Fibrodysplasia Ossificans Progressiva

Clinical aspects and genotype phenotype correlation

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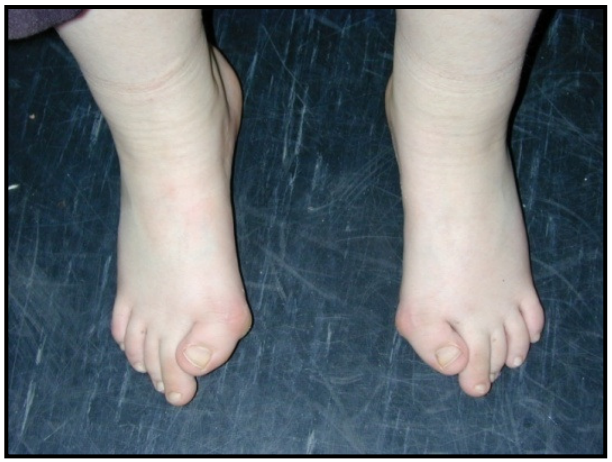
Fibrodysplasia ossificans progressiva (FOP)

- Congenital malformations of the great toes >95%
- Congenital malformations of the thumbs 50%
- Progressive heterotopic ossifications 100%



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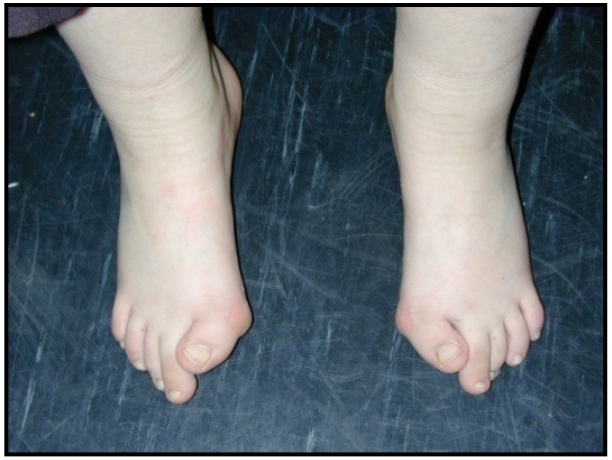
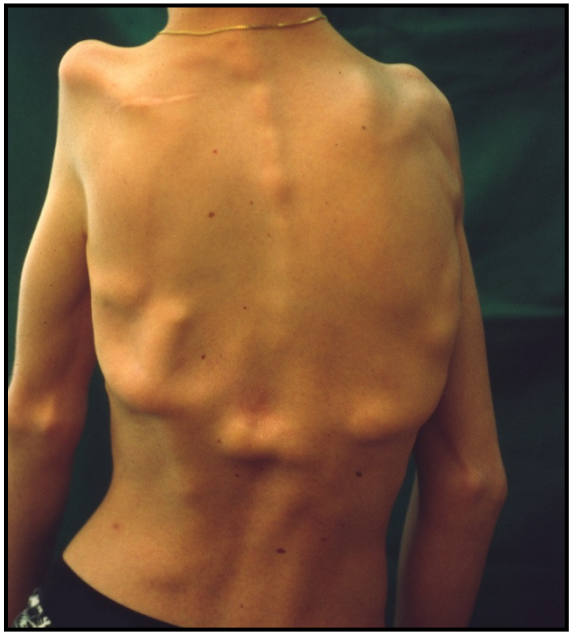




Fibrodysplasia ossificans progressiva (FOP)

- Progressive immobility 100%
- Thorax insufficiency syndrome >95%
- Conductive hearing loss, teeth anomalies
- Normal intelligence

- Frequency 1 / 2 000 000
- no effective treatment

History of FOP

- first desciption by Guy Patin 1692

- John Freke 1740:

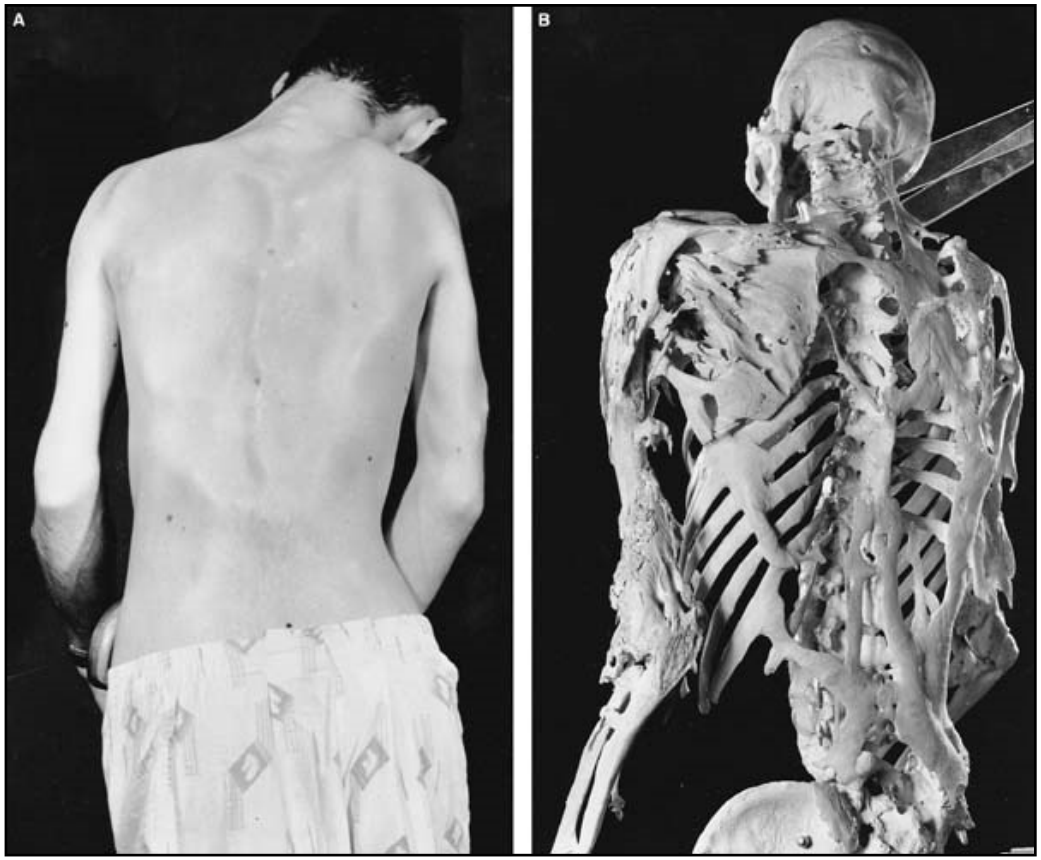
  „…a boy of a healthy look and 14 years of age… to be cured of many large swellings, arising from every rib of his body and joining together in all parts of his back, as the ramifications of coral do…“

- Helferich 1879:

  brachydactyly of the great toe in FOP patients

History of FOP

- Harry Raymond Eastlack, Jr. (1933-1973)



As a result of the bridges of bone, Harry Eastlack's skeleton is almost completely fused into one piece.

www.ifopa.org


For reference

2006 - Nature Genetics:

A recurrent mutation in the BMP type I receptor ACVR1 causes inherited and sporadic fibrodysplasia ossificans progressiva

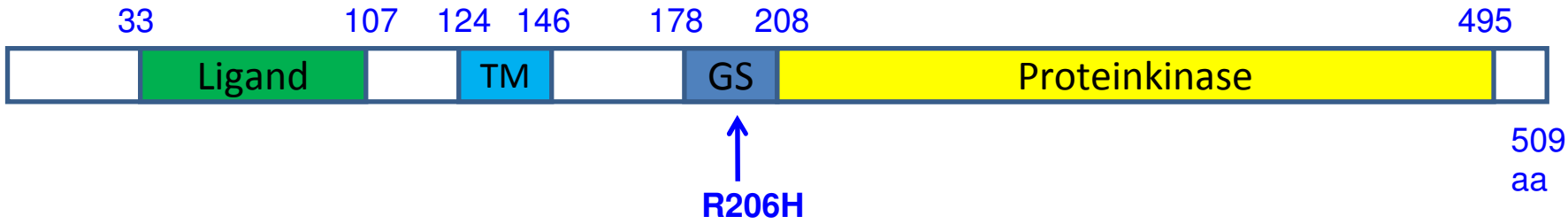
Eileen M Shore[1–3], Meiqi Xu[1,2], George J Feldman[1,2], David A Fenstermacher[4–6], Tae-Joon Cho[7], In Ho Choi[7], J Michael Connor[8], Patricia Delai[9], David L Glaser[1,2], Martine LeMerrer[10], Rolf Morhart[11], John G Rogers[12], Roger Smith[13], James T Triffitt[14], J Andoni Urtizberea[15], Michael Zasloff[1,2,16,17], Matthew A Brown[14,18] & Frederick S Kaplan[1,2,19]

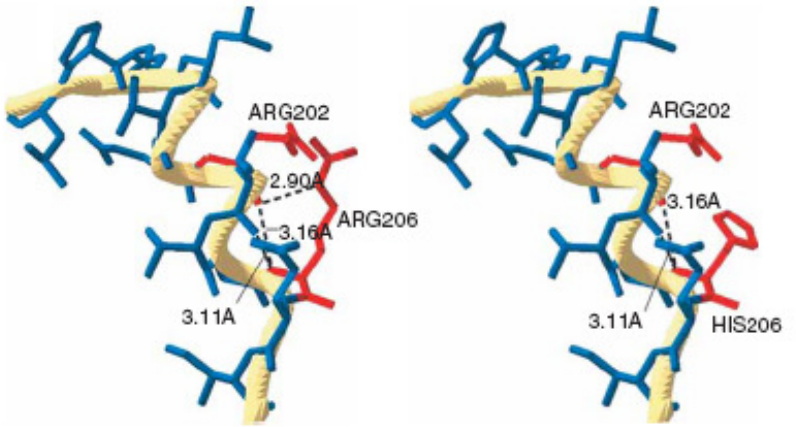
c.617G→A; p.R206H

ACVR1

- Activin A receptor type 1,

  BMP (bone morphogenic protein) 1 receptor





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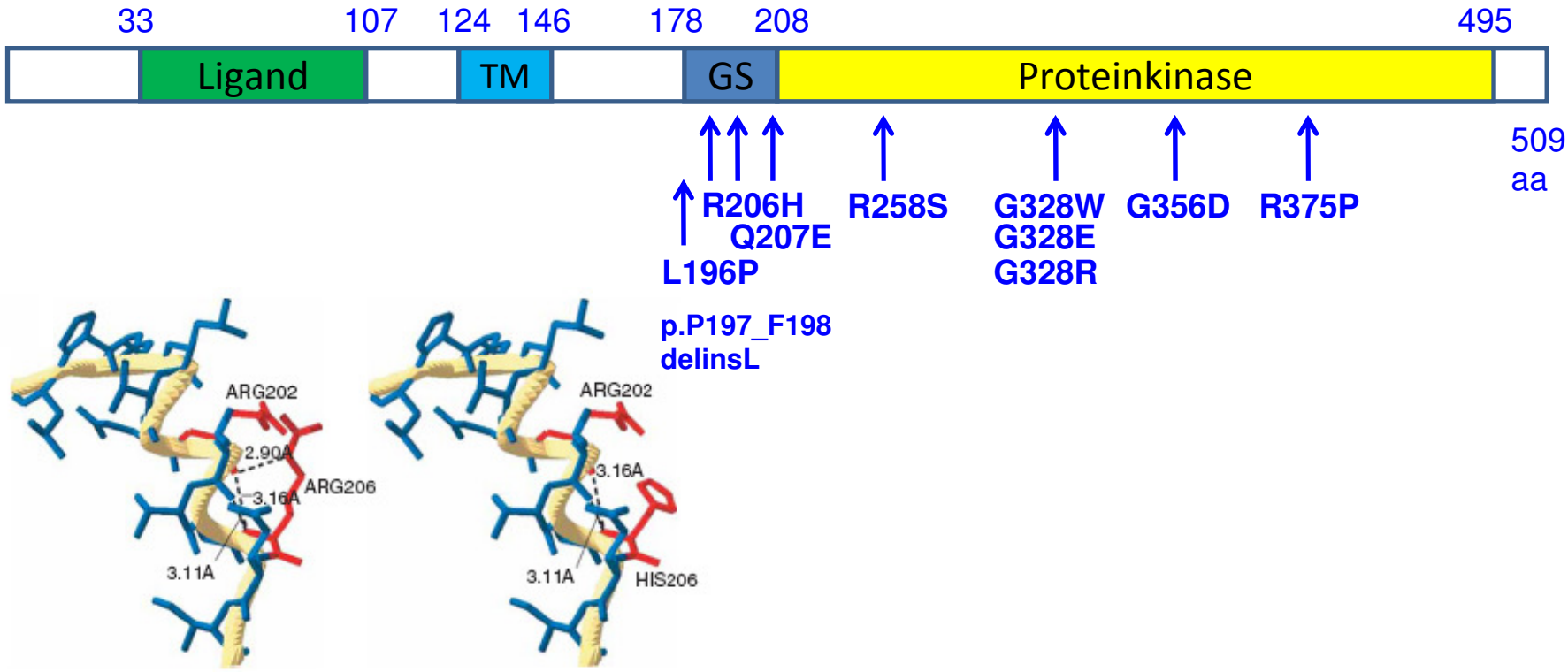
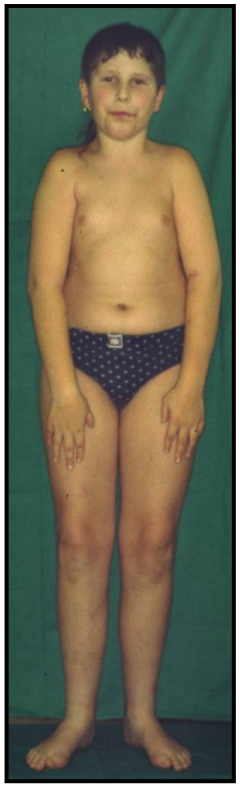
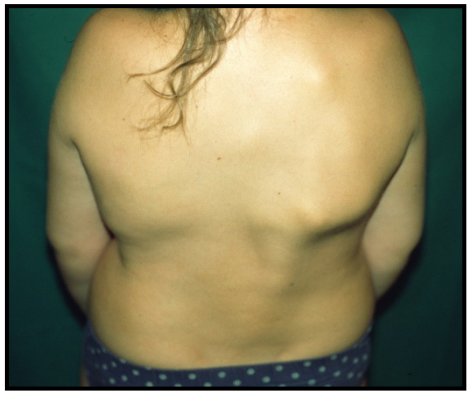
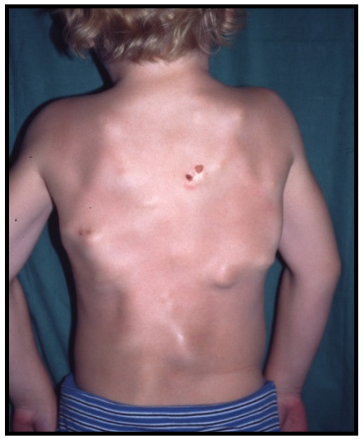
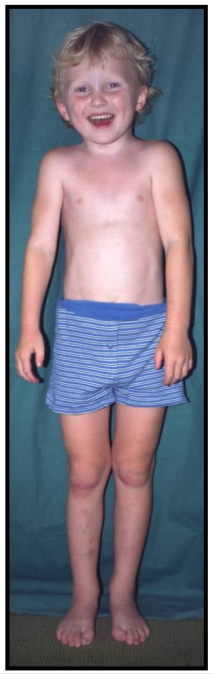


R206H mutation (29 patients)

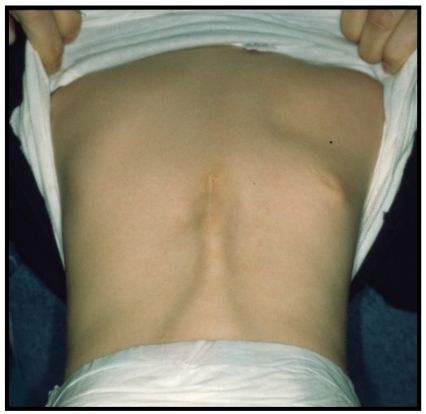




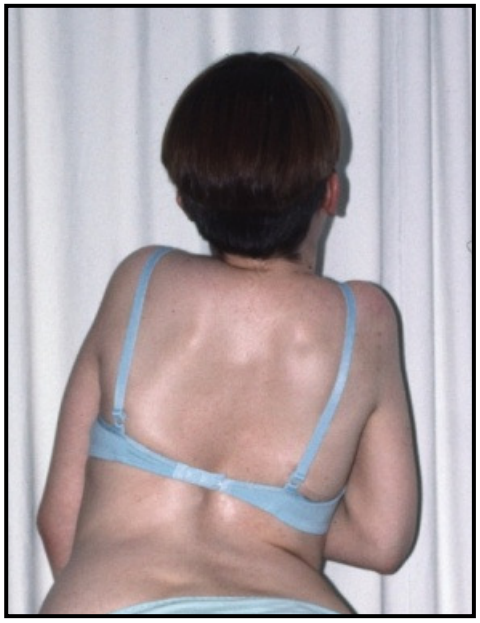


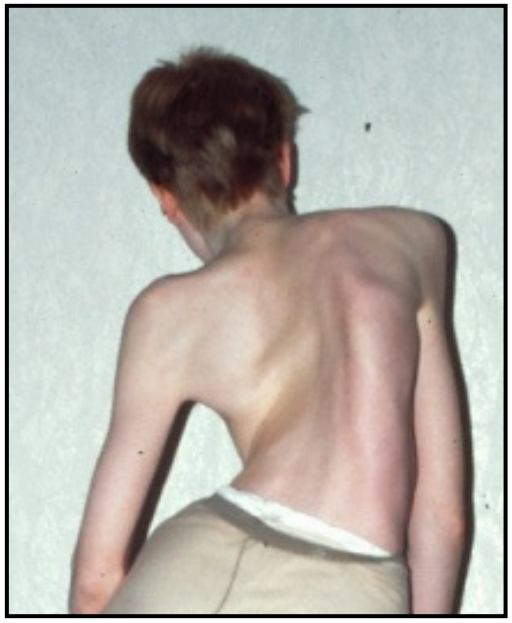


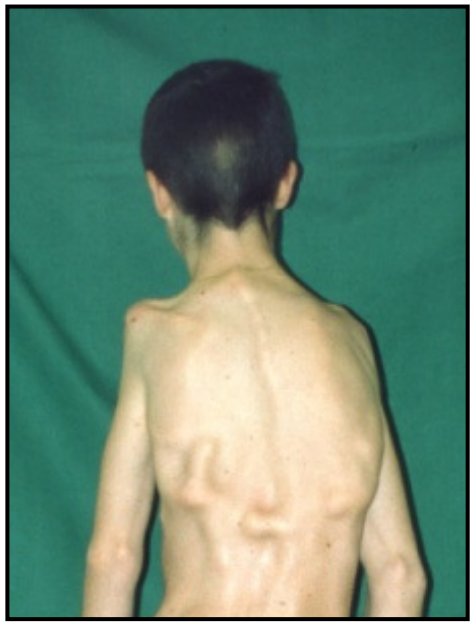
- Onset in early infancy (1-13 LJ)
- Ossifications begin in the regions back, neck and shoulders
- Diagnosis often after 2-3 years after ossification onset



R206H mutation (29 patients)

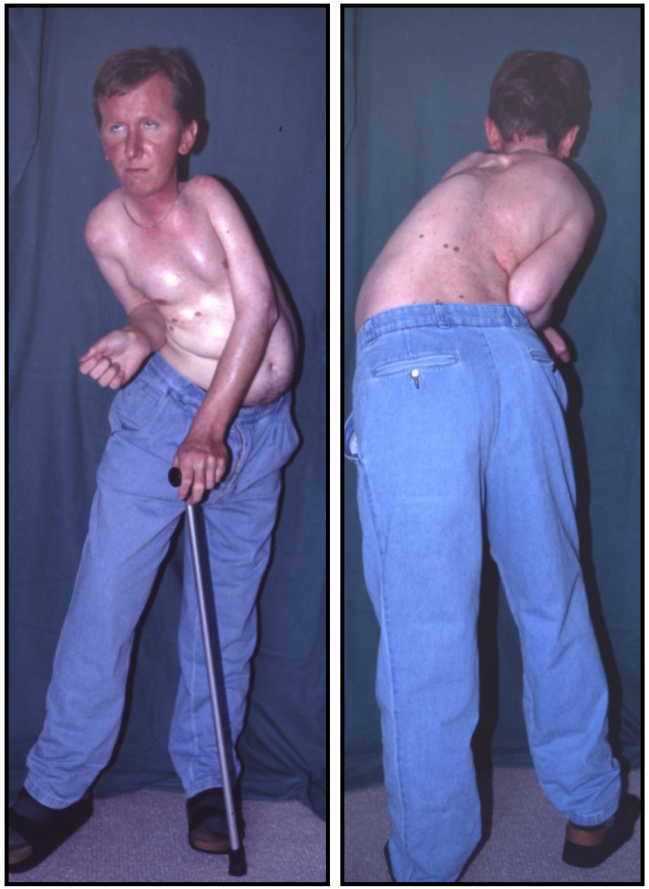


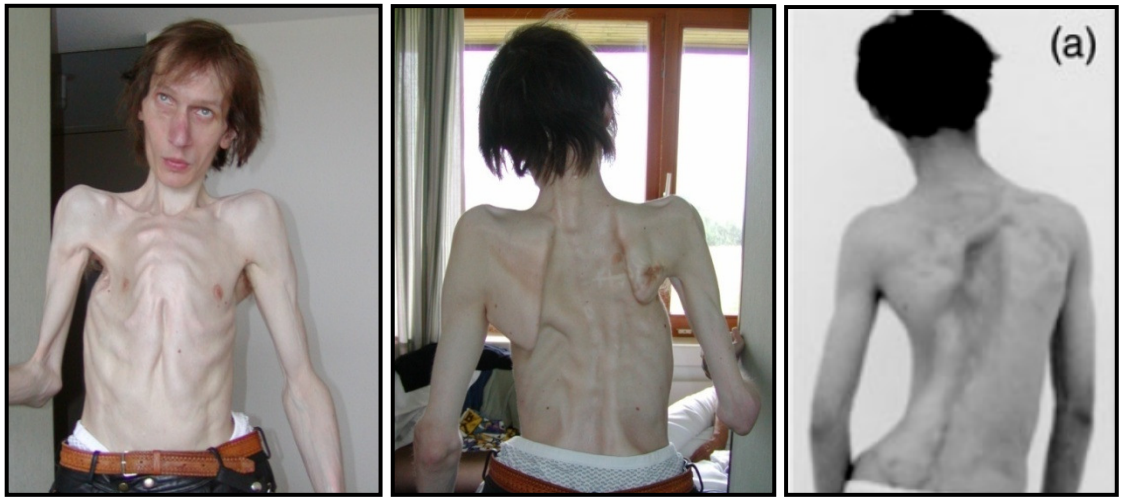




- Ossifications in typical anatomical pattern
- Scoliosis
- Thorax insufficiency

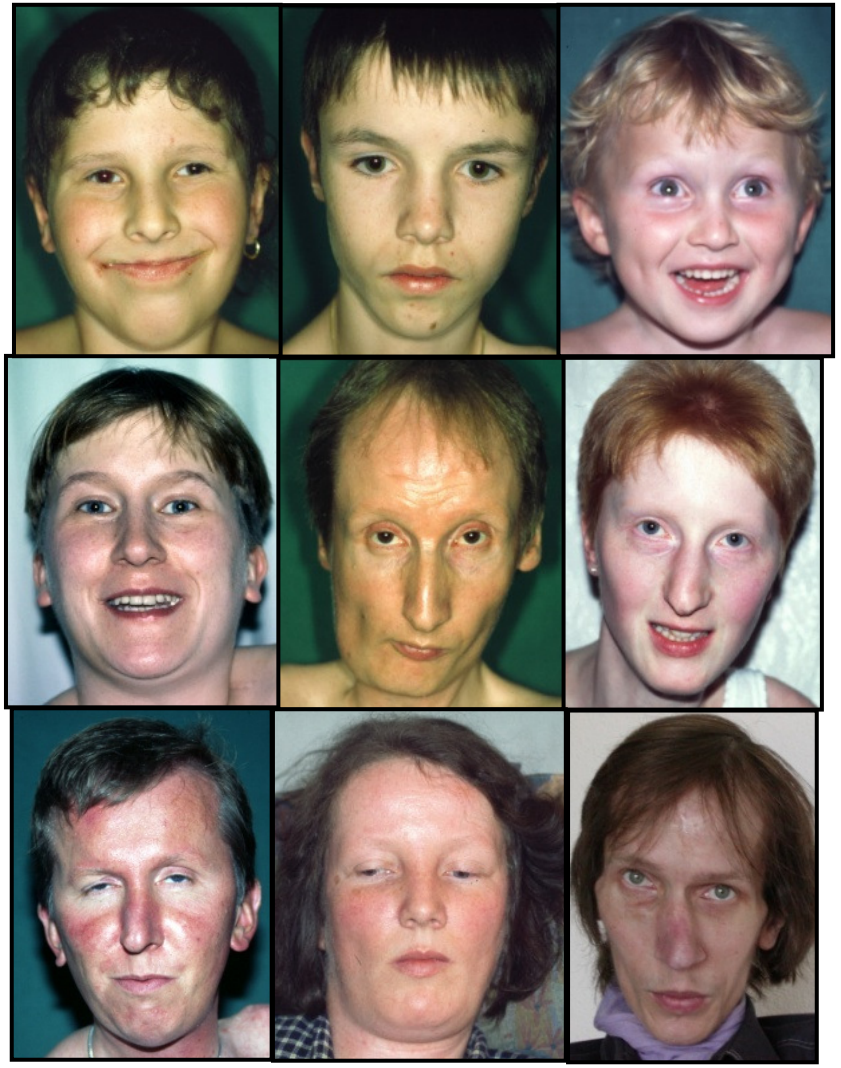
R206H mutation (29 patients)





- Restriction of the temporomandubular joint
- Kachexia
- Thorax insufficiency

R206H mutation (29 patients)



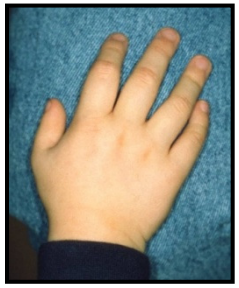
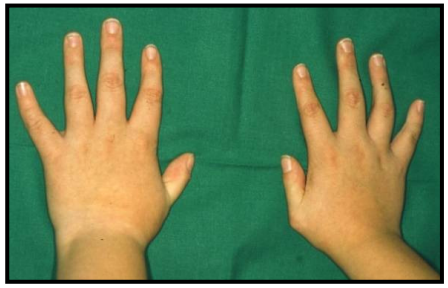
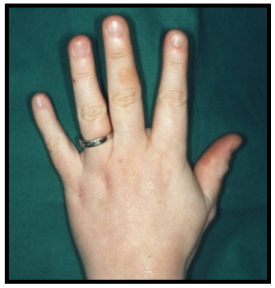
Craniofacial aspect:

- Sparse hair
- Thin skin
- Missing eyebrows

sopracciglio

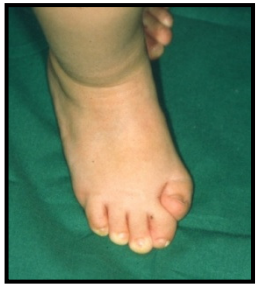
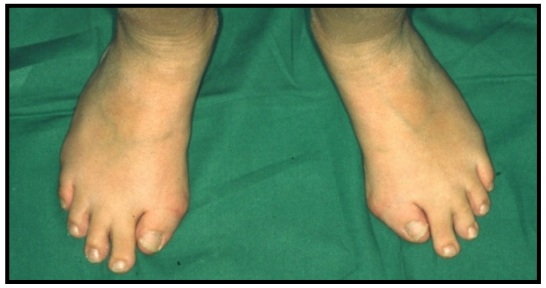
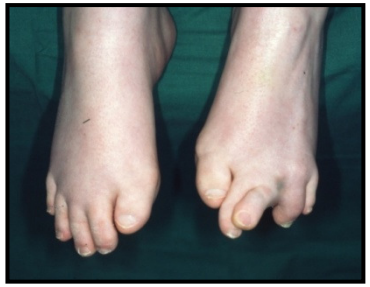
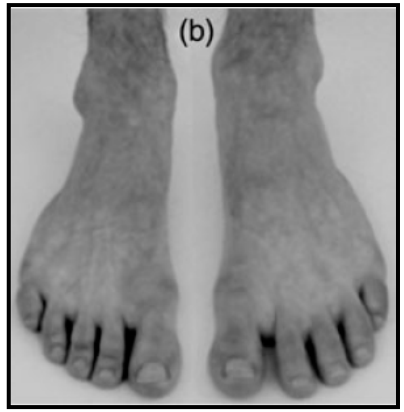
- Teeth abnormalities

R206H mutation (29 patients)

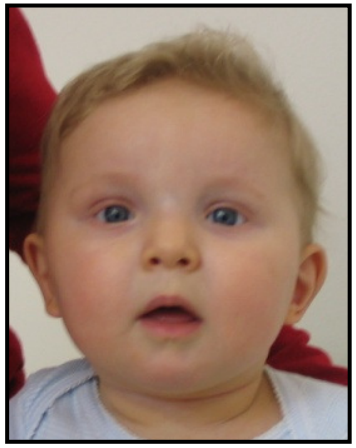




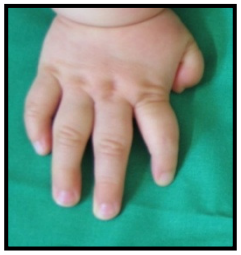
Limbs:

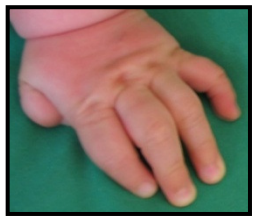
- Hypoplasia of the great toes
- Valgus deformity
- Thumb hypoplasia

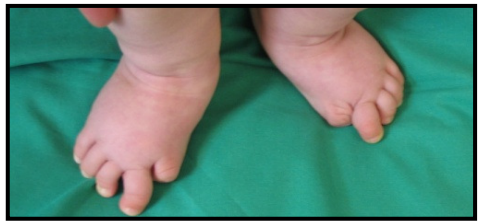





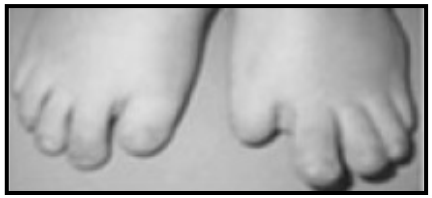
G356D mutation (4 patients)

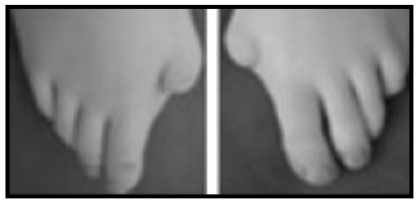










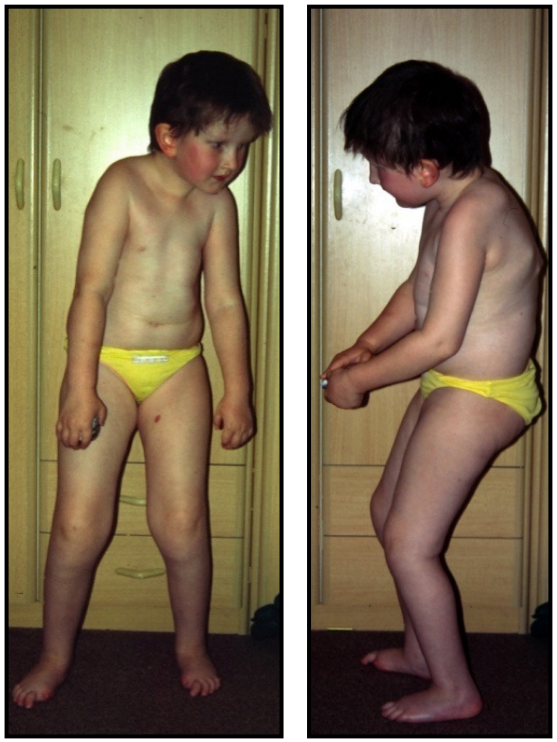


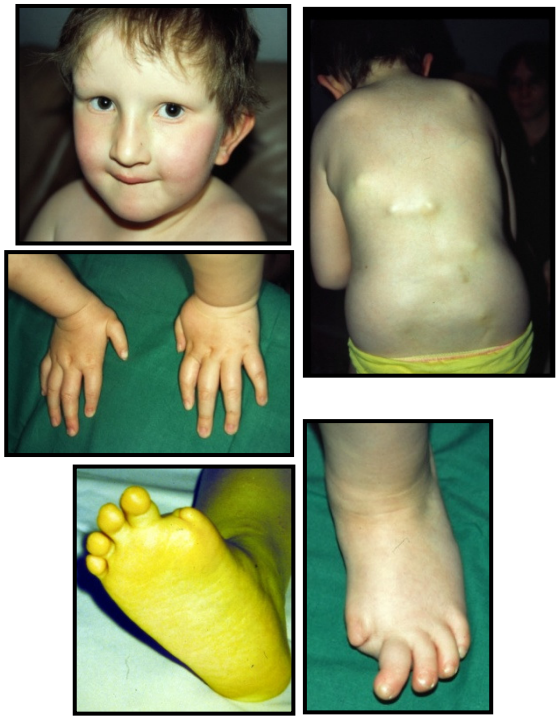
- Aplasia of the great toes
- Ossifications at age 10-15 y
- Immobility at age 36 y
- Alopecia (1)
- Hearing loss (1)
- Hypospadias (1)
- Primary amenorrhoea (1)

Kaplan et al. 2009

Furuya et al. 2008

G328W mutation (2 patients)





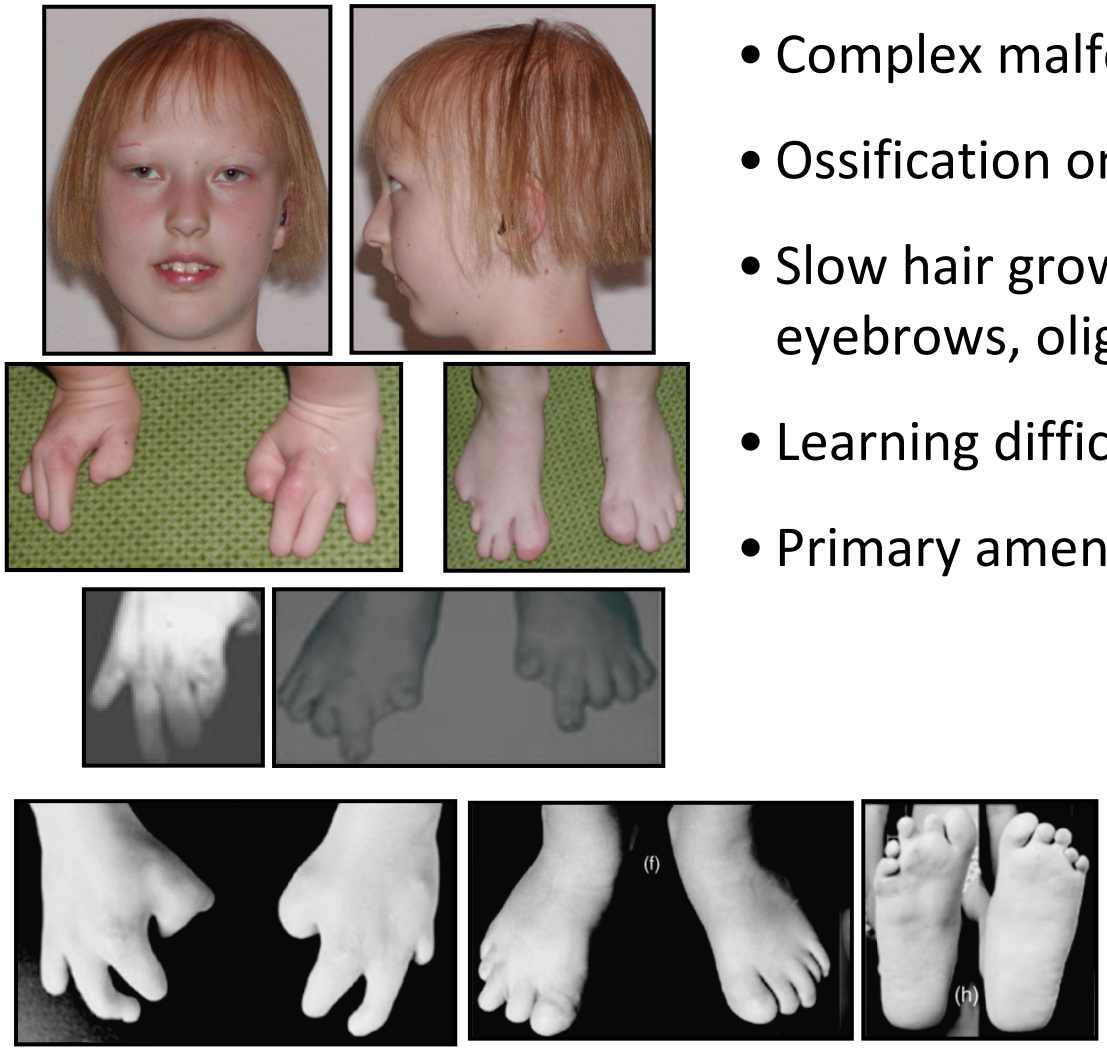
- Aplasia of the great toes
- Slow hair growth,

  sparse eyebrows
- Ossification onset 2 & 8 y
- Learning diffuculties

Kaplan et al. 2009

Connor and Evans 1982

G328E mutation (3 patients)

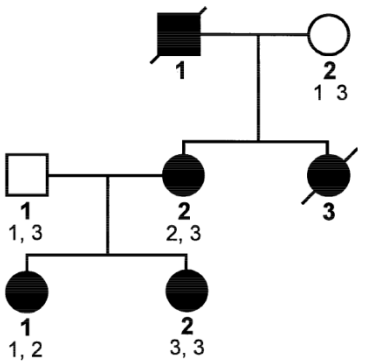


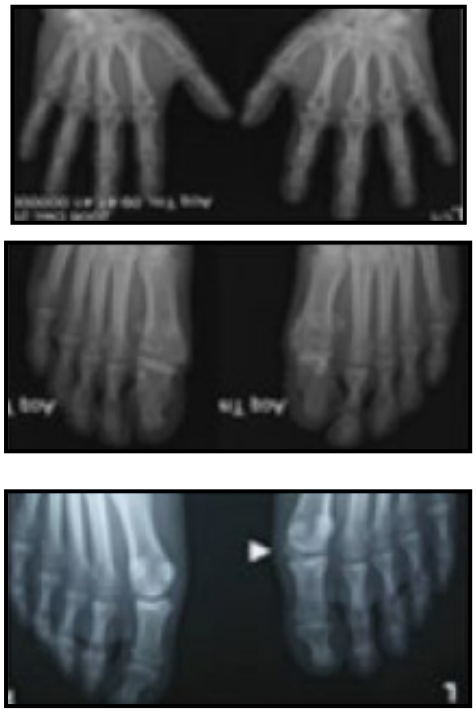
- Complex malformations of the limbs
- Ossification onset 0-1 y
- Slow hair growth, sparse hair and eyebrows, oligodontia
- Learning difficulties
- Primary amenorrhoea, gonadal aplasia (1)

Kaplan et al. 2009

Carvalho et al. 2009

G328R mutation (5 patients)





- No or very mild hypoplasia of the great toes
- Ossifications after trauma at ages 13, 21, 22, 26 y
- mild course of disease
- CCM (1)
- cerebellar hypoplasia (1)

Kaplan et al. 2009

Virdi et al. 1999

L196P mutation (1 patient)

Gregson et al. 2010:

- Late onset of ossifications
- Very mild course
- No abnormalities of the great toes

p.P197_F198delinsL mutation (1 patient)

Kaplan et al. 2009:

- Painful flexure contracture of the hip with ossification at age 11 y
- Ankylosis of all major joints
- No abnormalities of the great toes

R258S mutation (3 patients)

Borcciadi et al. 2009, Ratbi et al. 2010

- Swellings at age 4-8 y
- Ossifications at age 18 y
- No or very mild hypoplasia of the great toes

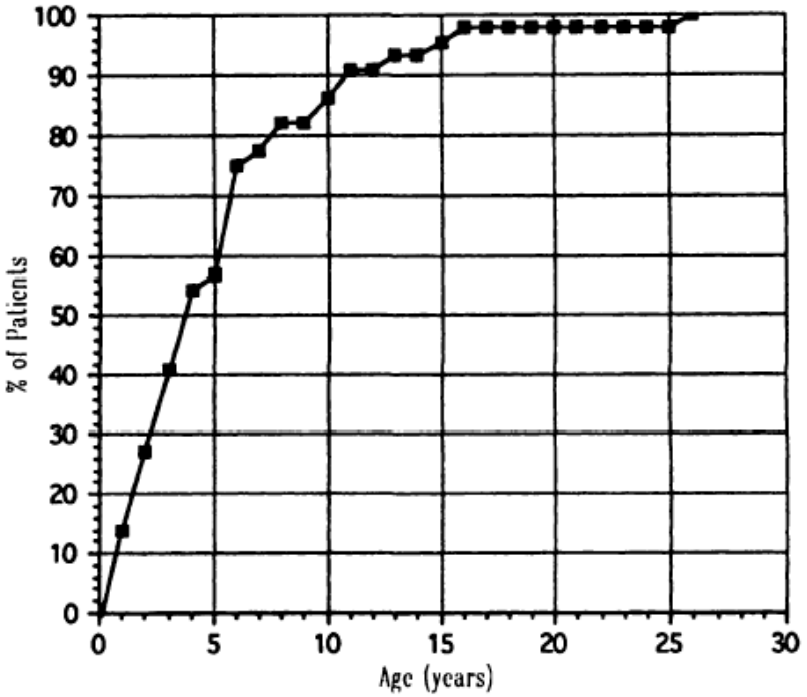
R375P mutation (1 patient)

Kaplan et al. 2009:

- Swellings at age 14 y
- Limited mobility at age 40 y
- No abnormalities of the great toes

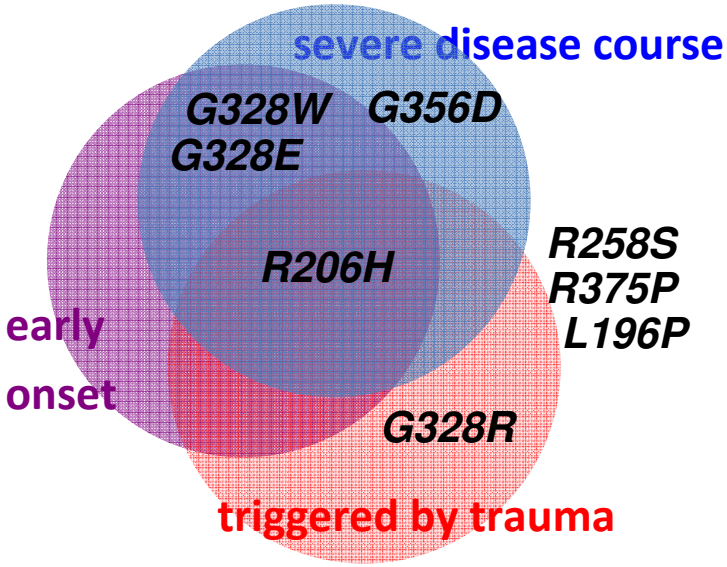
Summary

Ossifications



Summary

Ossifications



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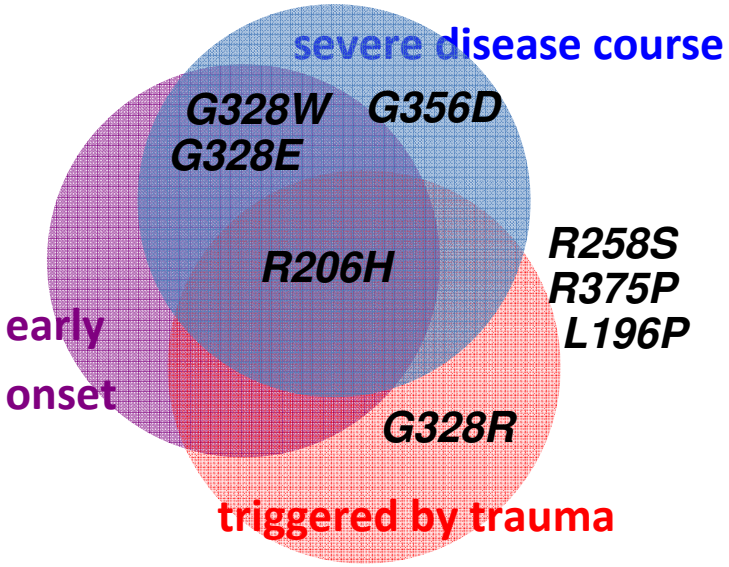
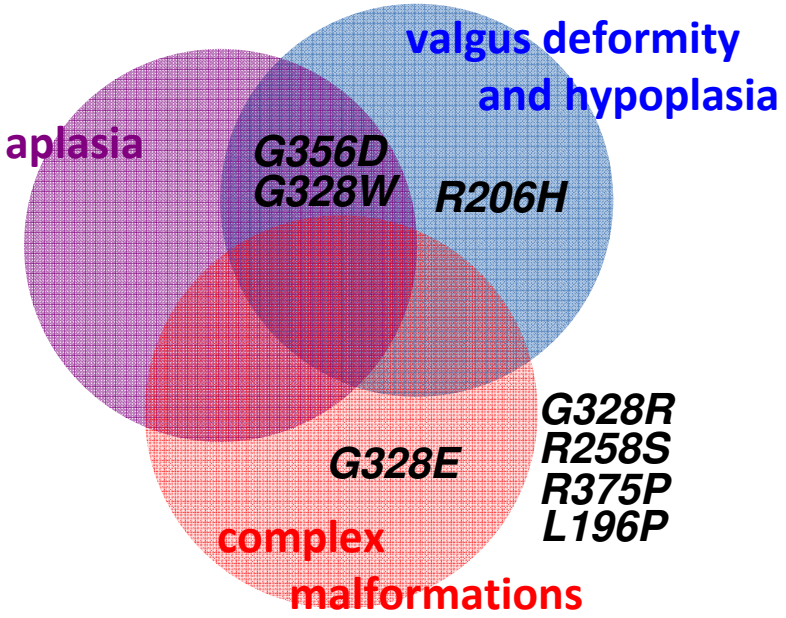


Maformations of the great toes



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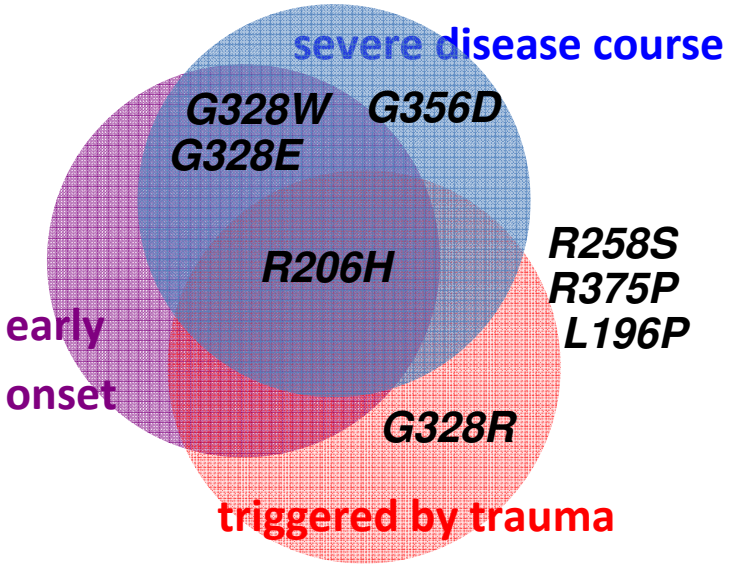

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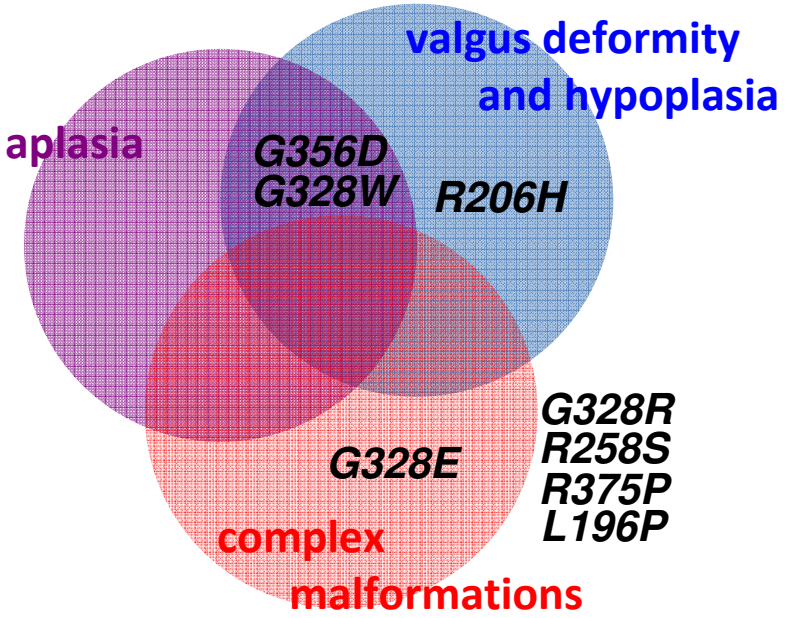


Ectodermal aspects: R206H, G328E, G328W, G356D(?)

Learning difficulties: G328E, G328W

Amenorrhoea: G328E, G356D

Thank you!

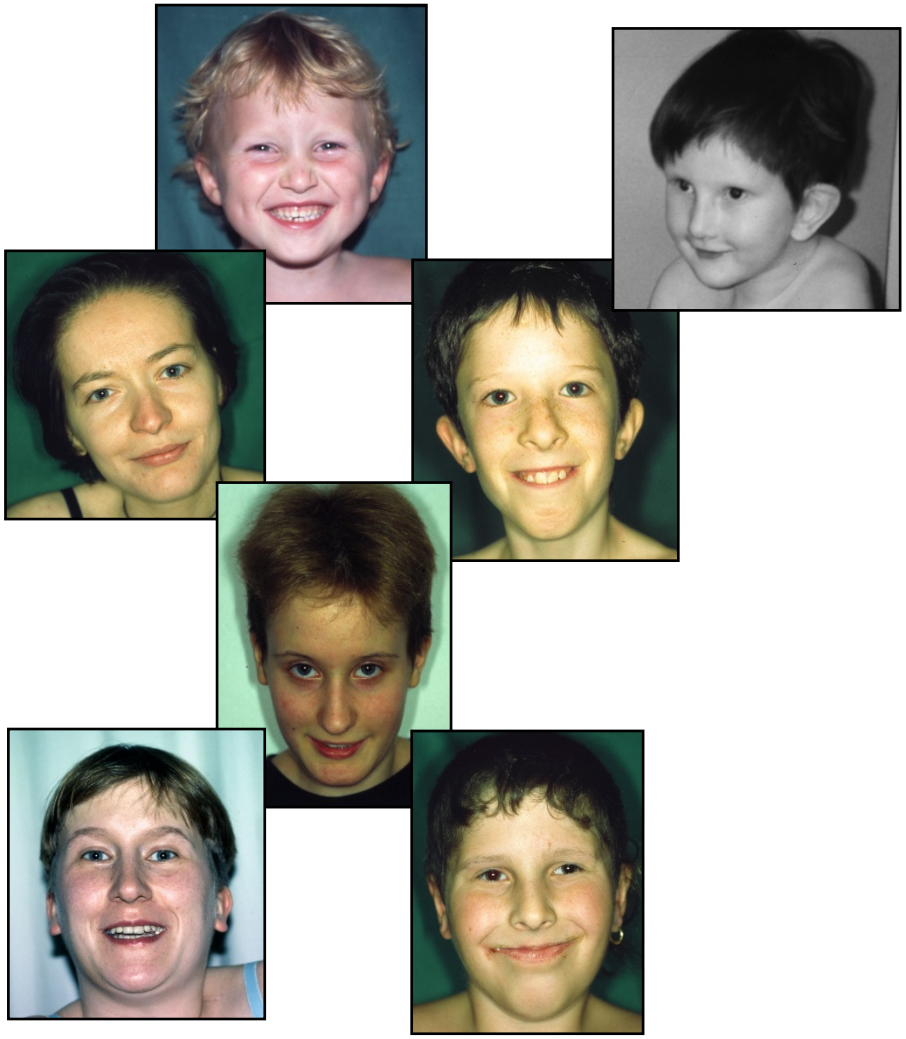
- Gabriele Gillessen-Kaesbach

  Institut für Humangenetik, Universität zu Lübeck
- Christian Grünberg

  Klinik für Orthopädie und Unfallchirurgie, Allg. Krankenhaus Hagen
- Stefan Mundlos

  Institut für Medizinische Genetik, Charité Berlin

Everyday life and medical care



Everyday life and medical care