Treatment landscape and unmet need in Achondroplasia

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Disclosures

Dr Irving has received honoraria for consultancy, scientific advisory board and speaker services from:

- QED/Bridge Bio
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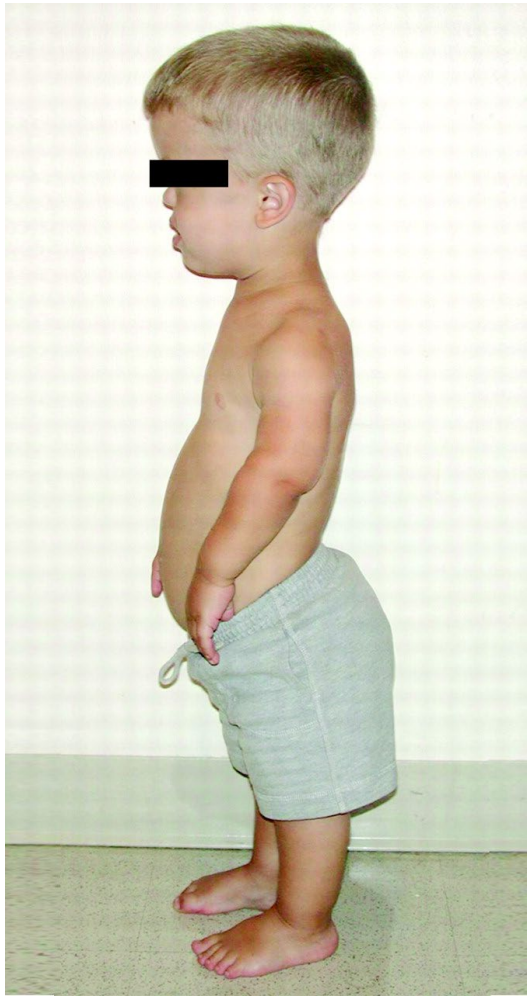
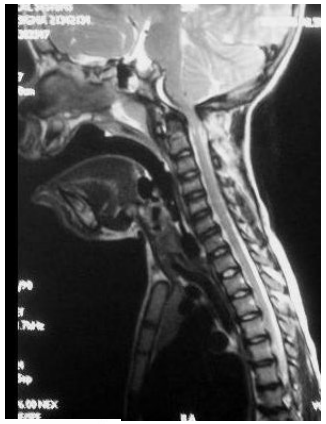
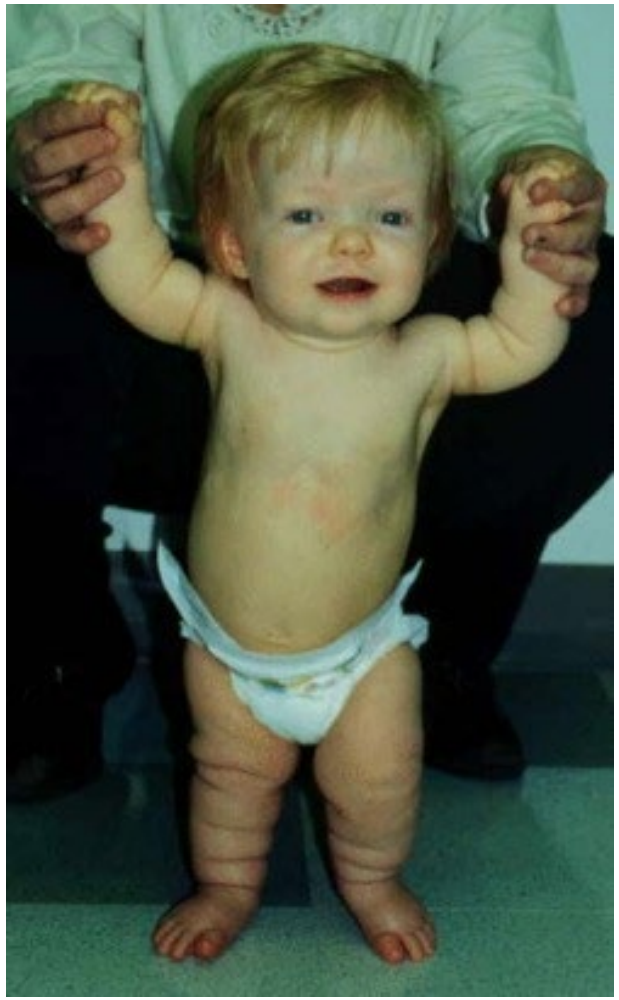
- Ascendis Pharma
- Sanofi
- Innoskel
- Ipsen
- Alexion
- Kyowa Kirin
- NovoNordisk

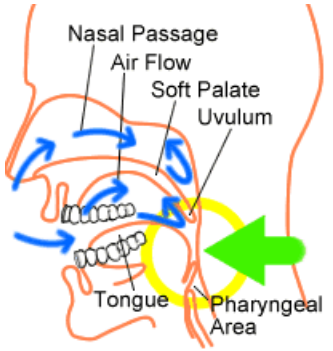
Achondroplasia is the most common cause of disproportionate short stature

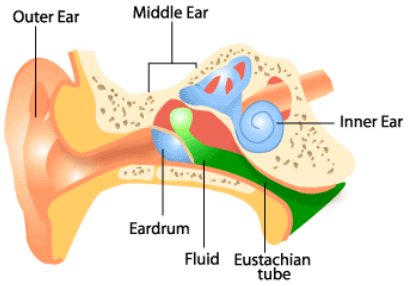


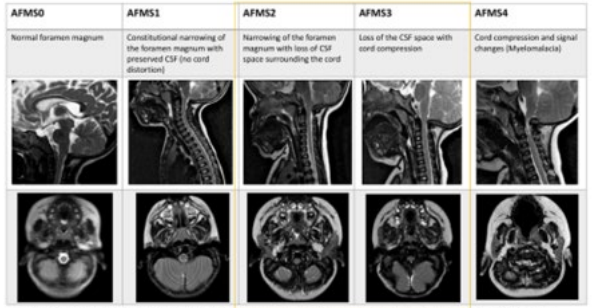
Multisystem complications as a consequence of the secondary abnormal bone formation







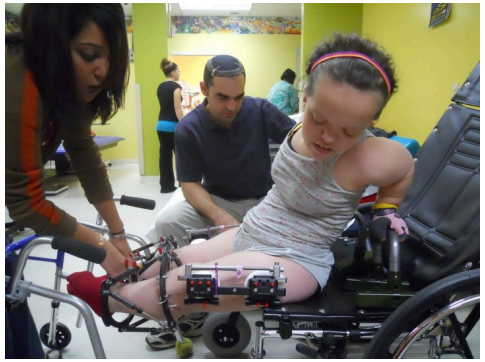


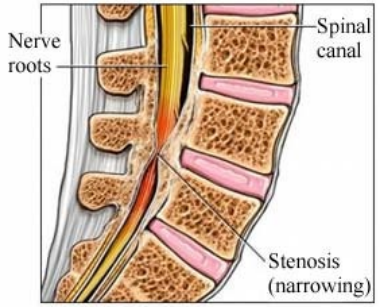


Ref: Cheung MS, Irving M, Cocca A, *et al* Achondroplasia Foramen Magnum Score: screening infants for stenosis *Archives of Disease in Childhood* Published Online First: 03 September 2020. doi: 10.1136/archdischild-2020-319625

The baby's lower spine is curved. This is more noticeable when the baby is sitting in an upright position.

When the baby lies down the curve flattens out. The is a much better position for babies with achondroplasia.





MH data from PROPEL highlight the significant complications experienced during infancy and childhood

Surgical and medical procedures occurring in≥1 subject

- A total of 58 children (67.4%) had undergone surgical or medical procedures, with a mean of 2.9 procedures per individual (1–11 interventions per child)

- The most common types of surgery/procedure were:
  - Adenoidectomy, adenotonsillectomy, and tonsillectomy: 34 children; 53 procedures; 1–4 surgeries per child
  - Ear-related procedures: 32 children; 58 procedures; 1–5 procedures per child
  - Spinal or cranial decompression: 21 children; 28 procedures; 1–5 surgeries per child

Term	No. of subjects (%)*
Adenoidectomy/adenotonsillectomy/tonsillectomy	34 (39.5)
Spinal and cranial surgeries	21 (24.4)
Decompressive craniectomy	14 (16.3)
Spinal decompression	5 (5.8)
Spinal laminectomy	3 (3.5)
Foraminotomy	1 (1.2)
Spinal fusion surgery	1 (1.2)
Spinal operation	1 (1.2)
Ear procedures and operations	32 (37.2)
Ear tube insertion	32 (37.2)
Myringotomy	3 (3.5)
Middle ear operation	1 (1.2)
Ear tube removal	1 (1.2)
Orthopedic procedures	6 (7.0)
Device therapy	3 (3.5)
Meniscus operation	1 (1.2)
Orthopedic procedure	1 (1.2)
Osteotomy	1 (1.2)
Rhizolysis	1 (1.2)
Ventriculo-peritoneal shunt	2 (2.3)
Mechanical ventilation	2 (2.3)
Palatal implant	2 (2.3)
Turbinectomy	2 (2.3)

*Subjects are counted once if they presented more than one event with the same preferred/lower-level term (e.g., if they presented ear tube insertion more than once) but could be counted more than once if they presented more than 1 type of event (e.g., a child that had ear tube insertion and cranial decompression is counted once for each of the preferred term/lower term).

Data presented at the 2022 ISDS meeting.

Data based on 86 children enrolled in PROPEL (snapshot January 2022) at 19 sites in Europe, Australia, and North America.

Infections, Respiratory and Musculoskeletal disorders

- A history of infections and infestations was reported in 46 children (53.5%). The most common of these were ear infections (n=43; 50.0%)
- A history of respiratory disorders was reported in 40 children (46.5%). The most common was sleep apnea (n=35; 40.7%)
- A total of 33 children (38.4%) had a history of musculoskeletal disorders, the most common of which was kyphosis (n=18; 20.9%). Spinal stenosis was reported in 8 children (9.3%)

Respiratory disorders	No. of subjects (%)*
Obstructive sleep apnea syndrome	20 (23.3)
Sleep apnea	9 (10.5)
Obstructive sleep apnea hypopnea syndrome	4 (4.7)
Central sleep apnea syndrome	2 (2.3)
Adenoidal hypertrophy	8 (9.3)
Snoring	3 (3.5)
Chronic nasal congestion	2 (2.3)
Cough	1 (1.2)
Deviated nasal septum	1 (1.2)
Nasal congestion	1 (1.2)
Nasal turbinate hypertrophy	1 (1.2)
Subglottic stenosis	1 (1.2
Tonsillar hypertrophy	1 (1.2

Musculoskeletal disorders	No. of subjects (%)*
Kyphosis	18 (20.9)
Genu varum	6 (7.0)
Lumbar hyperlordosis	5 (5.8)
Bow legs	3 (3.5)
Spinal stenosis	3 (3.5)
Lumbar spinal stenosis	2 (2.3)
Cervical spinal stenosis	1 (1.2)
Spinal canal stenosis	1 (1.2)
Thoracic spinal stenosis	1 (1.2)
Knee pain	2 (2.3)
Tibia vara	2 (2.3)
Contracture	1 (1.2)
Elbow deformity	1 (1.2)
Enlarged fontanelle	1 (1.2)
Genu valgum	1 (1.2)
Hyperlordosis	1 (1.2)
Joint dysfunction	1 (1.2)
Joint instability	1 (1.2)
Joint laxity	1 (1.2)
Leg pain	1 (1.2)
Low back pain	1 (1.2)
Lumbar scoliosis	1 (1.2)
Muscle weakness	1 (1.2)
Nose deformity	1 (1.2)

*Children could be counted more than once if they presented ≥1 type of event

Data presented at the 2022 ISDS meeting.

Data based on 86 children enrolled in PROPEL (snapshot January 2022) at 19 sites in Europe, Australia, and North America.

Other conditions/events reported as medical history

- Ear and labyrinth disorders were found in 15 children (17.4%), all of whom presented hearing impairment

- Disorders in the central nervous system were reported in 16 children (18.6%). Two children (2.3%) had hydrocephalus and 4 (4.6%) had ventriculomegaly without intracranial hypertension. Two children (2.3%) had spinal cord compression

Ear and labyrinth disorders	No. of subjects (%)*
Hearing loss	6 (7.0)
Conductive hearing loss	5 (5.8)
Hypoacusis	4 (4.7)
Middle ear effusion	1 (1.2)
Dysfunction of eustachian tube	1 (1.2)

CNS disorders	No. of subjects (%)*
Cerebral ventricle dilatation	4 (4.7)
Hydrocephalus	2 (2.3)
Gross motor delay	2 (2.3)
Speech disorder developmental	2 (2.3)
Spinal cord compression	2 (2.3)
Balance disorder	1 (1.2)
Cervical cord compression	1 (1.2)
Dysarthria	1 (1.2)
Febrile convulsion	1 (1.2)
Hypotonia	1 (1.2)
Paresthesia	1 (1.2)
Radiculopathy	1 (1.2)

*Children could be counted more than once if they presented ≥1 type of event

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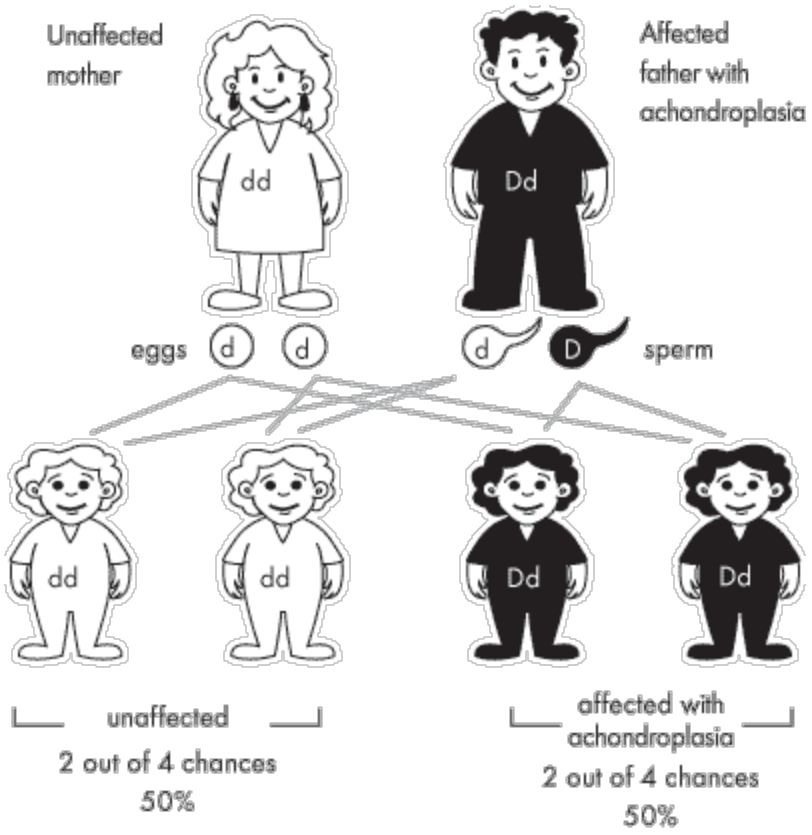
HRQOL tools and height Z-score

Box 2 Complications of achondroplasia (%) in childhood

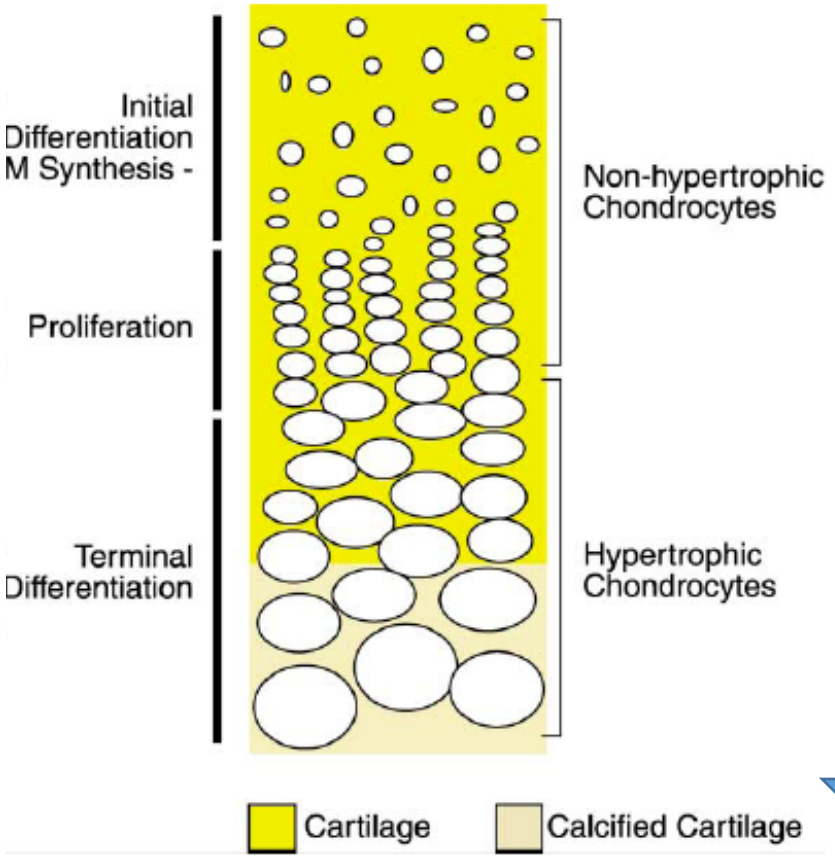
- Neurological
  - Foramen magnum compression (5–10%)
  - Craniocervical instability (very rare)
  - Symptomatic hydrocephalus (6%)
- Orthopaedic
  - Progressive, unresolving thoracolumbar kyphosis
  - Decreased range of movement, elbows and hips
  - Tibial bowing (10%)
  - Symptomatic lumbar spinal stenosis (20%)
- ENT
  - Recurrent otitis media (89%)
  - Adenotonsillar hypertrophy (25%)
- Dental
  - Dental overcrowding (>50%)
- Respiratory
  - Sleep apnoea (75%)
- Growth
  - Short stature
  - Increased body mass index
- Development
  - Comparative motor delay
  - Speech delay (25%)
  - Conductive hearing loss (40%)
- Activities of daily living
  - Restricted through short stature, rhizomelic shortening of upper limbs
- Pyschosocial impact for child and family

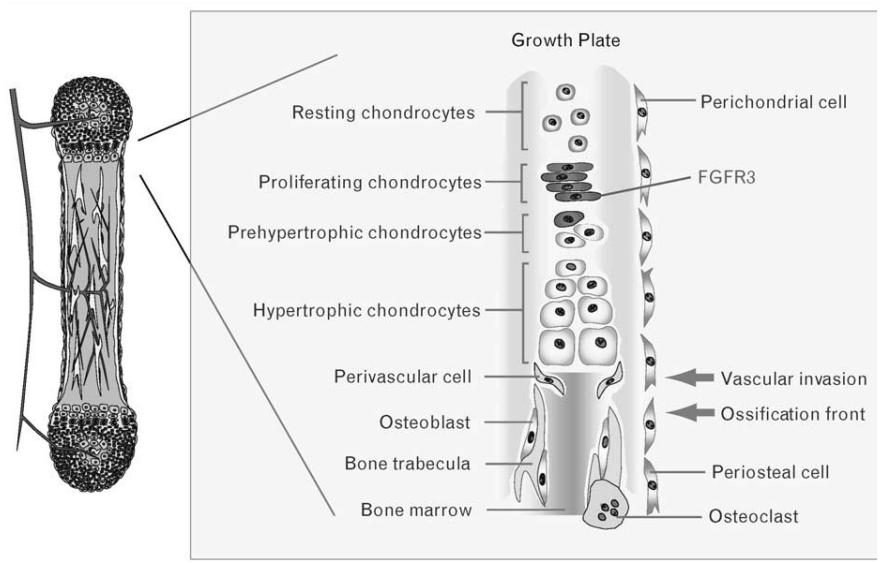
Achondroplasia is a genetic disorder of FGFR3: de novo event or inherited from a parent with Ach



FGFR3 acts to regulate the growth plate through inhibition of other growth signals

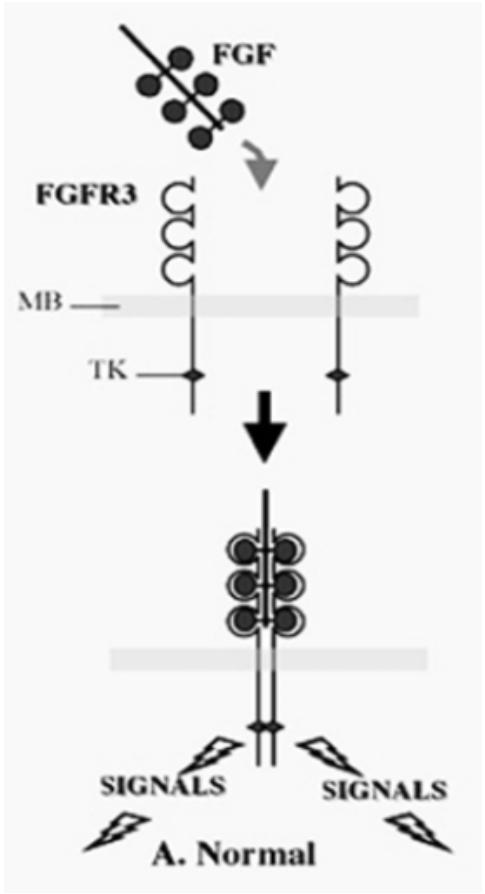
Immature
cartilage cells

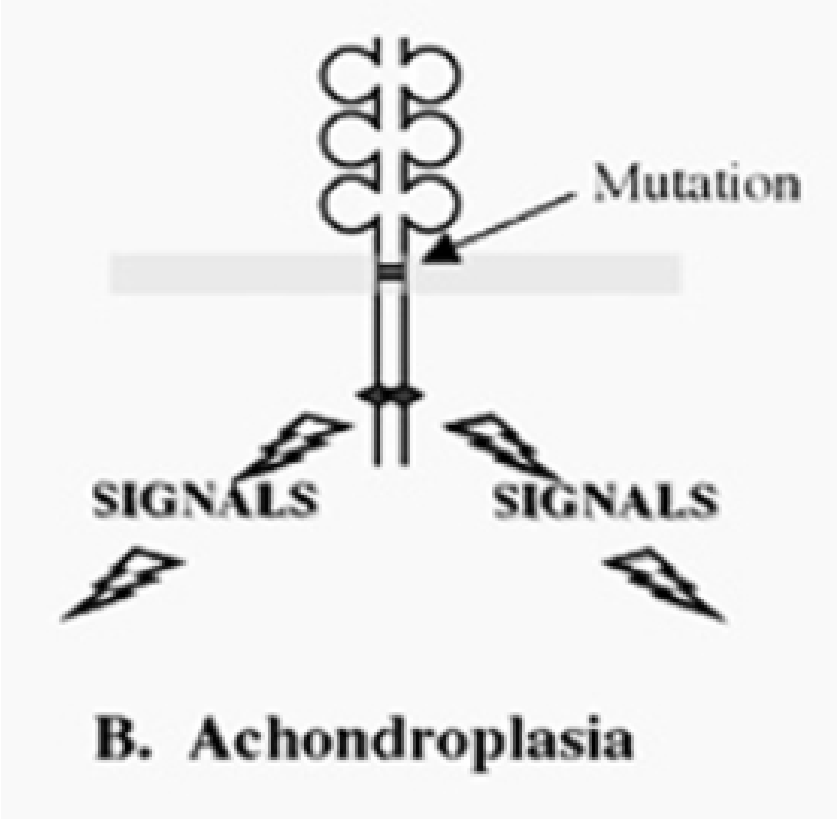




Bone
formation

Activating mutation in *FGFR3* - G380R





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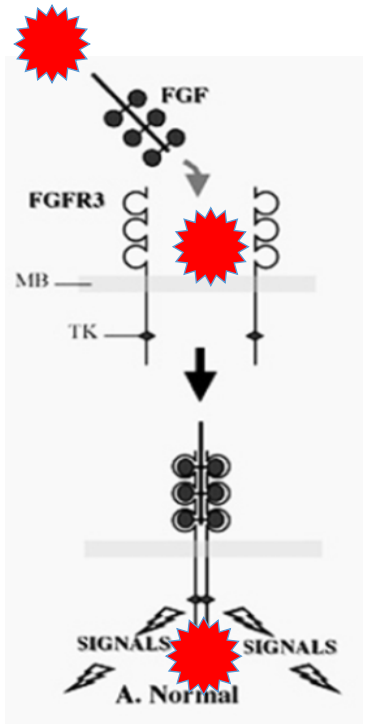

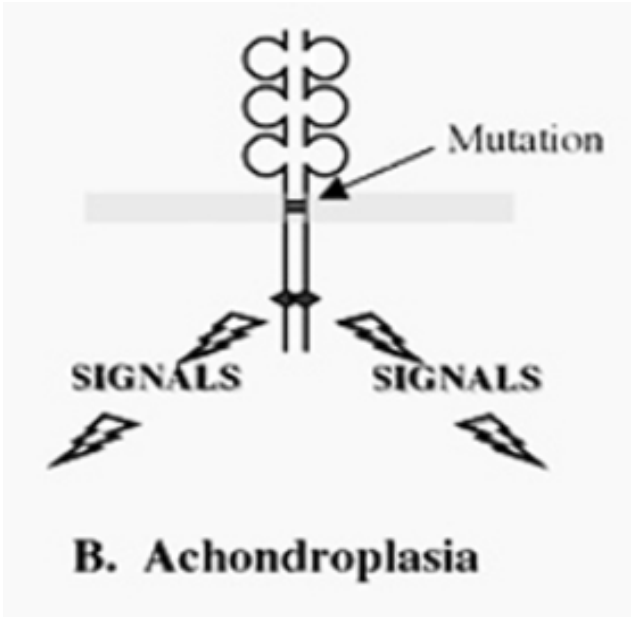

Summary

- Achondroplasia is a medical condition with lifelong multisystem complications
- It is secondary to abnormal bone growth, the consequence of a recurrent genetic variant
- Interventions to attempt to restore skeletal growth present encouraging opportunities to improve quality of life and significantly reduce the burden of complications
- Addressing age-specific morbidities that can be life-changing and life-limiting