Achondroplasia: The Effects of a Point Mutation on Nucleotide 1138

This is Jyoti Amge who is currently the World's smallest woman. At approximately 2 feet and 1 inch tall, she suffers from an extreme case of Achondroplasia.

Physiology

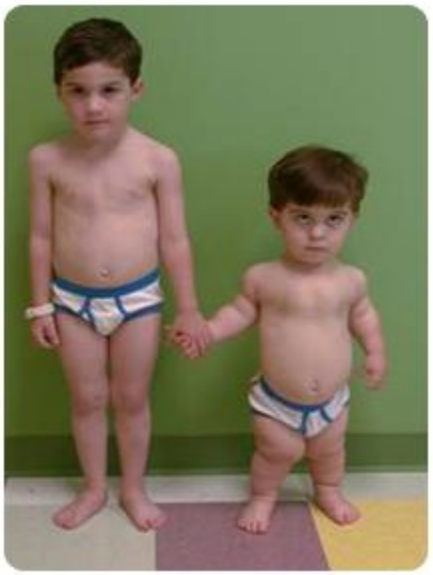


Figure 1

- Achondroplasia is the most common cause of dwarfism
- An autosomal dominant, bone growth disorder found in 1 in every 15 to 40 thousand people
- Can be inherited but in 80%+ of cases, they are spontaneous.
- The disease name literally means without cartilage formation.

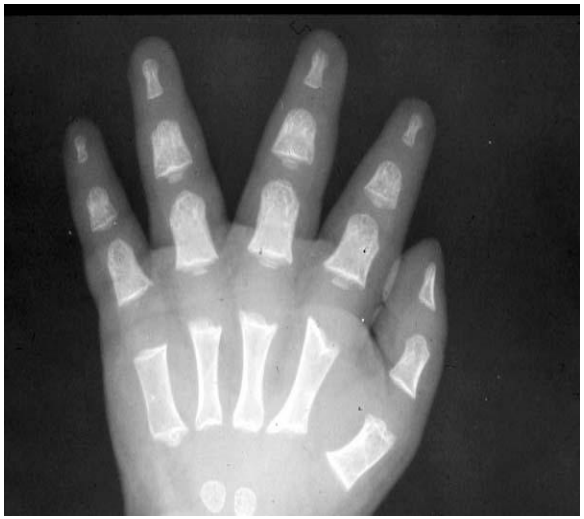


Figure 2

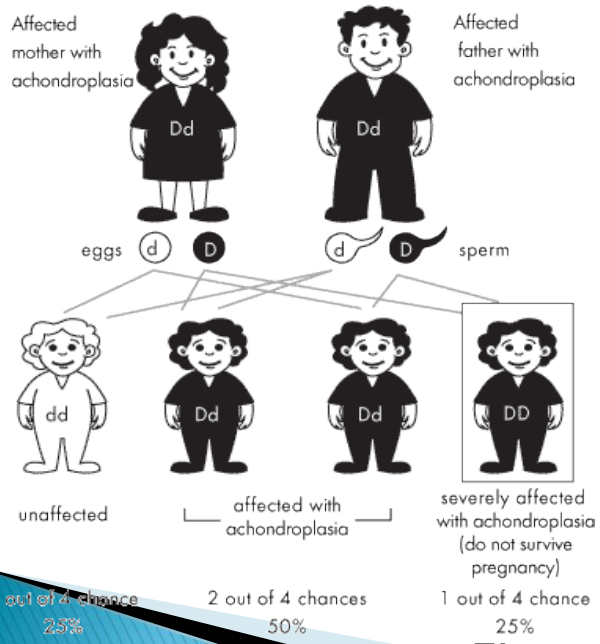


Figure 3

Symptoms include:

- •Shortened limbs
- •Disproportional body sizes (see figure 1:above left), including macrocephaly
- •Divergence between middle and ring finger (see figure 2:above)
- •Hydrocephalus (excess fluid in skull)
- •Hypotonia- low muscle tone (causes delays in motor skills, learning how to walk, and learning to sit, walk, and even standing up!)
- •Spinal problems
  - -Spinal stenosis (narrowing and compression of the spinal cord)
  - -Spine curvatures

Figure 4

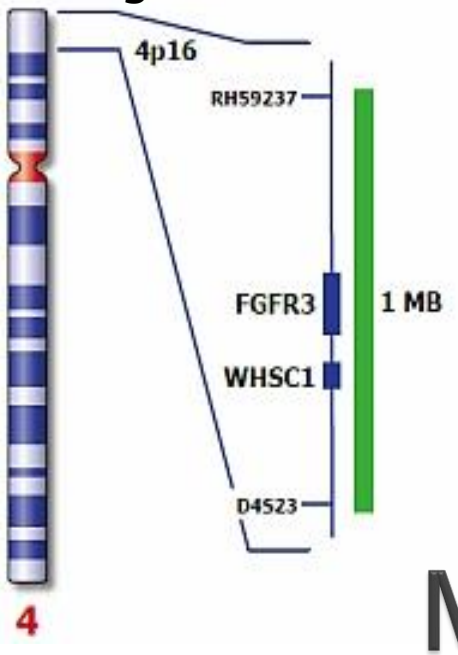


Figure 5

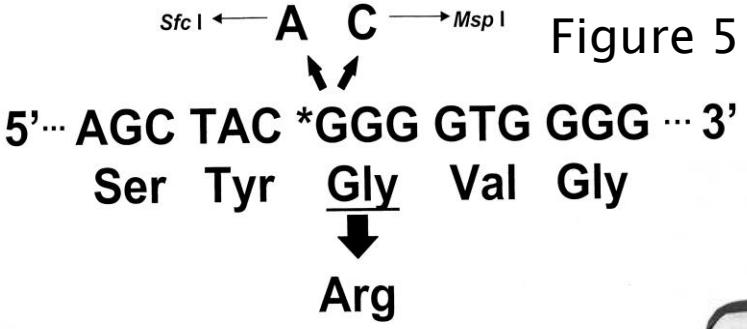
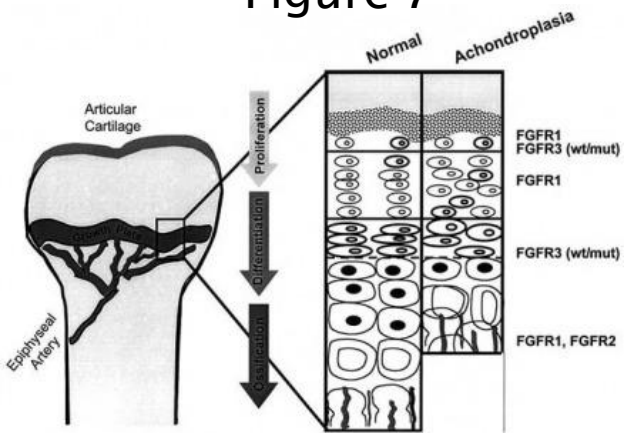


Figure 6

Figure 7



Molecular Cause

- The FGFR3 gene, fibroblast growth factor receptor, is responsible for the receiving and processing of growth hormones.
- This disorder is caused by a point mutation at location 16.3 on chromosome 4.
- In 98% of cases, there is a G to A mutation on nucleotide 1138, in 1% of cases there is a G to C mutation on the same nucleotide.
- The FGFR3 gene becomes overactive and is not able to take in growth hormones properly.
- It only takes one bad gene to manifest the disorder because it is autosomal dominant.

Treatments/Risks and Limits

- Currently, there is no cure.
- Because this disease is so random, over 80% of cases are unpredicted, there is no prevention drugs or treatments with the exception of the affected parents not reproducing.
- Some treatments include therapy, growth hormones, as well as correction procedures/surgeries.
- Therapy is used to monitor the affected patient's growth; height, weight, as well as circumference. [Those affected tend to put on extra weight in their younger years.]
- Growth hormones are only known to be useful in the first two years. Hormones are injected into the patient and it helps with growing for a while before it completely becomes useless.
- Correction surgeries as well as procedures are used to lengthen short limbs, drain fluid from ears, and help with back and spinal problems.
- These treatments are very limiting because they are either only temporary or do not help treat this disease genetically. They are not there to fix the problem but rather help it.
- In addition to that, not everyone is able to afford surgeries to help them lengthen their legs/arms or enlarge their foramen magnum.

Proposed Cure/Limits

- There has been studies with FGFR3 RNAi which stands for RNA interference, which is also known as PTGS, posttranscriptional gene silencing.
- FGFR3 RNAi can be found online and is sold for $379 per 20 nmol in the U.S. It is only being sold for scientific research purposes! It cannot be distributed to the public and is not given away easily.
- RNAi is used all the time by scientists but not necessarily for the purpose of gene therapy.
- The proposal here is to inject FGFR3 RNAi into the affected patient.
  - In order to do this, a culture of the person's cells needs to be grown first.
  - Then, the RNAi may be added to this culture.
  - After observations and making sure there is no problems with the RNAi and the culture, a double-stranded RNA complementary to the person should be made.
  - Lastly, this would then be introduced into the organism's body.
- A few problems. . .
  - When should all of this be done? When the patient is born? Grown-up? Still-growing?
  - How should this be introduced in the body?
  - If this were injected while the body was growing, in what ways would this affect the bones or cartilage that have are already fully grown?
  - If the gene were silenced, should properly working FGFR3 genes be injected as well?

References

- "Achondroplasia - Genetics Home Reference." *Genetics Home Reference - Your guide to understanding genetic conditions*. N.p., n.d. Web. 20 Mar. 2013. <http://ghr.nlm.nih.gov/condition/Achondroplasia>.
- "Achondroplasia: MedlinePlus Medical Encyclopedia." *National Library of Medicine - National Institutes of Health*. N.p., n.d. Web. 20 Mar. 2013. <http://www.nlm.nih.gov/medlineplus/ency/article/001577.htm>.
- "AchondroplasiaÂ |Â BabyÂ |Â Birth defectsÂ |Â March of Dimes." *Pregnancy, Baby, Prematurity, Birth DefectsÂ |Â March of Dimes*. N.p., n.d. Web. 20 Mar. 2013. <http://www.marchofdimes.com/baby/birthdefects_Achondroplasia.html>.
- Application. "FGFR3 RNAi | Novus Biologicals." *Novus Biologicals | Antibodies, Antibody, Antibody Suppliers, Antibody Database, Antibody Catalog*. N.p., n.d. Web. 16 May 2013. <http://www.novusbio.com/rnai/fgfr3>.
- "Learning About Achondroplasia." *National Human Genome Research Institute (NHGRI) - Homepage*. N.p., n.d. Web. 20 Mar. 2013. <http://www.genome.gov/19517823>.
- Stappler, Melissa C. . "Achondroplasia." *Medicinenet.com*. N.p., n.d. Web. 20 Mar. 2013. <www.medicinenet.com/Achondroplasia/article.htm>.