



**ACHONDROPLASIA:
INHIBITING THE FGFR3
PROTEIN USING RNAI**

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PHYSIOLOGY



Figure 1



Figure 2



Figure 3

- Most common cause of dwarfism: prevalent in 1:10000 to 1:40000.
- Achondroplasia literally means “without cartilage formation.”
- Inhibited endochondral ossification causes improper skeletal structure: cartilage cannot be converted into bone.
- Symptoms can be seen during prenatal development.
- Significantly low stature (males 131cm, females 124 cm), bowed legs, disproportionately small limbs. prominent forehead, chubby hands with separation between ring and middle fingers.
- Constant pressure throughout lifetime causes spinal stenosis and curvatures (kyphosis and lordosis).

MOLECULAR CAUSE

- Fibroblast growth factor receptor 3 (FGFR3), located in the transmembrane, controls endochondral ossification through negative mechanism after binding to fibroblast growth factors (FGF).
- Autosomal Dominant : one allele causes phenotype; two mutated genes are incompatible with life.
- 80% of cases occur through sporadic mutation.
- Mutation caused by single base substitution at nucleotide 1138 of chromosome 4p16.3: arginine substituted for glycine at amino acid 380.
- FGFR3 becomes overactive, causing inhibition of bone growth.

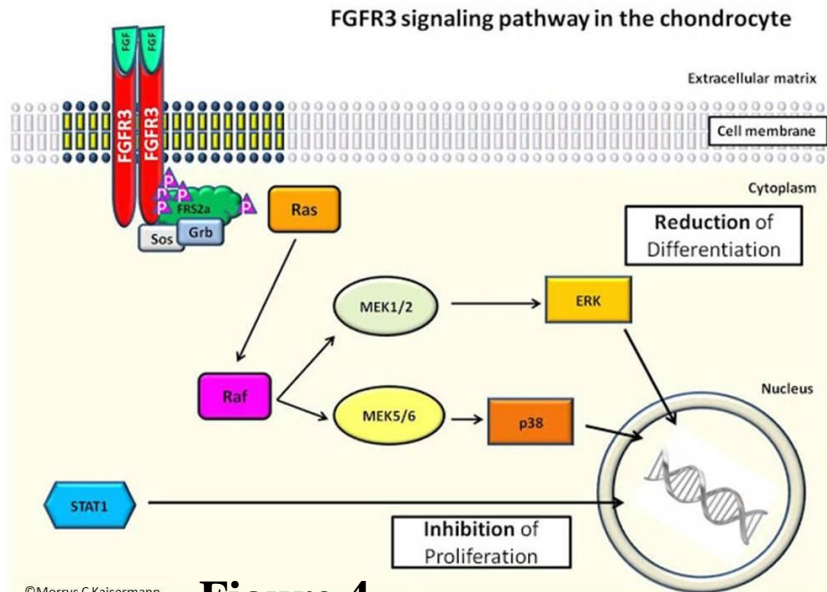


Figure 4

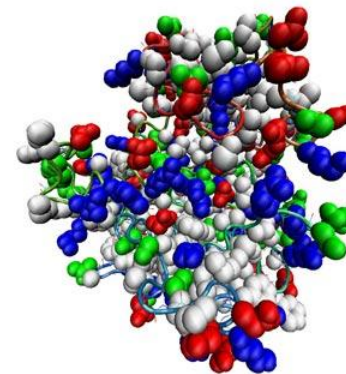


Figure 5

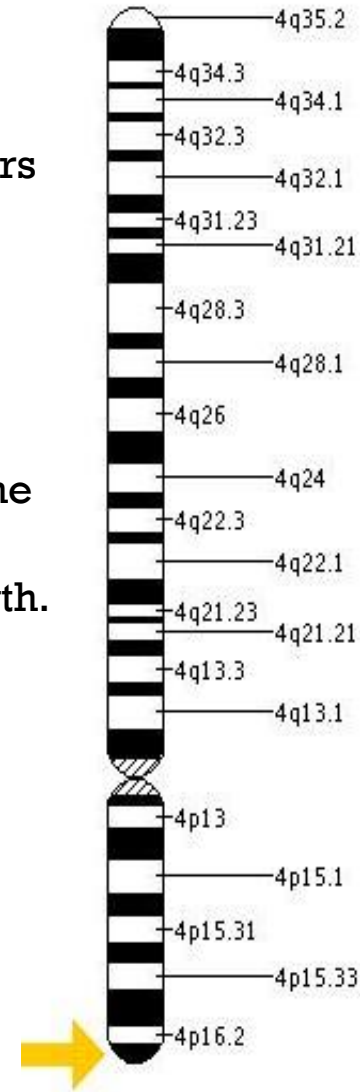


Figure 6

TREATMENTS/RISKS AND LIMITS

- Manifestation is hard to predict since over 80% of mutations are sporadic; many families are unaware of the risks.
- As of now, no permanent gene therapy exists for achondroplasia.
- Antibodies such as NF449 and A31 can temporarily inhibit mutant FGFR3 tyrosine kinase activity when injected into affected individual, allowing for bone growth to some extent.
- Surgery can be conducted to relieve symptoms of disease: spinal fusion can permanently correct kyphosis, laminectomy can decompress spinal cord from spinal stenosis, osteotomy can corrects bowed legs, and cerebral shunts can be used to treat hydrocephalus (“water on the brain”).

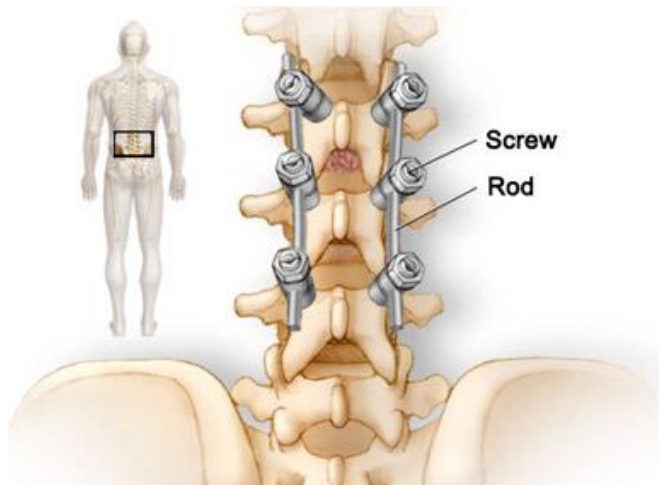


Figure 7

- The controversial method of limb-lengthening is a procedure which corrects appearance, but may lead to later complications.
- All forms of correction **MUST** be conducted by a specialist, or improper procedures can lead to permanent negative effects.
- Growth hormones are currently being developed to increase bone growth, but effects usually decline after first year.
- Only symptoms are treatable; the offspring is still at risk for achondroplasia or even death by homozygous mutant genes.

PROPOSED CURE/LIMITS

- **RNA interference (RNAi)** is a biological process involving the inhibition of foreign RNA expression using the RNA-induced silencing complex (RISC).
- RNAi is the cell's defense against viruses and foreign genes: incorporating single interfering RNA into the RISC allows the cell to develop immunity.
- Proposal: Harvest lentiviruses containing dsRNA complementary to the mutant FGFR3 RNA, and inject the virus into the body cell through plasmids.
- When foreign FGFR3 gene sequences complementary to the single strand RNAs are detected, RNAi allows eradication of the gene.
- It is still unclear how exactly the virus can be injected into the cell.
- Proposal might cure the individual, but mutation may still remain in germ line.

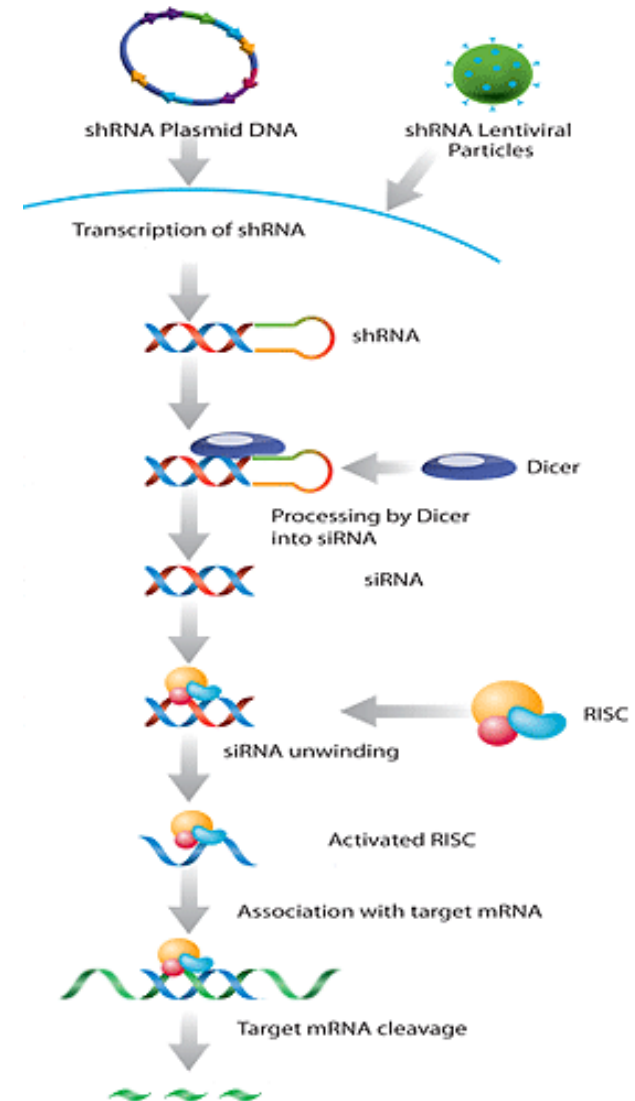


Figure 8

REFERENCES

PHYSIOLOGY

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<http://www.therichest.org/celebnetworth/celeb/actors/peter-dinklage-net-worth/> (Figure 3)

<http://health.nytimes.com/health/guides/disease/achondroplasia/overview.html>

MOLECULAR CAUSE

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TREATMENTS/RISKS AND LIMITS

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<http://www.mayoclinic.org/spinal-fusion/enlargeimage5540.html> (Figure 7)

PROPOSED CURE/LIMITS

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http://www.scbt.com/gene_silencers.html (Figure 8)