

Dwarfism

Justin Lee

Professor Doug Brutlag

Biochem 118Q, Winter 2011

Outline

- Dwarfism
- Achondroplasia
- FGFR gene and protein
- Role of genomics
- Social stigmatization
- Conclusion



<http://modernmedicalguide.com/achondroplasia/>

Dwarfism

Misconceptions?



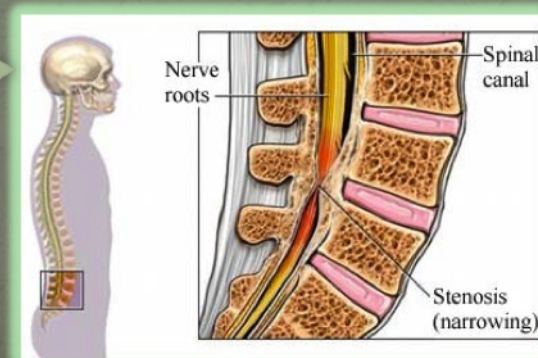
Curious about actual
“little people”

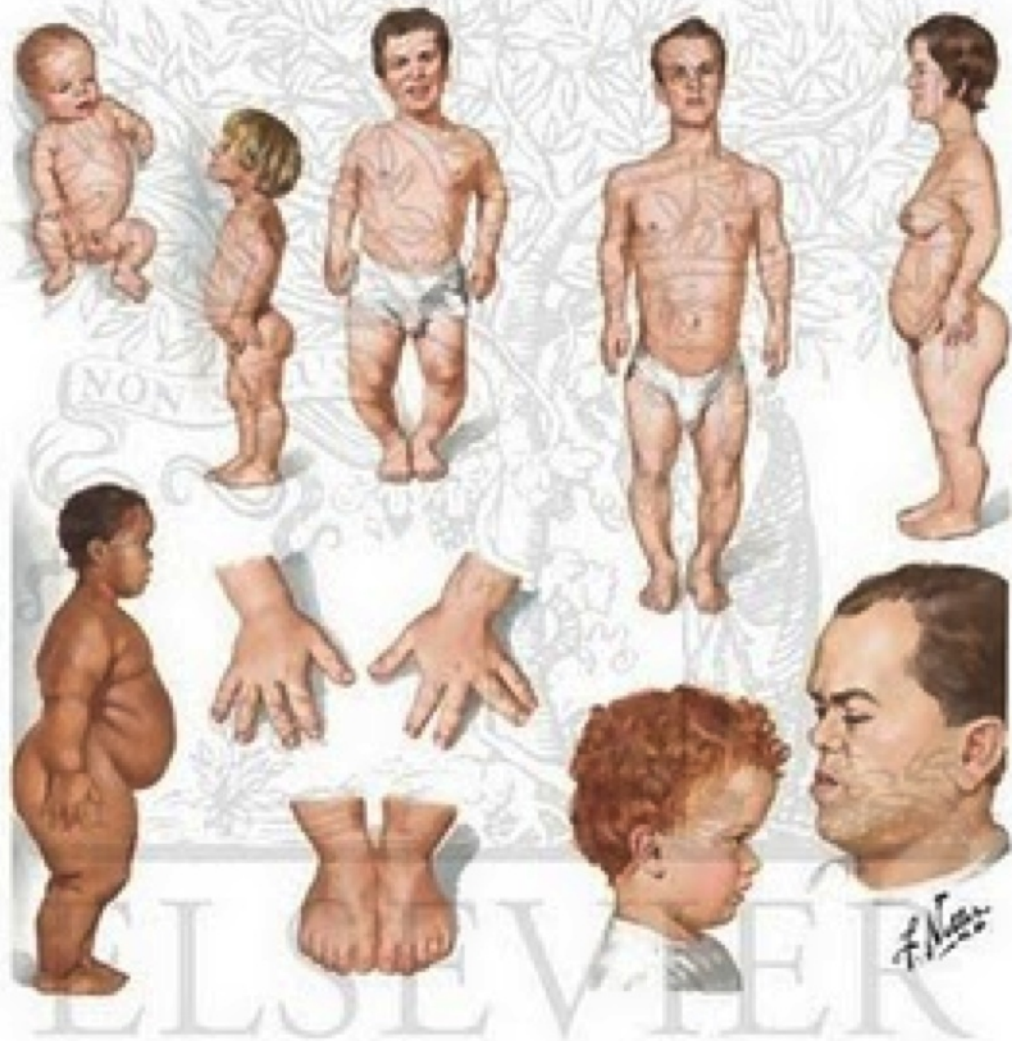
Achondroplasia

- 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





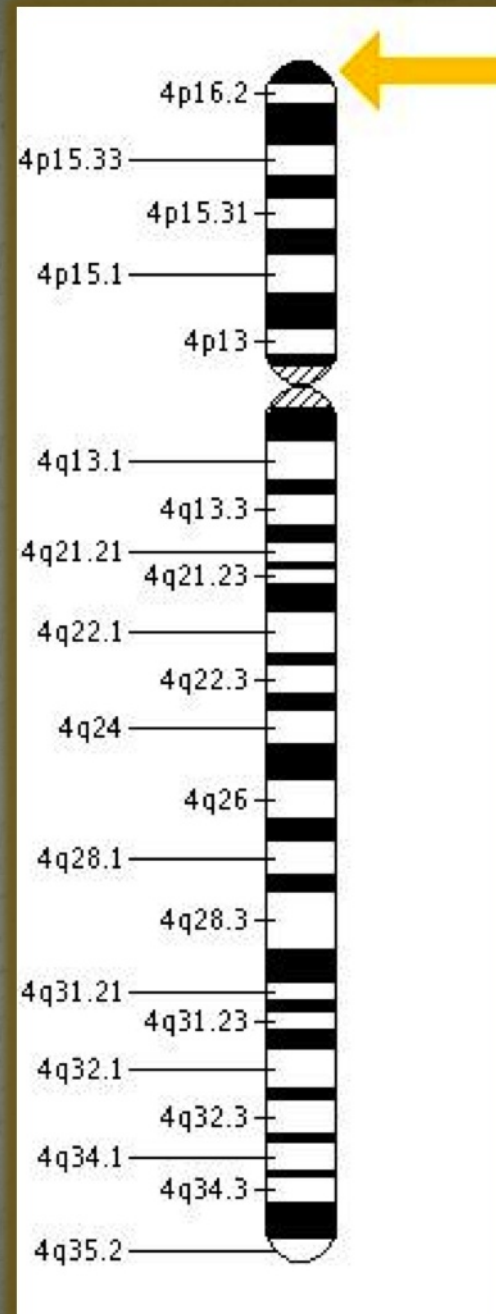
© ELSEVIER, INC. - NETTERIMAGES.COM

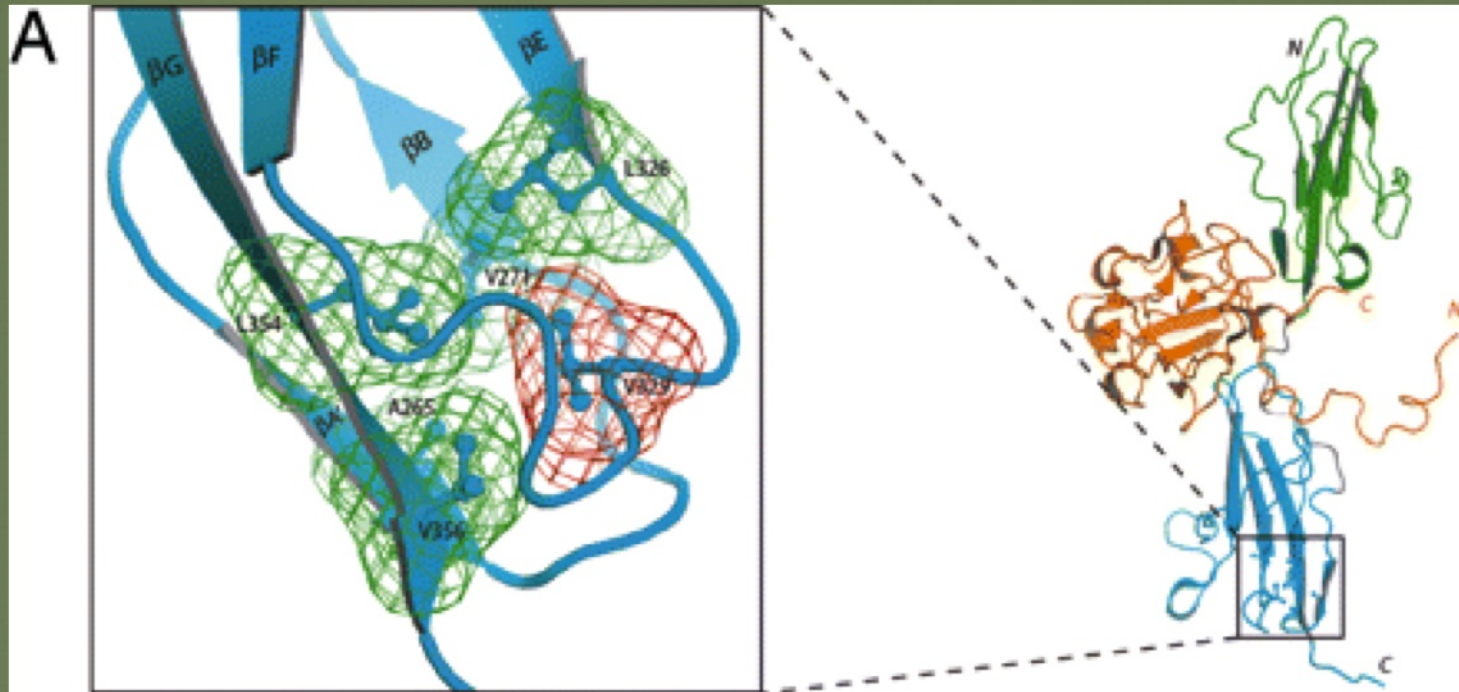
Genetic Background

- 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 cytosine) 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





B

V329I



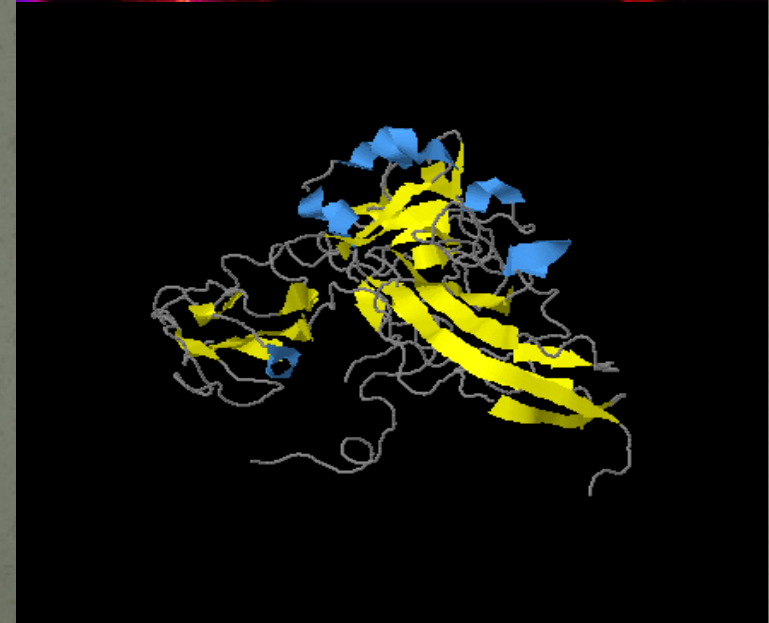
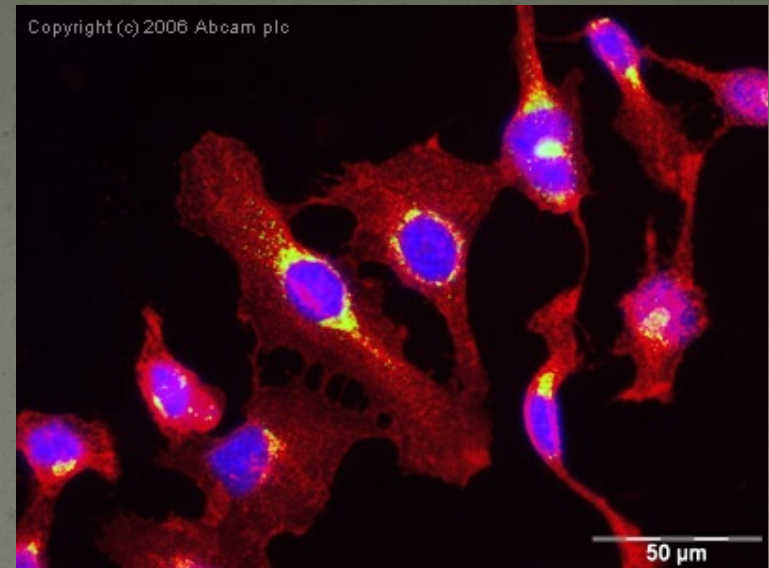
Human FGFR3	EVLSLHN V T F EDAGEYTCLAGNS
Chimp FGFR3	EVLSLHN V T F EDAGEYTCLAGNS
Dog FGFR3	EVLSLRN V T F EDAGEYTCLAGNS
Mouse FGFR3	EVLSLHN V T F EDAGEYTCLAGNS
Rat FGFR3	EVLSLHN V T F EDAGEYTCLAGNS
Chicken FGFR3	EILYLRN V T F EDAGEYTCLAGNS
Zebrafish FGFR3	EILYLTN V S F EDAGQYTCLAGNS
Human FGFR1	EVLHLRN V S F EDAGEYTCLAGNS
Human FGFR2	EVLYIRN V T F EDAGEYTCLAGNS
Human FGFR4	EVLYLRN V S A EDAGEYTCLAGNS

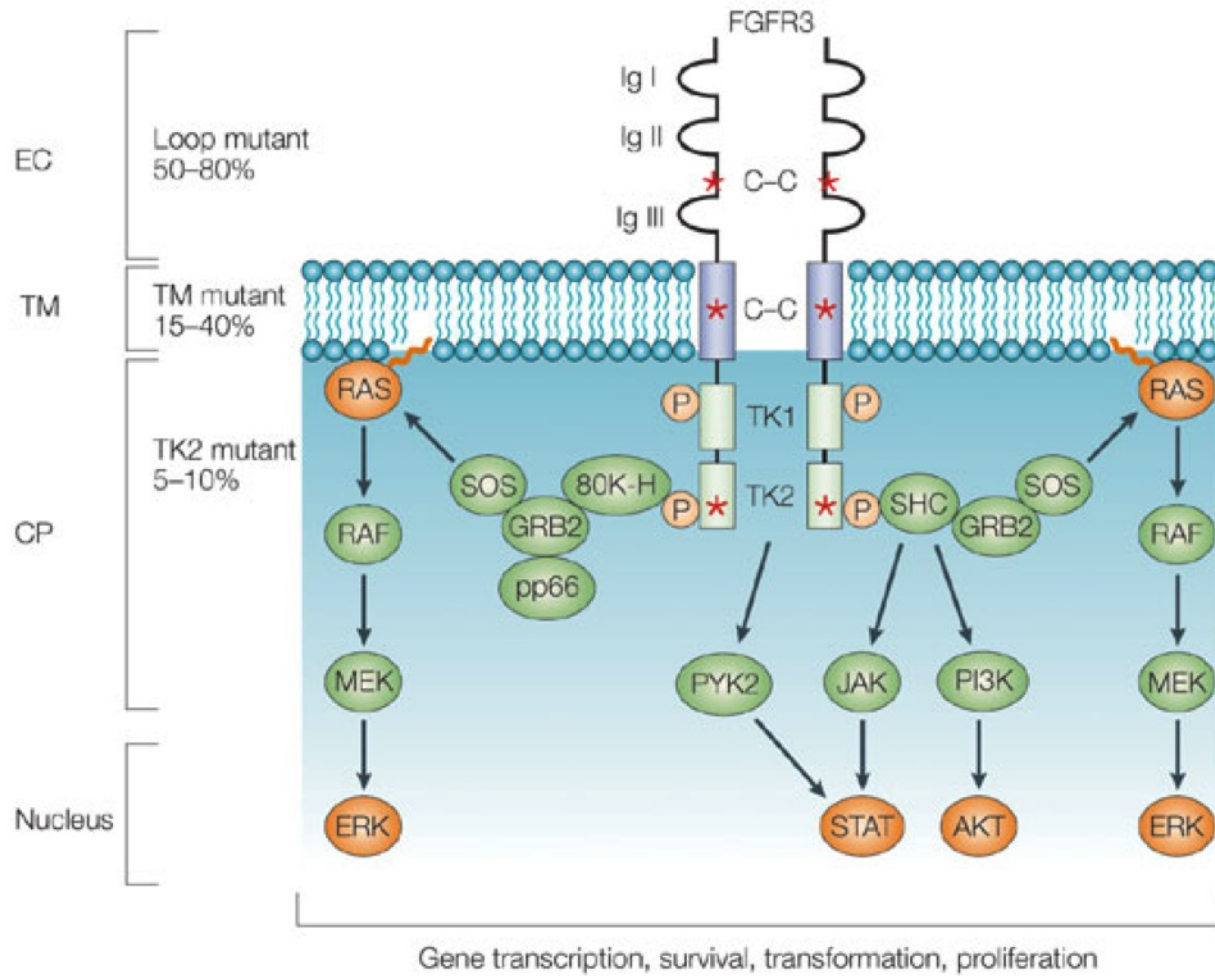
The FGFR₃ Protein

- 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.

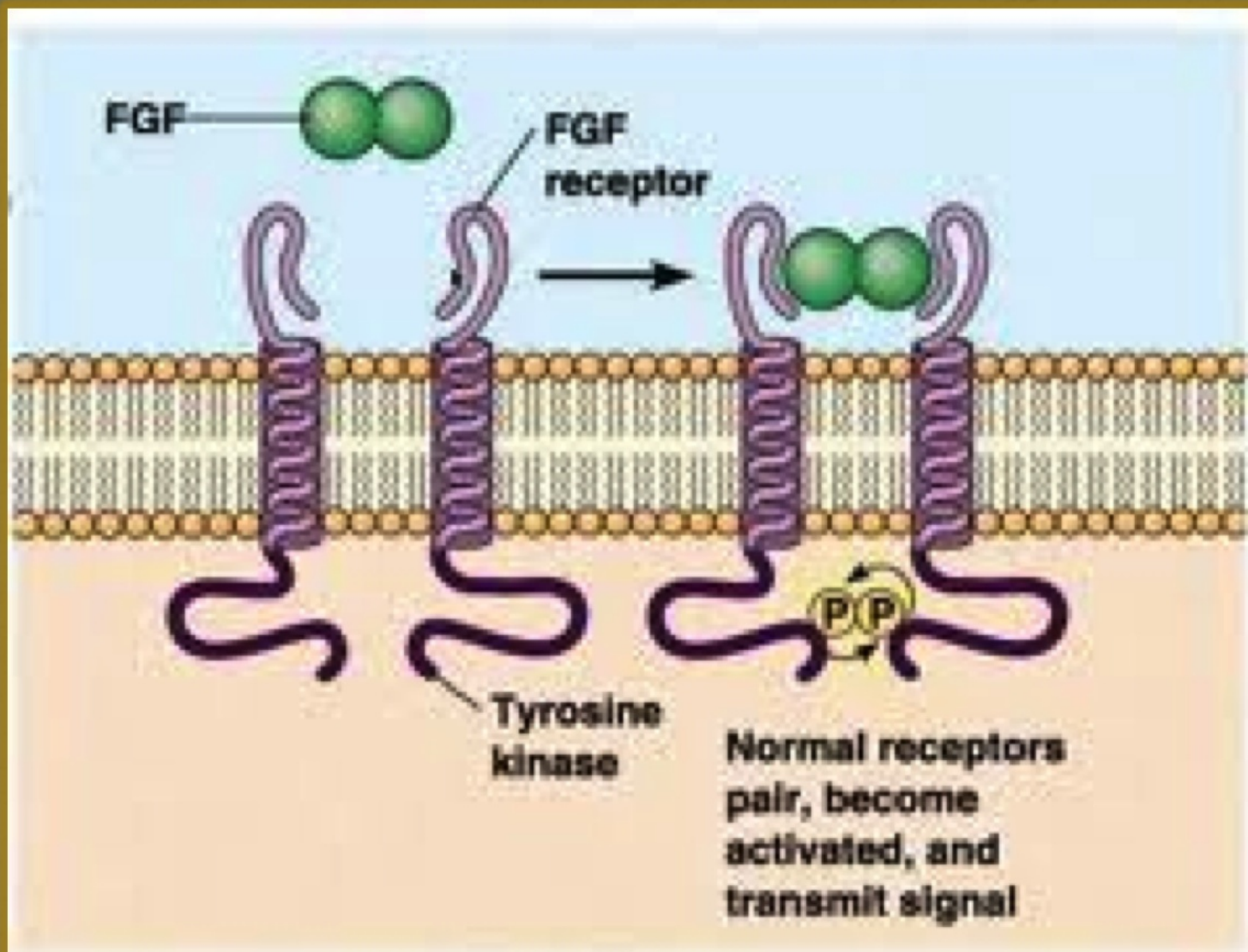
FGFR₃ Protein

- 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)

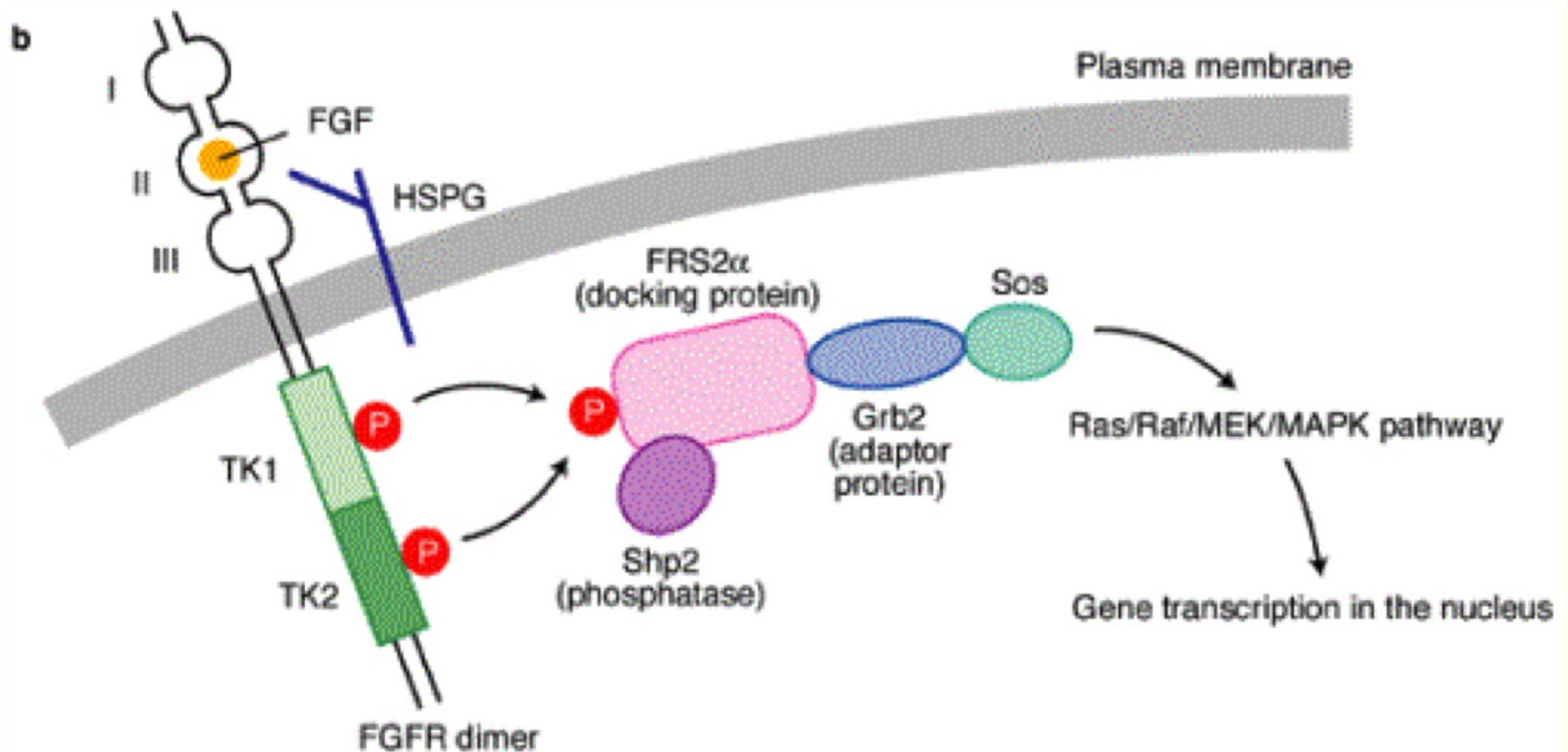




Copyright © 2005 Nature Publishing Group
Nature Reviews | Cancer



(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 marital and employment opportunities
 - Severe shortness = lower income
 - When, if ever, should companies discriminate based on height?
- “Little person”, “LP”, “dwarf”
- *Our Little Life*:
<http://tlc.discovery.com/videos/our-little-life-video/>



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



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

Citations

- JBC:
<http://www.jbc.org/content/early/2011/02/15/jbc.M110.2055>
- NCBI: <http://www.ncbi.nlm.nih.gov/omim/134934>
- NCBI:
<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2099236/>
- NIH: <http://ghr.nlm.nih.gov/gene/FGFR3>
- TLC:
<http://tlc.discovery.com/videos/our-little-life-video/>

The End

Questions?

Big Enough?

Jan Krawtitz
Professor of Art and Art History
krawitz@stanford.edu

Krawitz and Ott
Little People 1981
PBS Emmy Award

Krawitz
Big Enough 2004



FANLIGHT PRODUCTIONS

1.800.937.4113 • info@fanlight.com

FANLIGHT PRODUCTIONS is a leading distributor of innovative film and video works on the social issues of our time, with a special focus on healthcare, mental health, professional ethics, aging, disabilities, the workplace, and gender and family issues.

BIG ENOUGH

By Jan Krawitz. Meet Mark and Anu, Karla and John, Len and Lenette, and Sharon and Ron: four couples leading typical American lives, pursuing typical middle-class careers, and living in the suburbs with their children. Yet they have grown up facing challenges that are anything but typical. All but one of them are dwarfs, though they prefer to call themselves "little people." Jan Krawitz and Thomas Ott's 1981 film, *Little People*, chronicled the birth of a new consciousness among dwarfs as they struggled toward equal opportunity and enhanced self-esteem. Broadcast nationally by PBS, the film was nominated for an Emmy and won numerous other festival awards. In 2000, Krawitz set out to revisit many of the people she had profiled in *Little People*, to find out how the past twenty years had treated their hopes, expectations and fears.

Color, Closed-Captioned, 53 Minutes, Documentary / Educational
ISBN 1-57295-804-9, Catalog No. DVD-424 © 2004, Jan Krawitz