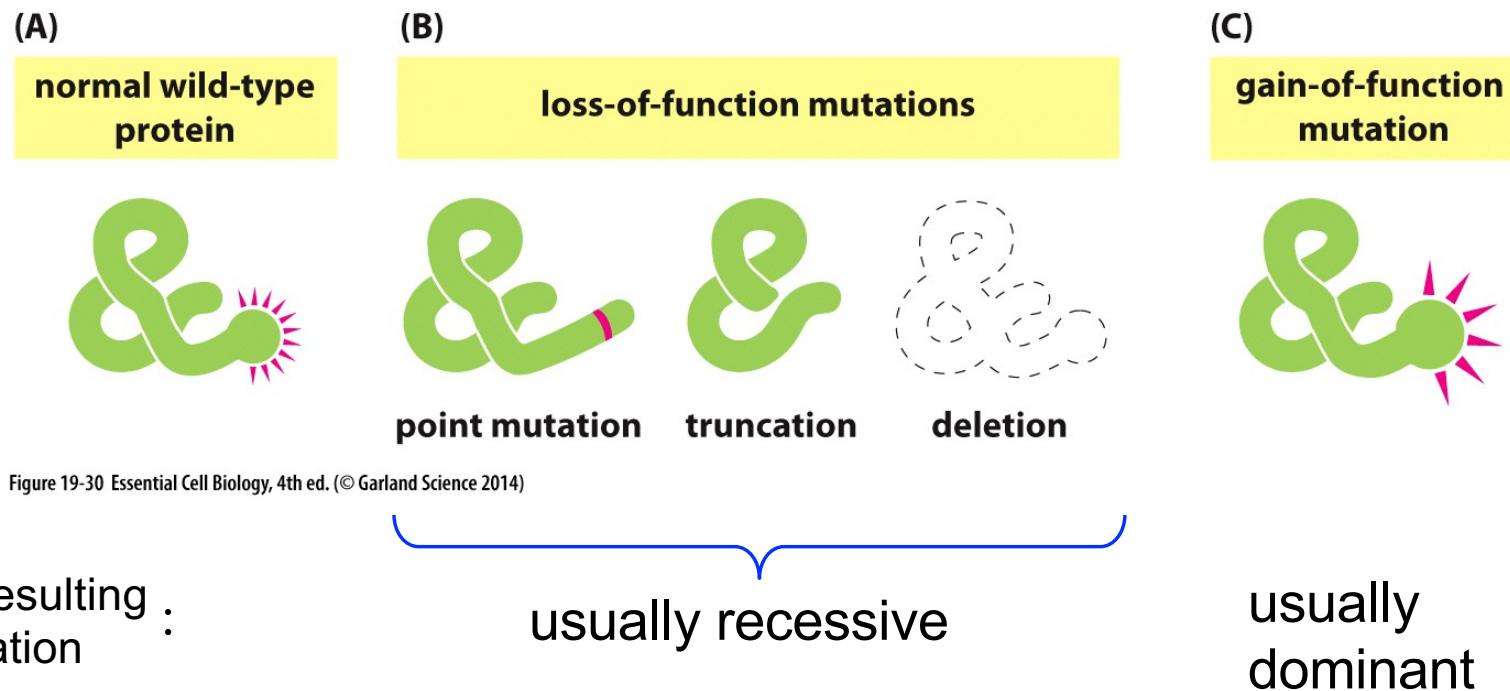


Figure 19-30 Essential Cell Biology, 4th ed. (© Garland Science 2014)

The same gene can be affected by a loss-of-function or a gain-of-function mutation.

FGFR3 knockout mice

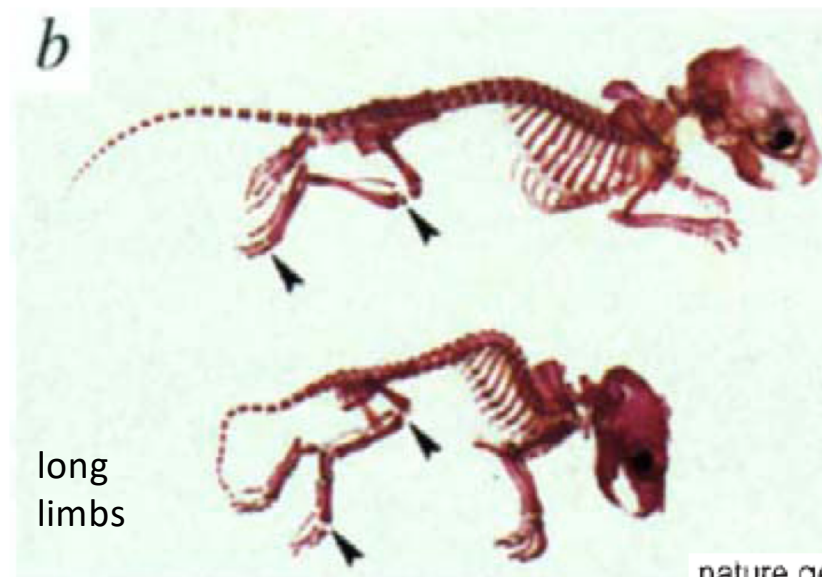
age : 12 days



FGFR3 +/-

FGFR3 -/-

Spider mouse

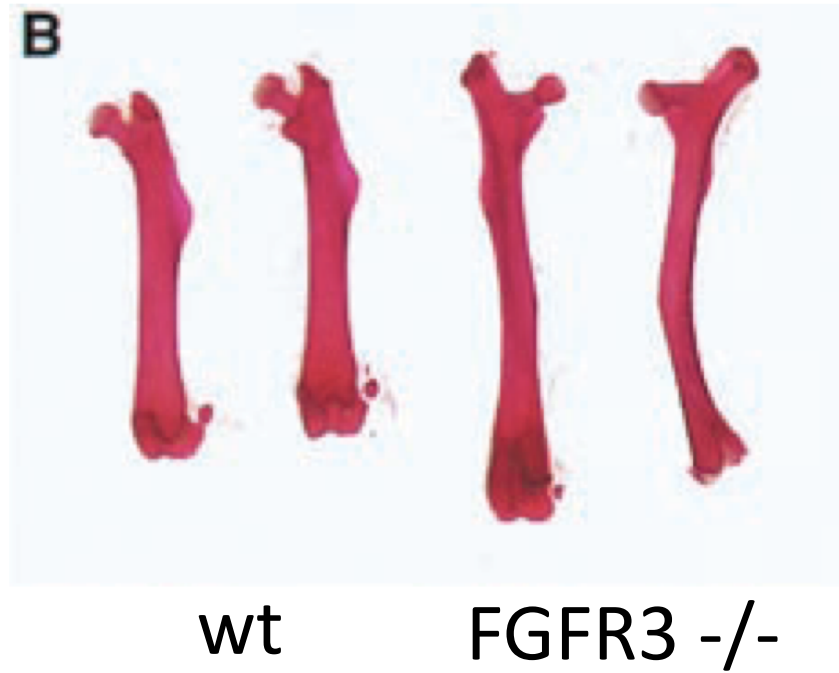


FGFR3 +/-

FGFR3 -/-

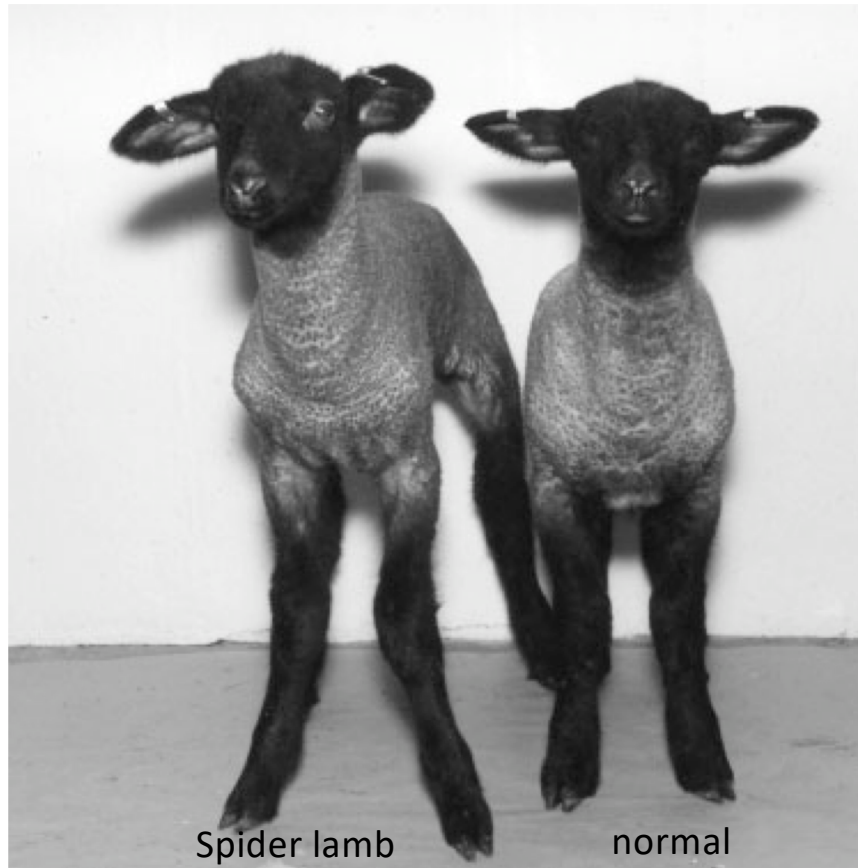
nature genetics volume 12 april 1996

Gene knockout always leads to a loss-of-function

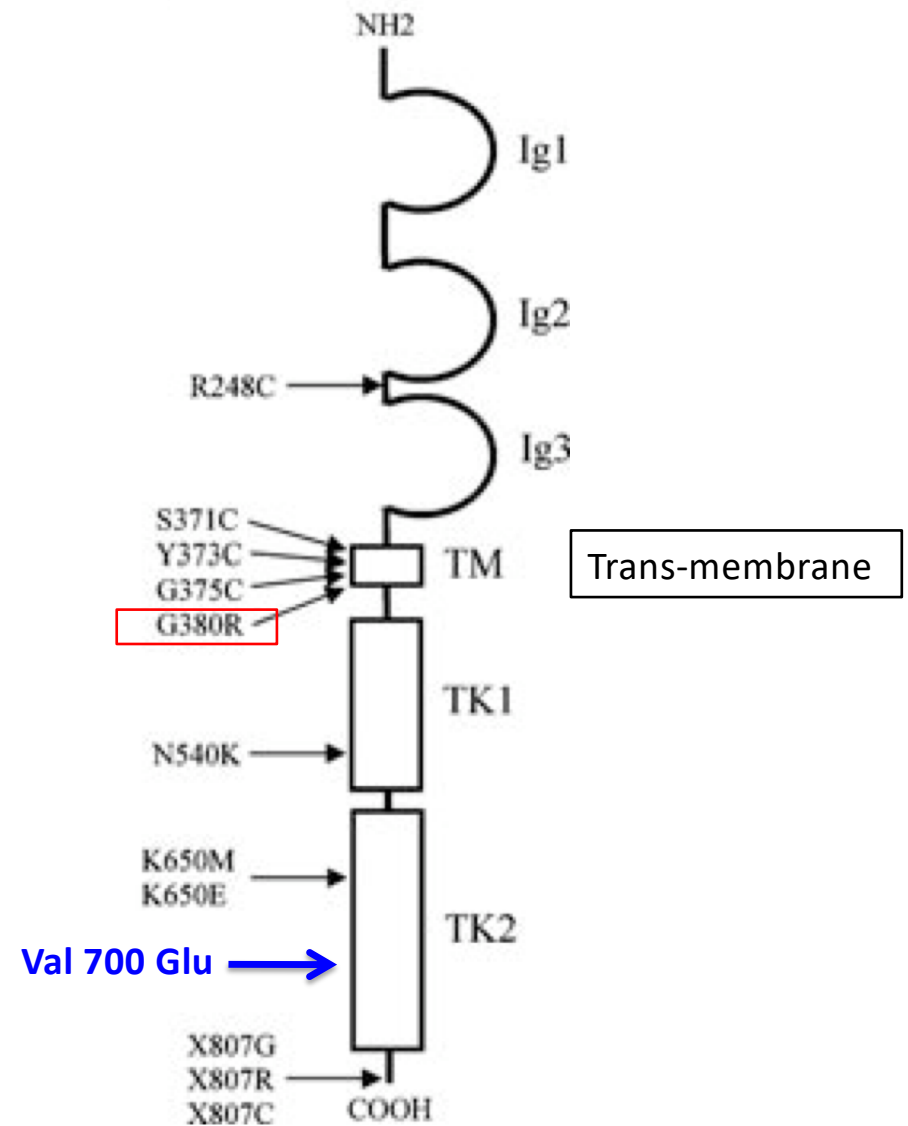


Bones are longer !

Loss-of-function in lambs:



Conformation of 2-month-old spider (left) and wild-type (right) lambs. Note the abnormally long legs and emaciation of the spider lamb.

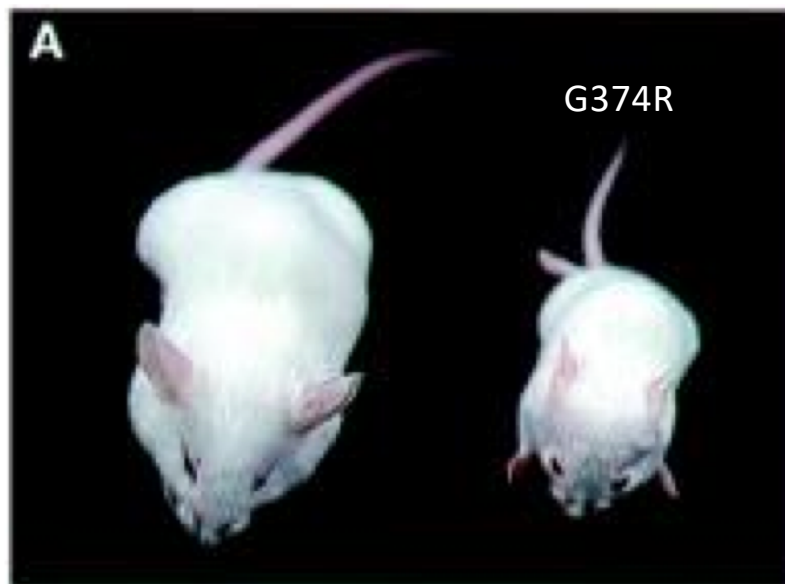


Conformation of
a 6-month-old
spider lamb.



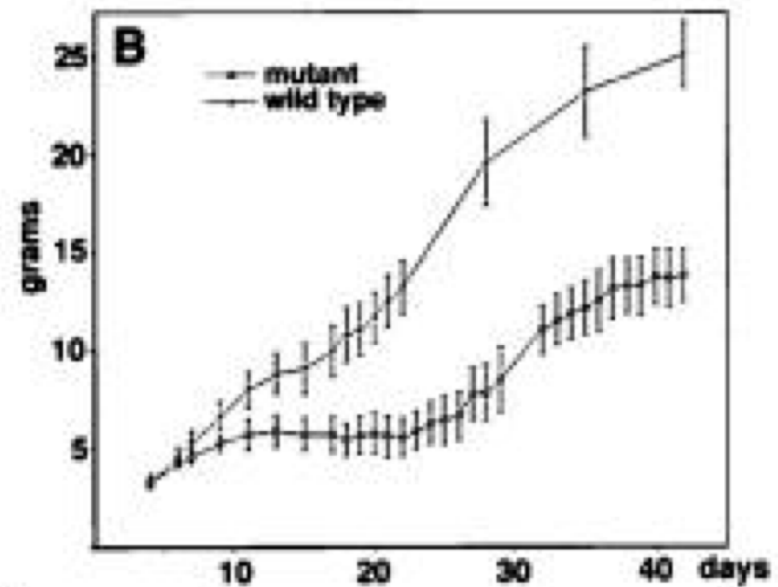
Mammalian Genome 10, 35–38 (1999).

Substitution of Glycine 374 with Arginine

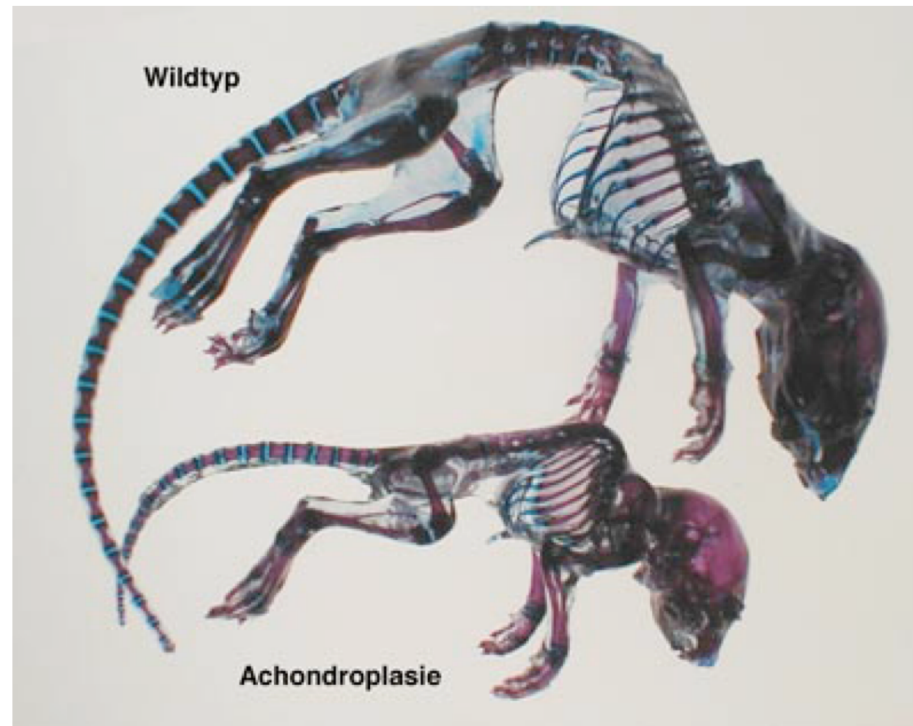


This phenotype is similar to achondroplasia

Body weight :



FGFR3 :

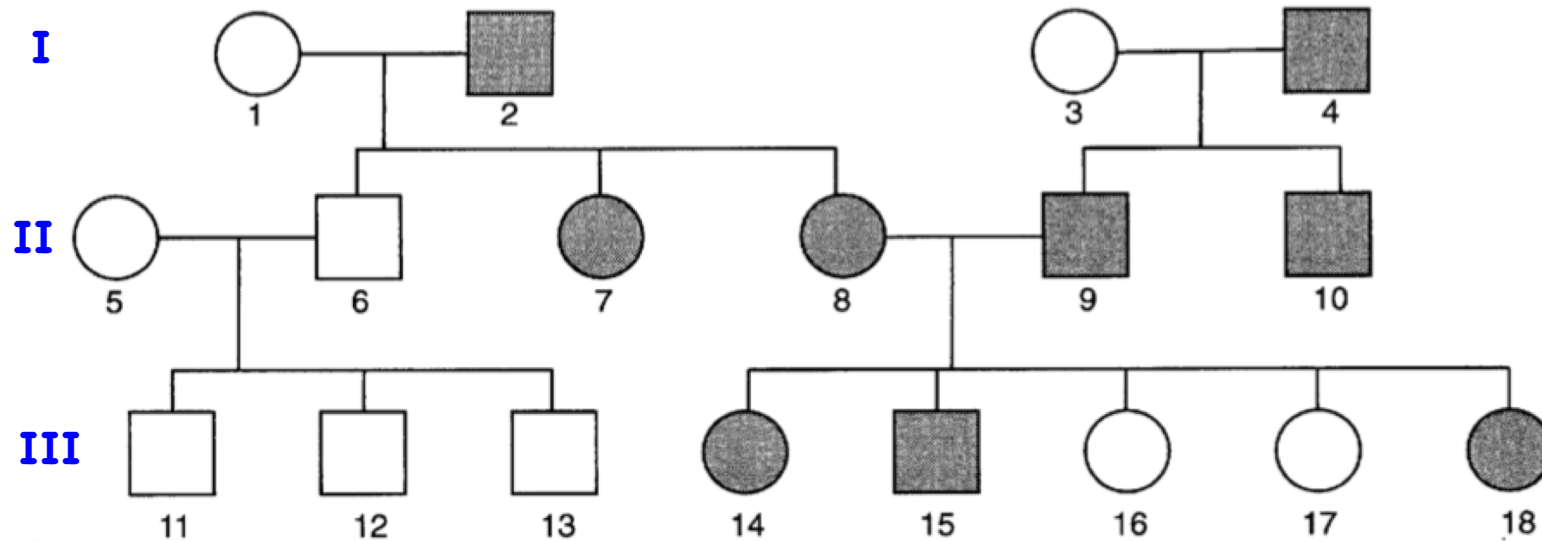
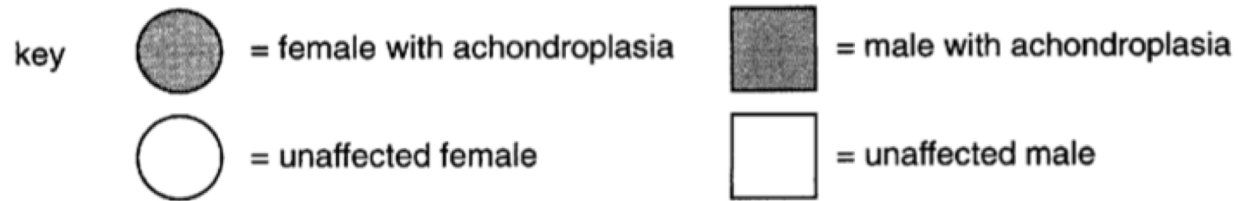


Gly / Gly

Gly / **Arg** (heterozygous)

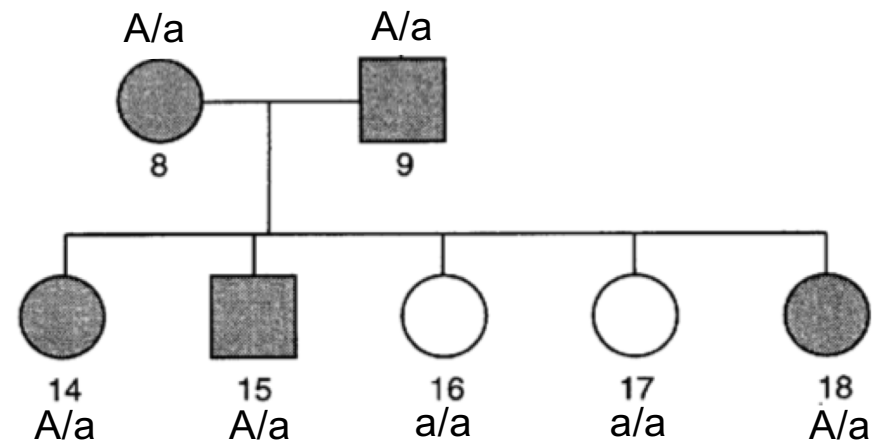
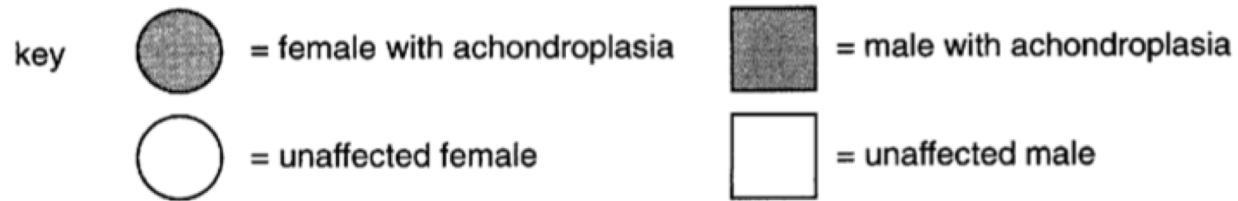
Transmission of achondroplasia:

autosomal dominant



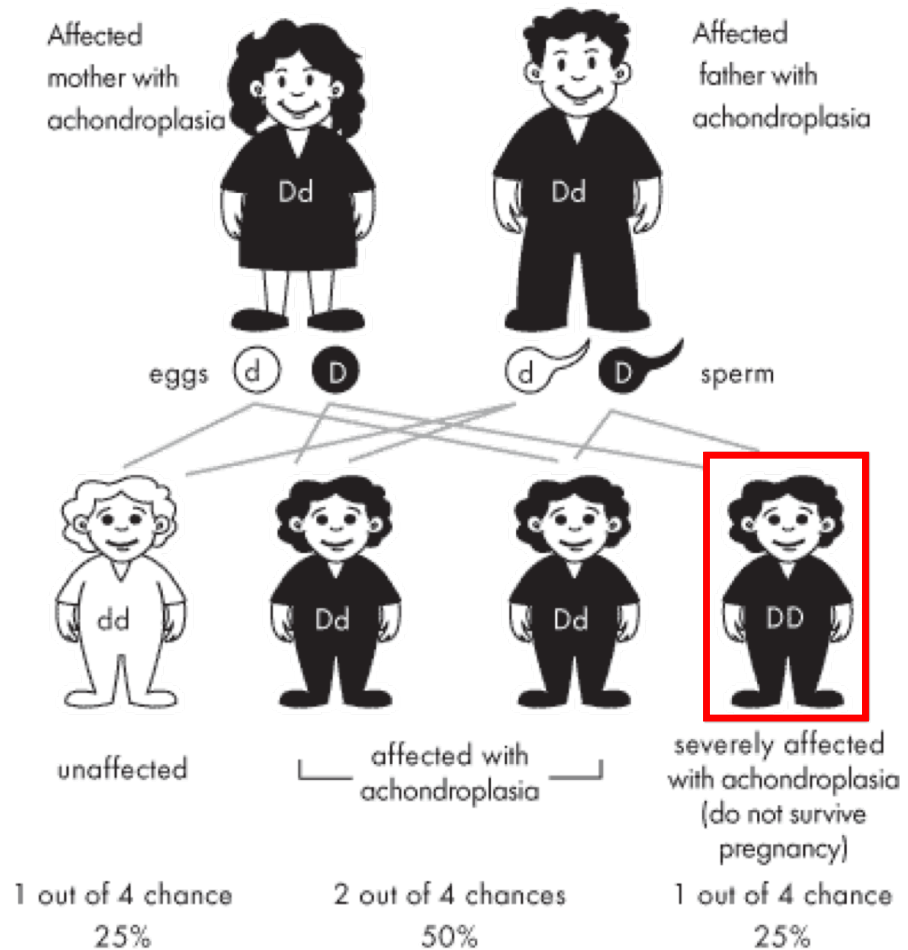
Transmission of achondroplasia:

autosomal dominant



A/A : non viable (lethal)

Achondroplasia : incomplete dominance



Transmission of achondroplasia:

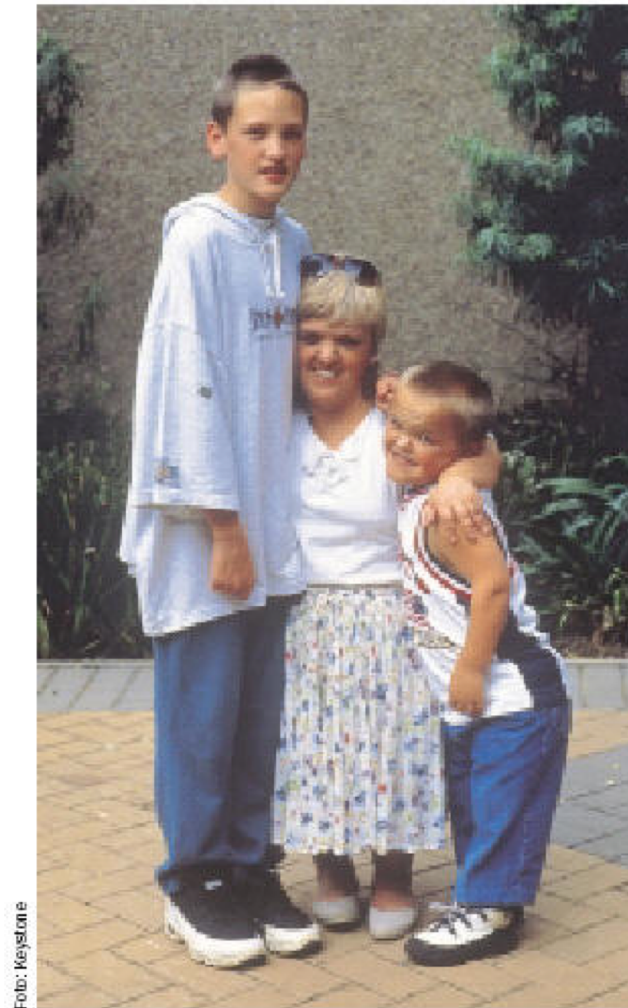
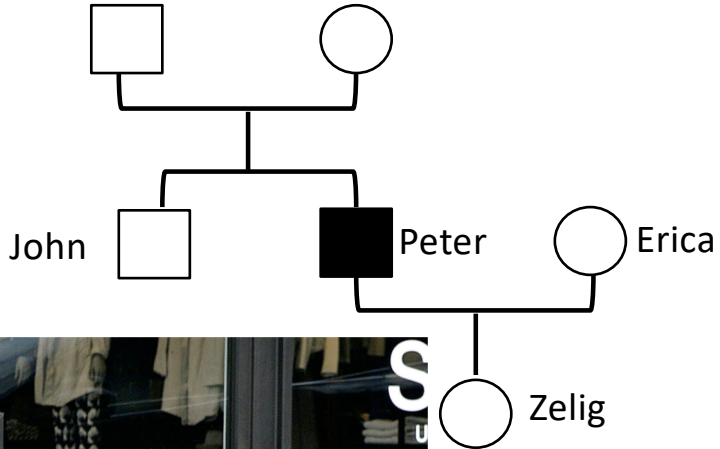


Foto: Keystone

a / a **A** / a **A** / a

A mother with her two children

Achondroplasia



Peter Dinklage has parents of average size
and an older brother of average size

90 % of achondroplasia cases are due to **de novo** mutation in the germinal line of one of the parent.