Dwarfism

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Dwarfism

Misconceptions?

Curious about actual “little people”

http://www.google.com/imghp?hl=en&tab=wi
Achondroplasia

- Achondroplasia literally means “without cartilage formation.”
- More likely to be passed down paternally
  - Likelihood increases if father is over 35
  - Spermatogenesis vs oogenesis
- Disorder occurs in about 1 out of in 25,000.
- Individuals can form cartilage, but not bone.
Disease Characteristics

• Physical characteristics:
  • Average male height is 52 inches; average female height is 49
  • Average-size trunk, short upper arms (rhizomelic) and thighs
  • Limited range of motion at the elbows
  • Enlarged head (macrocephaly) with prominent forehead
  • Short fingers with trident appearance
  • Normal intelligence

• Possible health problems:
  • Breathing slows or stops for short periods (apnea)
  • Pronounced and permanent sway of the lower back (lordosis)
  • Recurrent ear infections
  • Spinal stenosis
  • Bowed legs
  • Obesity
Genetic Background

- **Achondroplasia** is an autosomal dominant disorder
  - Homozygous dominant genotype is fatal.
- **Mutated gene:** FGFR3
  - A fibroblast growth factor receptor (FGFR) gene
  - Regulates the formation of bone from cartilage (ossification).
- **A single amino acid change**
  - Glycine to arginine (or cytocine) switch in FGFR3 causes over 99% of achondroplasia cases.
- In cases of achondroplasia, the FGFR3 gene is too aggressive, negatively impacting bone growth.
The FGFR3 Gene

- Located at 4p16.2
  - Tip of the short arm
- 19 exons spanning 16.5 kb
  - Base pairs 1,795,038 to 1,810,598
- Base pairs are highly conserved in evolution as well as in the FGFR gene family

Member of the fibroblast growth factor receptor family that regulates:

- Cell division and type determination
- Blood vessel formation
- Wound healing
- Embryo development

Interacts with growth factors outside the cell and triggers an inner cascade, which results in certain changes, such as cell differentiation.
**FGFR3 Protein**

- FGFRs have three regions:
  - ligand binding domain
  - a transmembrane region
  - a cytoplasmic region containing a protein tyrosine kinase core
- Extracellular binding domain is composed of three immunoglobulin-like domains (D1, D2, D3)

http://www.google.com/imghp?hl=en&tab=wi
(a) Normal FGFR: FGF binds; FGFRs form a dimer
Structure and function of fibroblast growth factor receptors (FGFRs)

Expert Reviews in Molecular Medicine ©2003 Cambridge University Press
Summary of Achondroplasia

Genetic causes:

http://www.youtube.com/watch?v=Bn7eGRsYYGI

- Overactive regulation of ossification because base #1138 is switched from glycine to an arginine or cytosine
- FGFR3 inhibits bone formation despite the absence of usual growth factor ligands
Other Effects of Faulty FGFR Proteins

- **FGFR3**
  - Platyspondylic lethal skeletal dysplasia
  - Camptodactyly, Tall Stature, Scoliosis, and Hearing Loss Syndrome
  - Cervical or bladder cancer
- **FGFR1, FGFR2, FGF8**
  - Cleft lip or palate
- **FGFR10**
  - Lacrimoauriculodentodigital (LADD) Syndrome
  - Deformation in tear and salivary ducts, teeth, ears
Social Stigmatization

- Media portrayal of dwarves
- Impede daily activities
- Painful walking, back problems
- Children with dwarfism feel isolated
- Heightism
  - Reduced martial and employment opportunities
  - Severe shortness = lower income
  - When, if ever, should companies discriminate based on height?
- “Little person”, “LP”, “dwarf”
- *Our Little Life:*

Role of Genomics

- Identify the mechanism for FGF and receptors
- Pituitary dwarfism (i.e. growth hormone deficiency) is treatable with injections
- No drug available for achondroplasia
  - Physical therapy
  - Braces
  - Distraction osteogenesis
  - Aesthetic enhancements
- Better understand Dwarfism, both from a genetic and social standpoint
Citations

- JBC: http://www.jbc.org/content/early/2011/02/15/jbc.M110.205583.long
- NCBI: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2099236/
The End

Questions?
Big Enough?

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Krawitz and Ott
Little People 1981
PBS Emmy Award

Krawitz
Big Enough 2004