Genetic mechanisms of development and disorders of locomotor system (skeleton)

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General Perspective

- clinically distinct
- genetically heterogeneous
- individually rare
- Neonatal lethality → mild growth retardation

Disorders of Skeletal Patterning

- The axial skeleton; the vertebrae and ribs
- the appendicular skeleton (the limb skeleton)
- the craniofacial skeleton

Skeletal Disorders

- isolated anomalies; ectrodactyly, brachydactyly, polydactyly, syndactyly, absence of radius etc.

Skeletal Disorders

- the component of the syndrome (multiple anomalies)
  - e.g.: Absence of radius or radial ray anomalies
    Fanconi anemia → The Fanconi anemia pathway
  - e.g.: Ectrodactyly

EEC syndrome (the dominant ectrodactyly, ectodermal dysplasia, and clefting syndrome)

Brachydactyly

Brachydactyly type B

- hypoplasia/aplasia of the distal phalanges and/or nails
- the thumb is usually unaffected
- heterozygot truncating mutations for ROR2
- Gain-of-function mutations

- homozygous loss-of-function → Robinow syndrome

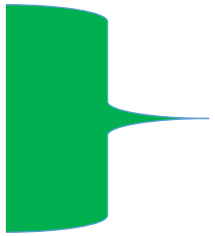
Syndactyly

- the fusion of certain fingers and/or toes
- isolated entity
- component of more than 300 syndromic anomalies
- inter- and intra-familial clinical variability
- unilateral or bilateral
- symmetrical or asymmetrical

non-syndromic syndactylies

Polydactyly Disorders

- Preaxial
- Postaxial



hedgehog pathway

Polydactyly

- Type I: Thumb duplication
- Type II: Triphalangeal thumb
- Type III: Extra Preaxial finger
- Type IV: Wide thumb

Polydactyly Disorders

- *GLI3* (the downstream effector of Shh and It has a zinc finger motif)
  - postaxial polydactyly type I
  - preaxial polydactyly type IV
  - *Greig* cephalopolysyndactyly
    - Hypertelorism
    - frontal bossing
    - Syndactyly
    - pre- or postaxial polysyndactyly
  - Pallister-Hall syndrome
    - malformations of the CNS
    - craniofacial abnormalities
    - syndactyly and polydactyly

FGF Receptors
Fibroblast Growth Factor Receptor

- Cell division, migration, differentiation
- Three main components: an extracellular region, a transmembrane segment and intracellular tyrosine kinase domains
- Mutations; two groups of developmental disorders
  - the craniosynostosis syndromes
  - Skeletal dysplasias

Developmental disorders caused by mutations in FGFRs

Reference: Emery's Elements of Medical Genetics, 15th ed. 2017

Gene	Chromosome	Syndrome
Craniosynostosis syndromes		
FGFR1	8p11	Pfeiffer
FGFR2	10q25	Apert Crouson Jackson-Weiss Pfeiffer
FGFR3	4p16	Crouson (+ akantozis nigrikans)
Skeletal dysplasias		
FGFR3	4p16	Achondroplasia Hypochondroplasia Thanatophoric dysplasia

Skeletal Dysplasias

Achondroplasia Group

- Thanatophoric dysplasia (perinatal lethal form)
- Achondroplasia
- Hypochondroplasia

Fibroblast Growth Factor Receptor 3 (FGFR3)

Achondroplasia

- Mutation; in transmembrane domain of *FGFR3*
- Gain-of function
- Ligand-independent activation
- Gly380Arg (1138G>A, 1138G >C) 98-99%

Achondroplasia

- Incidence;1/15.000-1/40.000
- Autosomal dominant
- Full penetrance
- De novo mutations (paternal age ↑) 80-90%
- Both partners are affected → a 25% risk for lethal homozygous achondroplasia

Skeletal Dysplasias

Type II Collagenopathies

- heterozygot mutations for *COL2A1*
- a heterogenous group of disorders
  - e.g.:Achondrogenesis II and hypochondrogenesis
    - large skulls
    - very small and short ribs
    - lack of mineralization of most vertebral bodies

Osteogenesis Imperfecta

- There are a large group of skeletal disorders that present with decreased bone density
  - E.g.: OI (brittle bone disease)
  - Type I (
  - Type II (perinatal lethal form)
  - Type III
  - Type IV

type I collagen production ↓ (Type I)

Changes of type I collagen structure (Type II, III and IV)

Osteogenesis Imperfecta

- Mutations (90%) → *COL1A1* and *COL1A2* genes
- Allelic heterogeneity (2000↑ different mutations)
- Incidence;1/15.000
- Two proα1(I) and one proα2(I) chains
- The triple helical (collagen) structure

Further reading

- Thompson&Thompson, Genetics in Medicine, eighth ed. 2016.
- Emery's Elements of Medical Genetics, 15th ed. 2017.