

Achondroplasia Dwarfism

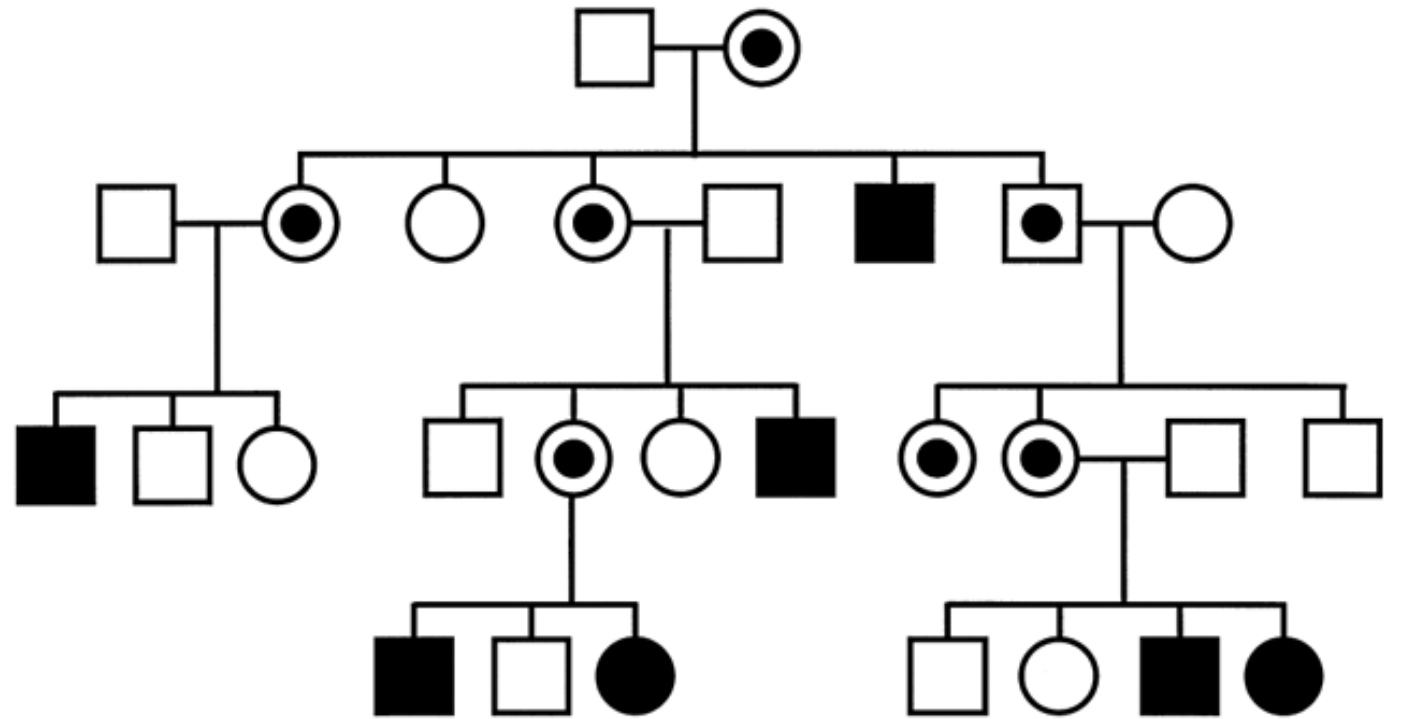
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Biol. 324: Genetics

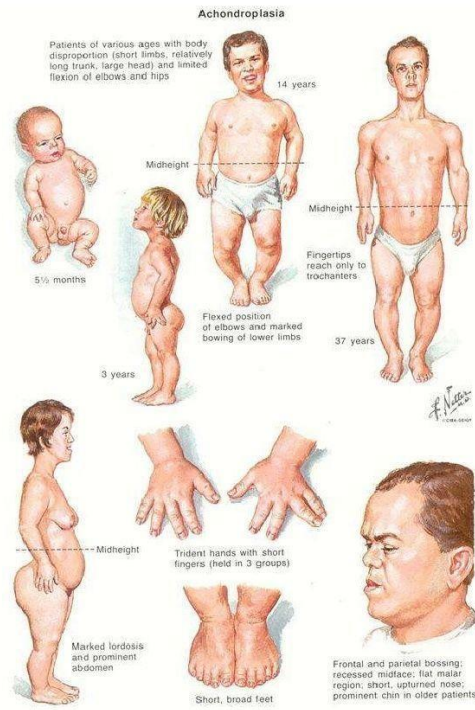
4/30/2018

What is Achondroplasia?

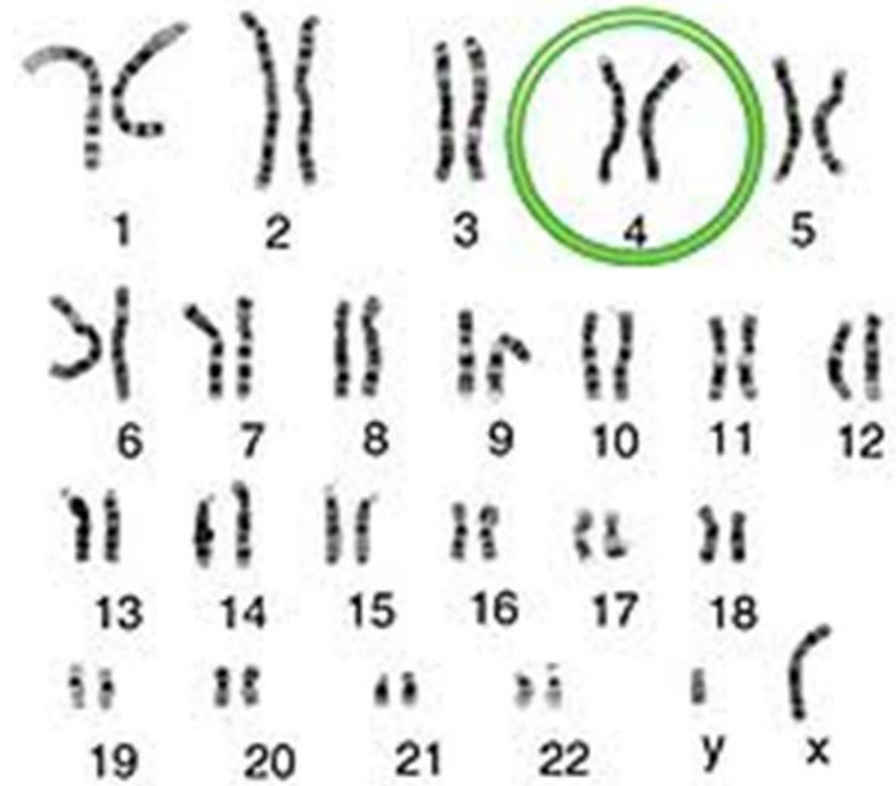
- Form of short-limb dwarfism.
- Most common form of dwarfism.
- It's an autosomal dominant disease.
- 80% of normal parents can have an affected child.



Achondroplasia



<https://apessay.com/order/?rid=cc49f4f3231bb03f>



<http://lawrencecabasan.wixsite.com/gr11achondroplasia/our-animals>

Common Phenotypes and Genotypes

Heterozygous Achondroplasia

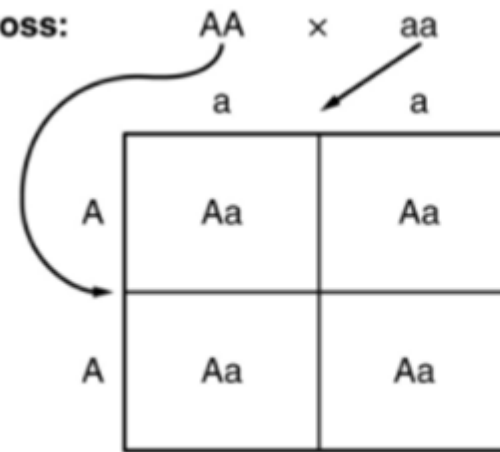
- Compatible with life.
- Affected people have the heterozygous alleles (Aa X Aa) cause the children to have a 1:2:1 ratio for being affected

	A	a
A	AA	Aa
a	Aa	aa

Homozygous Achondroplasia

- Incompatible with life.
- If one parent have two of the dominant alleles all of the children will be affected.
- The affected individual have two dominant alleles (AA).

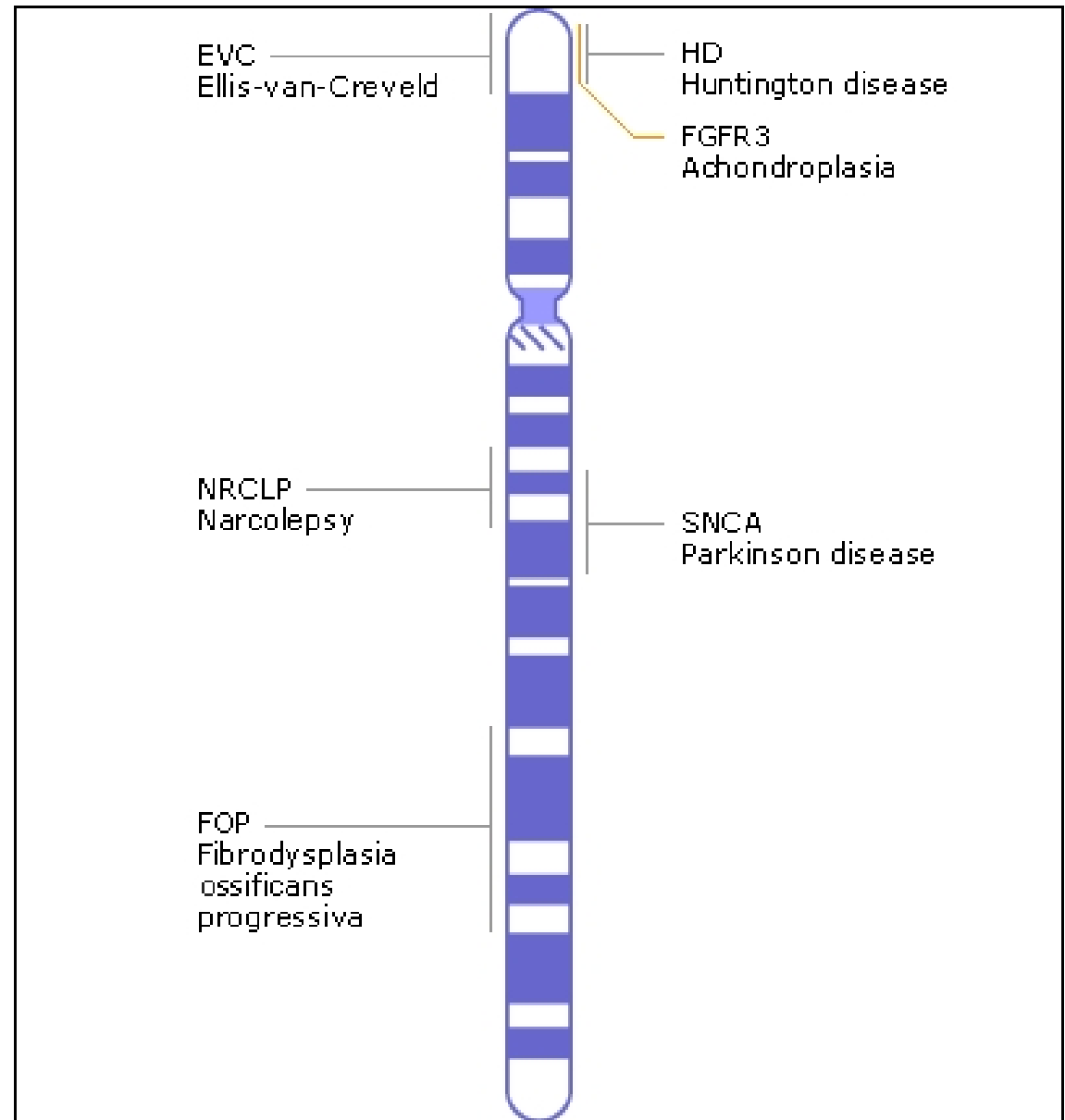
Generation 1 Cross:



Generation 2:
100% of offspring
are AA (dominant)

Affected Genes

- Achondroplasia caused by a mutation on the FGFR3 gene.
- Normal or average size parents have the new mutation cause their children to the disease.

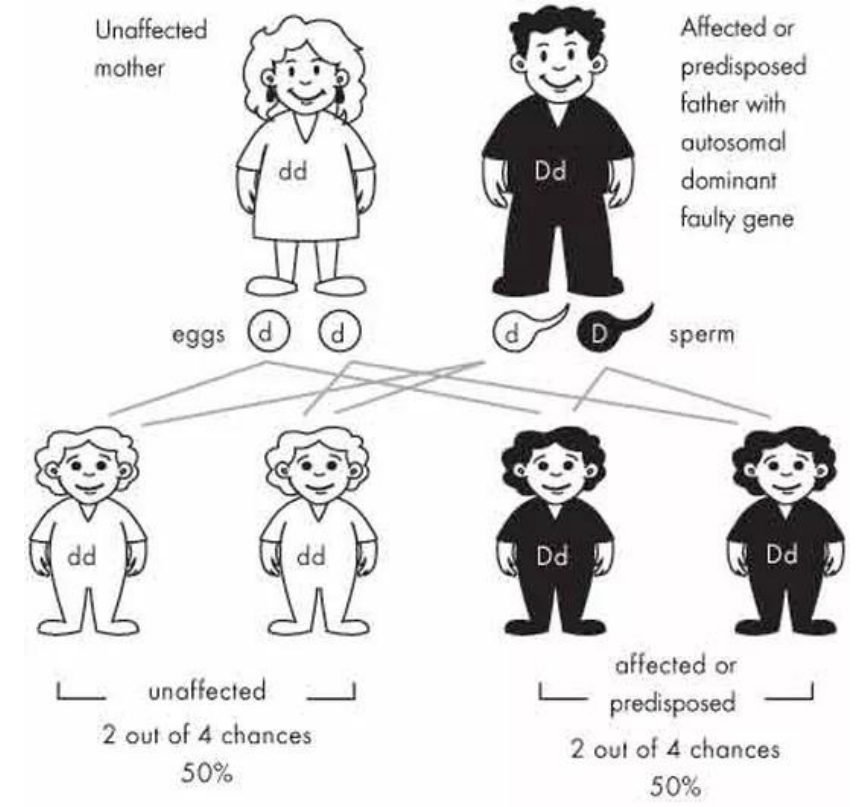
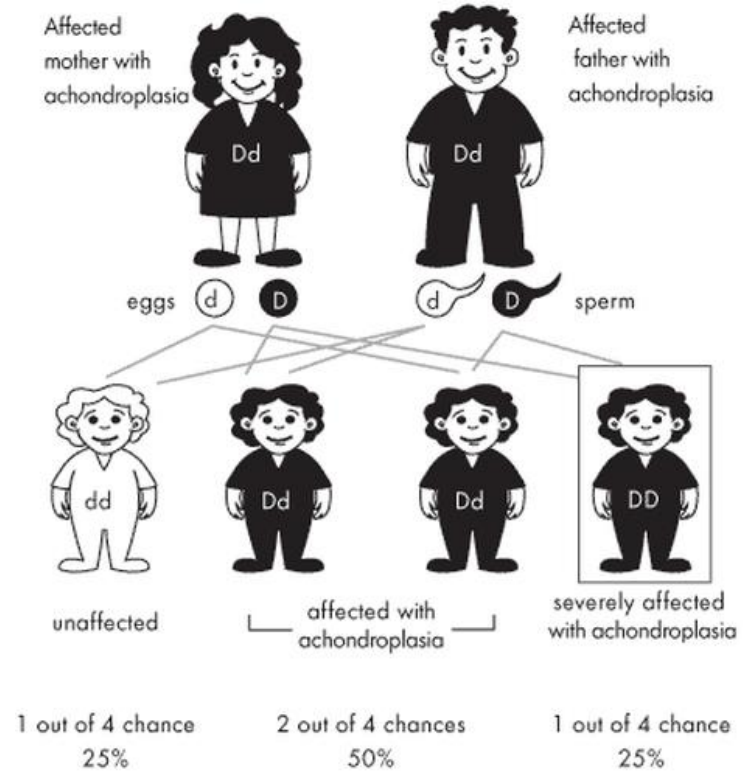


<https://cellularphysiology.wikispaces.com/Achondroplasia>



Inheritance Patterns

- Individuals affected with the disease can have one or two affected parents.
- Not all individuals with achondroplasia parents have or see the difference disease.



CABASAN, LAWRENCE. "What Is Achondroplasia?" *Achondroplasia*, 2014, lawrencecabasan.wixsite.com/gr11achondroplasia/our-animals.

Inheritance Patterns

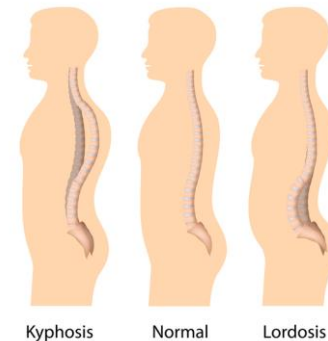
Most Common Alleles Affect



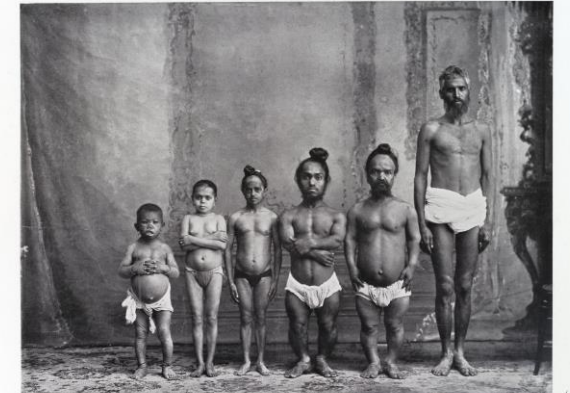
- Two difference mutation happen in FGFR3 genes that causes 99% of Achondroplasia.
- The amino acid glycine is replaced with the amino acid arginine located at the position 380 ○ This is written as Gly380Arg of G380R.

Phenotypes Associated with the Disease

- Individuals with disease have a shorter stature.
 - Shorter arms, short legs, and average size trunk.
 - They lack range of motion in their elbows.
- Lack developmental markers.
 - Spinal
 - Shorten bones
 - Brain
 - Underdeveloped rib cage



(From photographs most kindly sent by Major C. H. James, I.M.S.)



(a) Cretinous Dwarf, (b) and (c) Ateliotic Dwarfs, (d) and (e) Achondroplasia Dwarfs, (f) Normal Native.

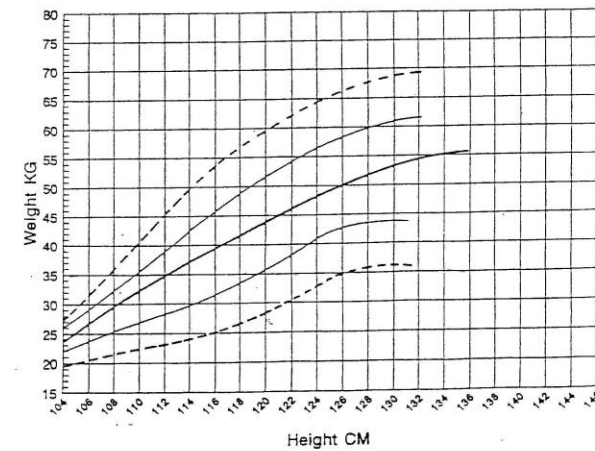
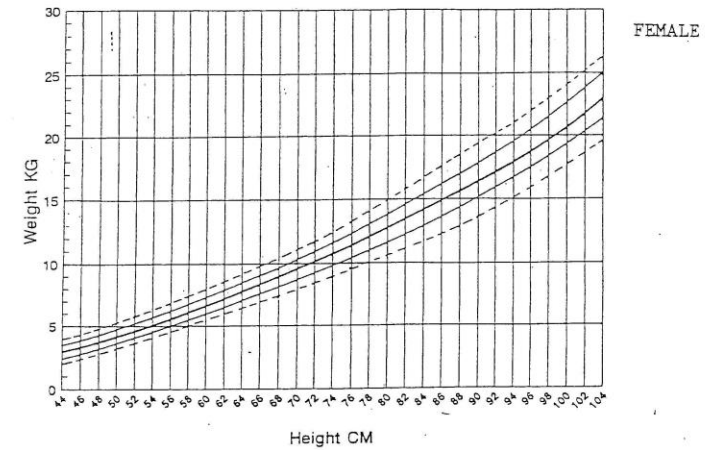


Back View of the same Figures. Cf. De Castejo, *Medical Record*, Vol. 104, November, 1916.

Phenotypes Associated with the Disease cont.

- Males are normally 131 centimeters tall.
- Females are normally 124 centimeter tall.

Standard Weight for Height Curves in Achondroplasia



American Journal of Medical Genetics 62:255-261 (1996)



Screening Methods/ Diagnostic Methods

- During pregnancies or an ultrasound may show an extra amount of amniotic fluid around the baby which is a clear sign.
- Ultrasound can detect Achondroplasia.



Current treatment?

- They are currently not any known cure.
- Nor are there specific treatments for Achondroplasia.
- People affected with disease can receive multiple surgery to help improve their life situations.

Previous Study

- Clinical and Molecular diagnosis of the skeletal dysplasia's associated with mutations in the gene encoding Fibroblast Growth Factor Receptor 3 (FGFR3) in Portugal

Background

- Research Question: The authors wanted to study why that was a large cohort of related skeletal FGFR3(Achondroplasia Dwarfism) in the Portuguese population.
- Ach/Hch cases, that molecular analysis plays a key role in the accuracy of clinical diagnosis.
- It makes an important contribution to a better pathobiological understanding of the phenotypic spectrum of mutations in the FGFR3 gene.

Why is this study important?

- In the 70 patients with the clinical diagnosis of Hypochondroplasia or Achondroplasia.
- Five different pathogenic mutations were identified.
- These are the most common forms of Dwarfism and they share the same molecular mechanism.

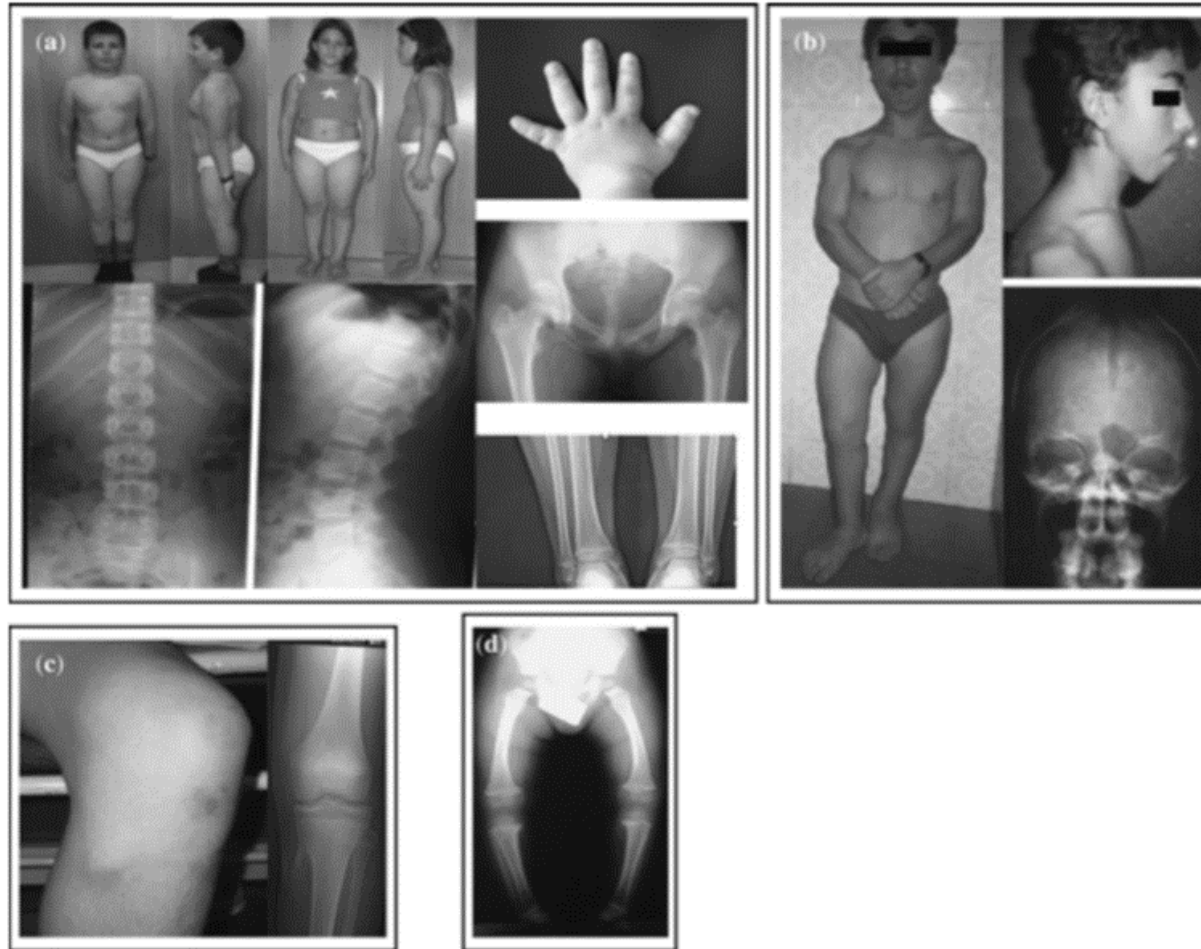


Fig. 1. Clinical and radiological findings . **(a)** (case 2) Patients with severe short stature and normal face. No rhyzomelic limbs shortness. Short trident hands. Lordosis. Radiographs revealed unchanged interpedicular distance and increased fibular length. **(b)** (case 3) - Exaggerated muscular development and rhyzomelic shortening. Elongated face with proptosis. Radiological studies - Cranyosinostosis with an open metopic suture. **(c)** (case 6) - An osteochondroma in the proximal metaphysis of the left tibia. **(d)** (case 1) - Radiograph showing severe bowing of the legs.

Study Design and Methods

- Total of 6 different cases (females and males).
- People aging from 3 years old to 34 years old.
- Total of 125 Portuguese's patients all affected with Achondroplasia or Hypochondroplasia.
- Observed their height, weight and stature.

Major Results

- Hypochondroplasia and Achondroplasia have 8 of the same mutation that is associated with the FGFR3 gene.
- The case 6, with Muenke syndrome also presented with a osteochondroma in the proximal metaphysis of the left tibia.
- There is even a phenotype correlation.

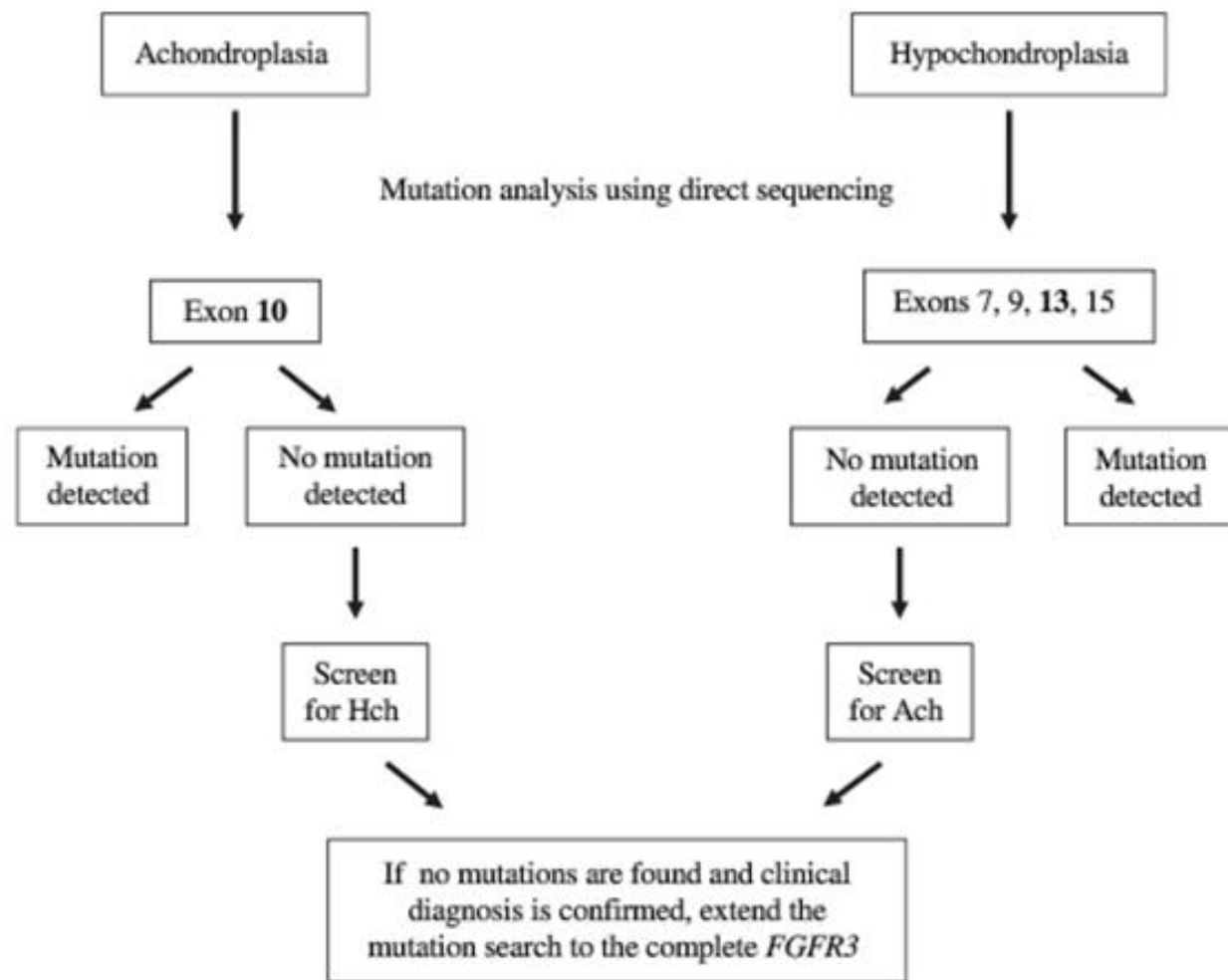


Fig. 2. Flowchart for the molecular strategy to test patients referred with the clinical diagnosis of Ach/Hch.

Major Conclusion

- Three very rare or novel mutations were also identified, R200C, G380K and E360K associated with the mutation on the FRFG3 gene.
- Achondroplasia is very common the most of the cases.
- There are two different types of Dwarfism on the FRFG3 gene.
 - Achondroplasia
 - Hypochondroplasia



Limitation of the Study

- The study is only conducted in one specific location.
- The study involved a small amount of people.
- There were only six case studies.

Future Direction

- Expand the field of study.
- Observe studies of Achondroplasia in the United States.
- Observe difference locations.
 - Observed more people.
 - Difference ages.
 - Difference races.



Work cited

- Almeida, M. R., Campos-Xavier, A. B., Medeira, A., Cordeiro, I., Sousa, A. B., Lima, M., ... & Sousa, S. (2009). Clinical and molecular diagnosis of the skeletal dysplasias associated with mutations in the gene encoding fibroblast growth factor receptor 3 (FGFR3) in Portugal. *Clinical genetics*, 75(2), 150-156.
- <https://cellularphysiology.wikispaces.com/Ach>
- CABASAN, LAWRENCE. "What Is Achondroplasia?" *Achondroplasia*, 2014, lawrencecabasan.wixsite.com/gr11achondroplasia/our-animals.