Hereditary Skin Disorders:

Potential Targets for Gene-Based Therapies

Obstacles to Translation Conference
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Issues

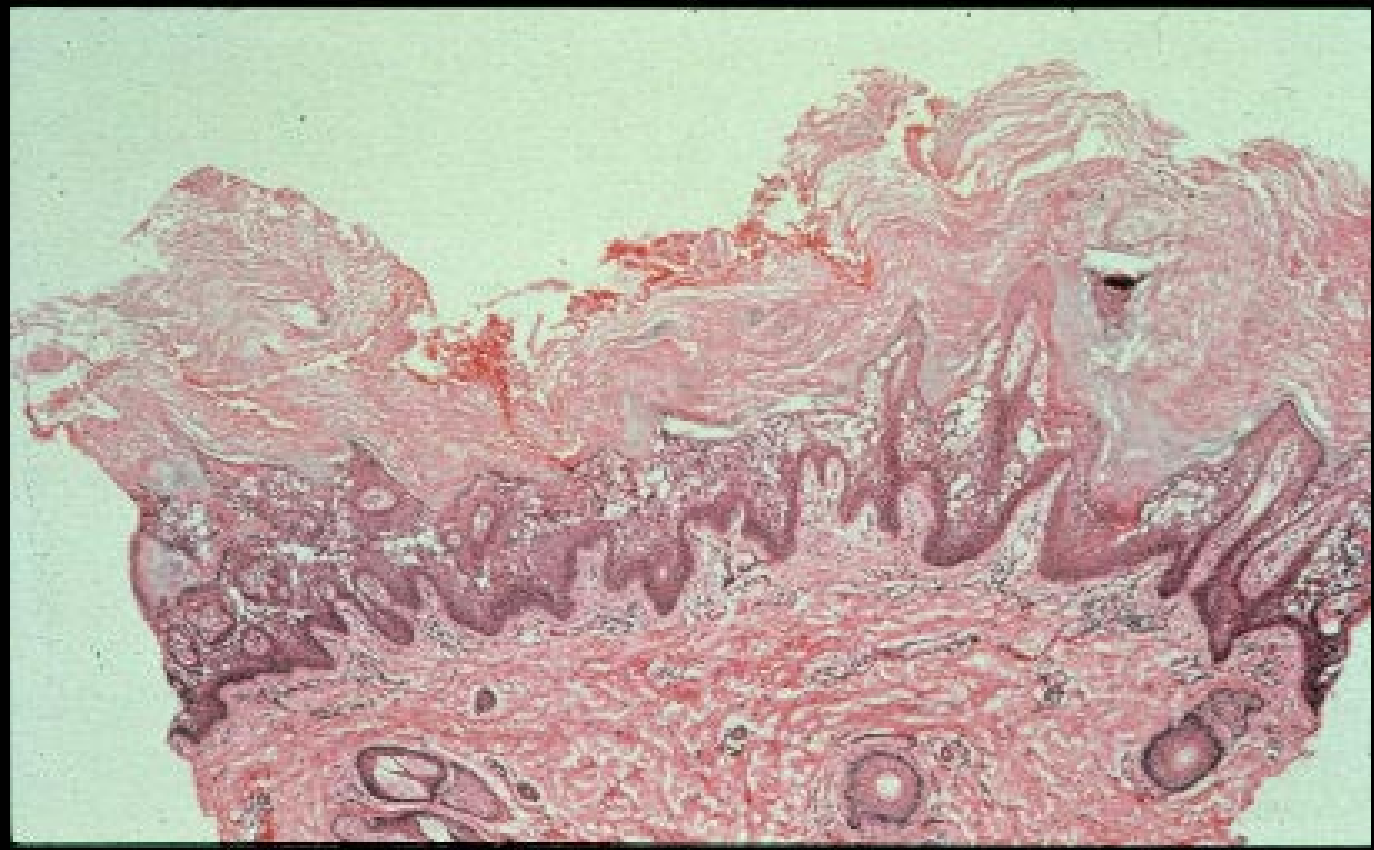
- Heterogeneity in inheritance pattern, clinical presentation
- Genetic Heterogeneity (different genes underlying same clinical phenotype)
- Genotype-Phenotype correlation
- Variability in age at onset
- Variability in gene product
- Variability in types of mutations

Disorders due to mutation in a Keratin Gene (s)

*Epidermolytic Hyperkeratosis	KRT1,10
*Epidermolysis Bullosa Simplex	KRT5,14
*Pachyonychia Congenita	KRT16,17,6A,6B
*Epidermolytic PPK of Vorner	KRT9
*Ichthyosis Bullosa of Siemens	KRT2E
Meesmann's corneal dystrophy	KRT3,12
White Sponge Nevus	KRT4,13

Epidermolytic Hyperkeratosis

Histology Epidermolysis involving supra-basal keratinocytes, Hyperkeratosis



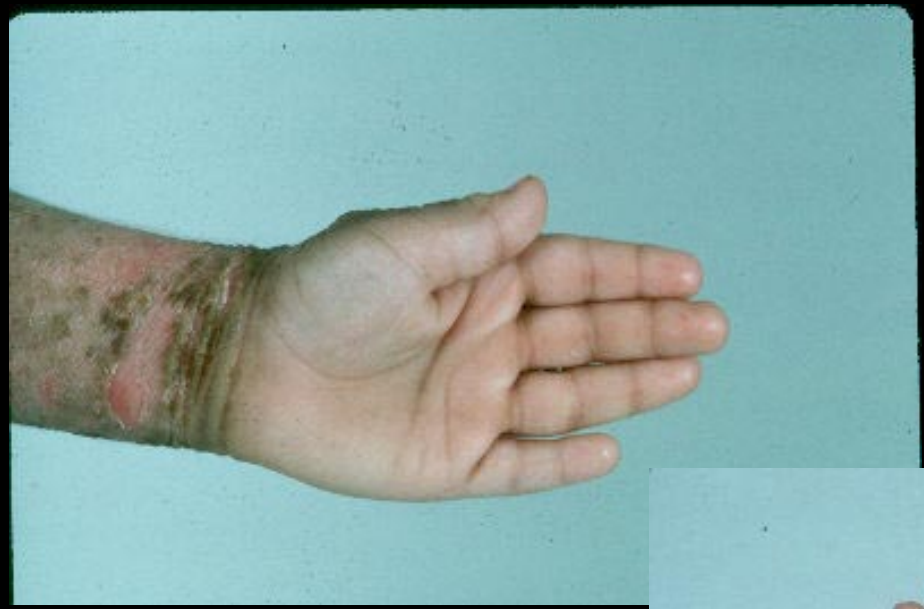
Epidermolytic Hyperkeratosis

- **Autosomal Dominant**

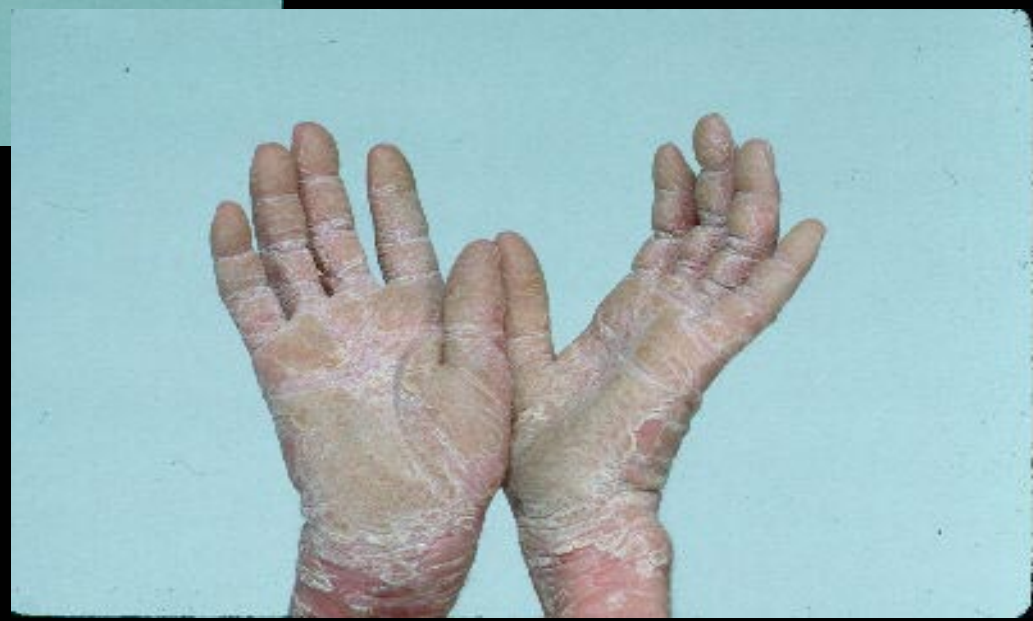
  (1/2 the cases are due to new mutations)

  – **Primary Features**
    - **Neonatal Blistering**
    - **Hyperkeratosis, especially of the flexures**
    - **Variable palm/sole involvement**
    - **Frequency, maybe 1:300,000?**

Genotype/Phenotype Correlation

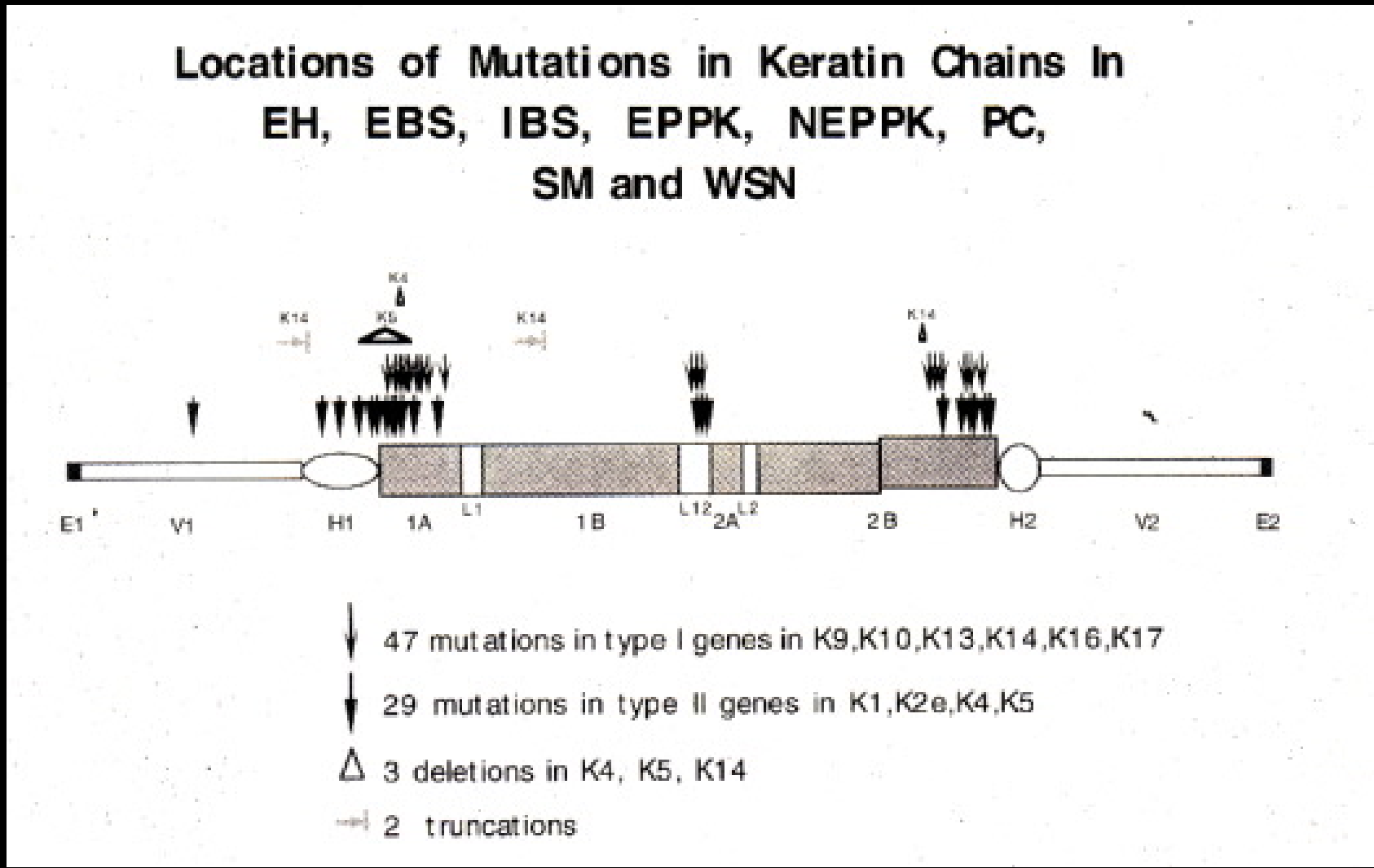


KRT 10 mutation



KRT 1 mutation

Mutation Distribution in KRT disorders



Lamellar Ichthyosis

- Autosomal Recessive
- Incidence 1:200,000
  - Primary Features:
    - Collodion baby phenotype
    - Plate-like, large, dark scale
    - Ectropion, Eclabium
    - Scarring alopecia

Lamellar Ichthyosis

- Genetic Heterogeneity, with vast majority of cases due to mutation in the **TGM1 gene**, coding for Transglutaminase-1

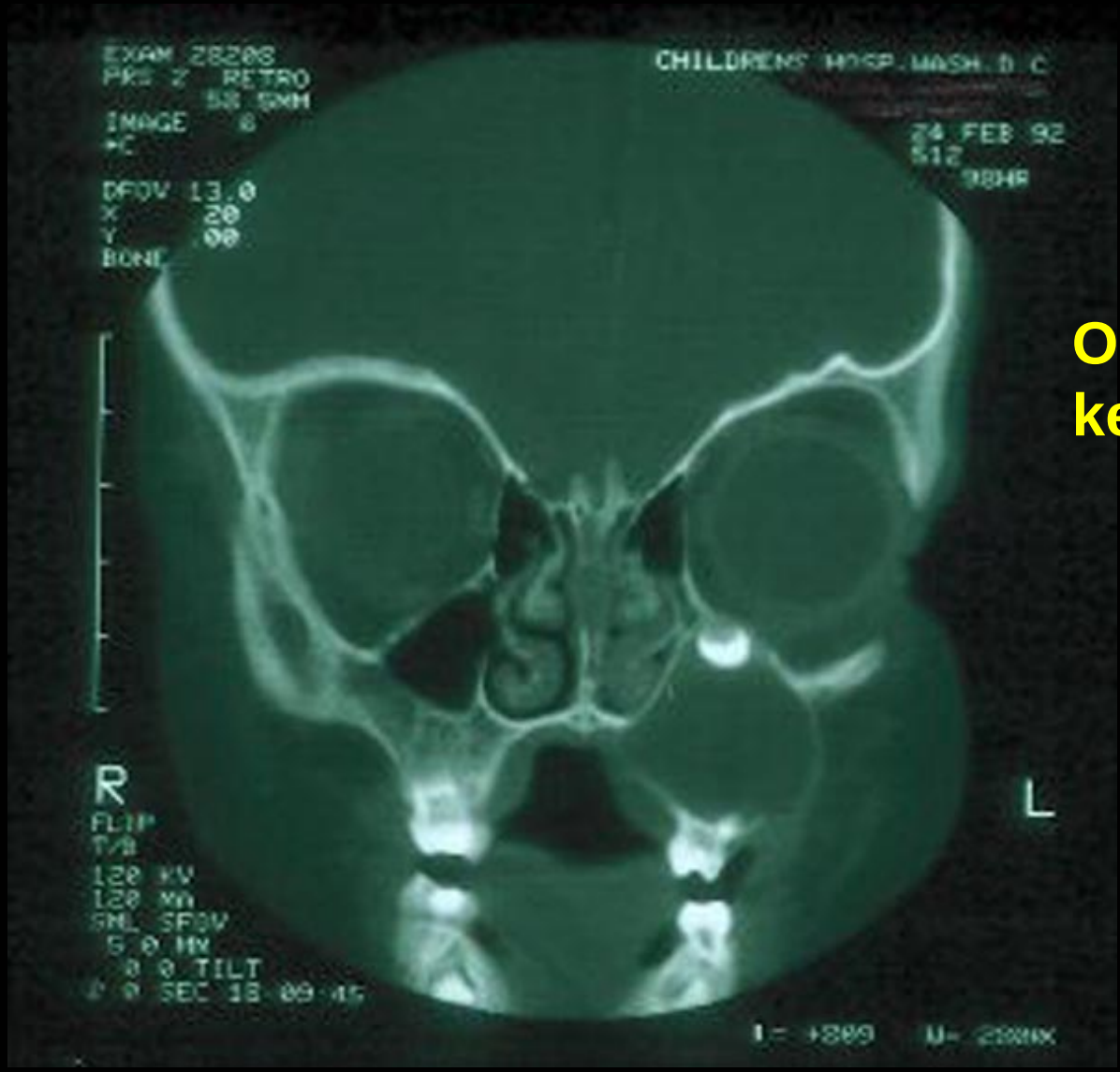
- Some "common" mutations:
  - IVS5-2 splice mutation (20% of disease alleles)
  - Arg141 and Arg142 in exon 3

- Other genes:
  - ALOX12B, ALOXE3 (erythrodermic phenotypes)
  - ABCA12
  - Ichthyin
  - Others

Nevoid Basal Cell Carcinoma Syndrome (Gorlin Syndrome)

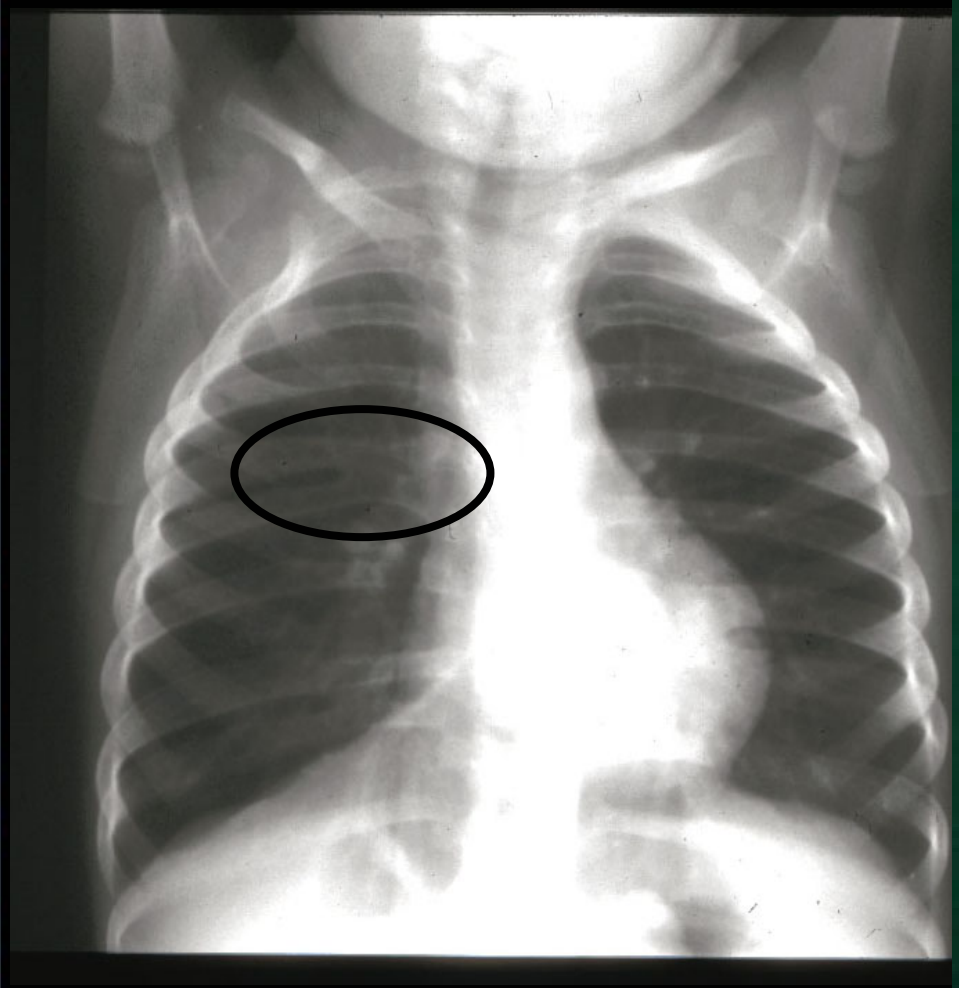
- Autosomal Dominant
  - Major Features:
    - Multiple basal cell carcinomas
    - Palmar and plantar pits
    - Jaw cysts
  - Minor Features:
    - Skeletal anomalies
    - Typical facies (CL/P in ~5%)
    - Medulloblastoma, ovarian fibroma
  - Frequency, ~1:100,000?

Gorlin Syndrome: Clinical Features

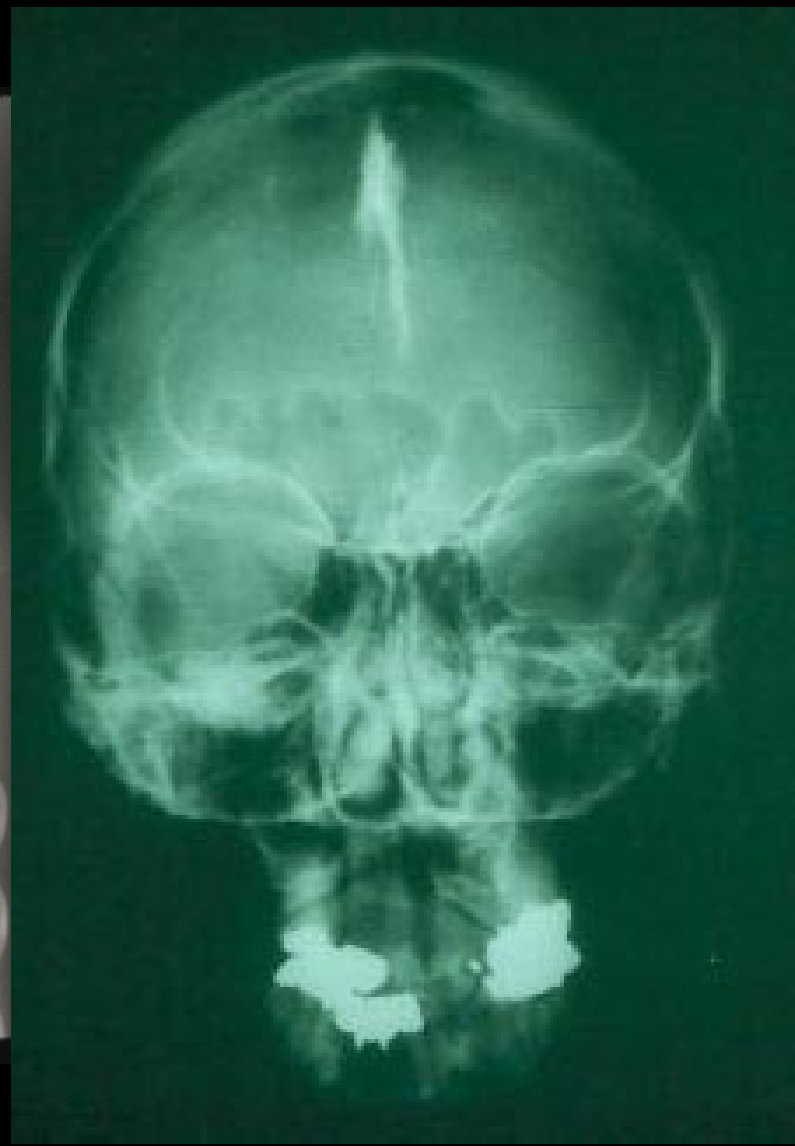


Odontogenic keratocysts

Gorlin Syndrome: Clinical Features



Rib anomalies



Ectopic Calcification: falx

Gorlin Syndrome: Molecular Basis

- Caused by mutation in the **PTCH gene**
  - Human homologue of Drosophila *patched*
  - PTCH protein is the receptor for the hedgehog (SHH) protein
  - Involved in the hedgehog signaling pathway
  - Regulates cell growth and differentiation

- Mutations are distributed throughout the gene
- Most mutations are “private”
- Vast majority result in premature truncation of the patched protein, or nonsense mediated mRNA decay

Ectodermal Dysplasia

- Congenital
- Not progressive
- Involves epidermis + at least one of:
  - Hair
  - Sebaceous glands
  - Nail
  - Teeth
  - Mucosa

Hypohidrotic ED (X-linked)

- Christ-Siemens-Tourraine Syndrome
  - Most common of the dozens of EDs
- Primary Features
  - Hypotrichosis, with fine, sparse hair
  - Hypo/Anhidrosis
  - Hypodontia, conical/pegged-shaped teeth
  - Periorbital hyperpigmentation, full lips, saddle nose
  - Carrier females may have some features

Hypohidrotic ED (X-linked)

- Due to mutation in the **EDA1 gene**, homologous to the *tabby* locus in mice
  - Mutations are of all types; a few "hot spots"
- Protein expressed in hair follicles and adult epidermis
- *Genetic Heterogeneity:*
  - There is an autosomal form due to mutation in the EDAR locus, homologous to the *downless* locus in mice. This form can be either recessive or dominant. It is clinically indistinguishable from the X-linked form, although much rarer.

Cartilage-Hair Hypoplasia

- **Autosomal Recessive**
  - **Disease of Finns and Old Order Amish**
  - **Incidence in Finland, 1:23,000**
  - **Also seen in other Caucasian ethnic groups**
- **Primary Clinical Characteristics**
  - **Short-limbed dwarfism**
  - **Ectodermal Dysplasia:** Hair (fine, sparse), Nails (dysplastic), Teeth (small, notched, doubling of lower premolar cusps)
  - **Immunodeficiency** (T-cell or combined B&T-cell; IgA, IgG2/IgG4 deficiency; neutropenia, lymphopenia; megaloblastic anemia)

Billy Barty

3’10” screen actor
Died at age 76 (cardiac)
Founded Little People of America in 1957
Founded the Billy Barty Foundation

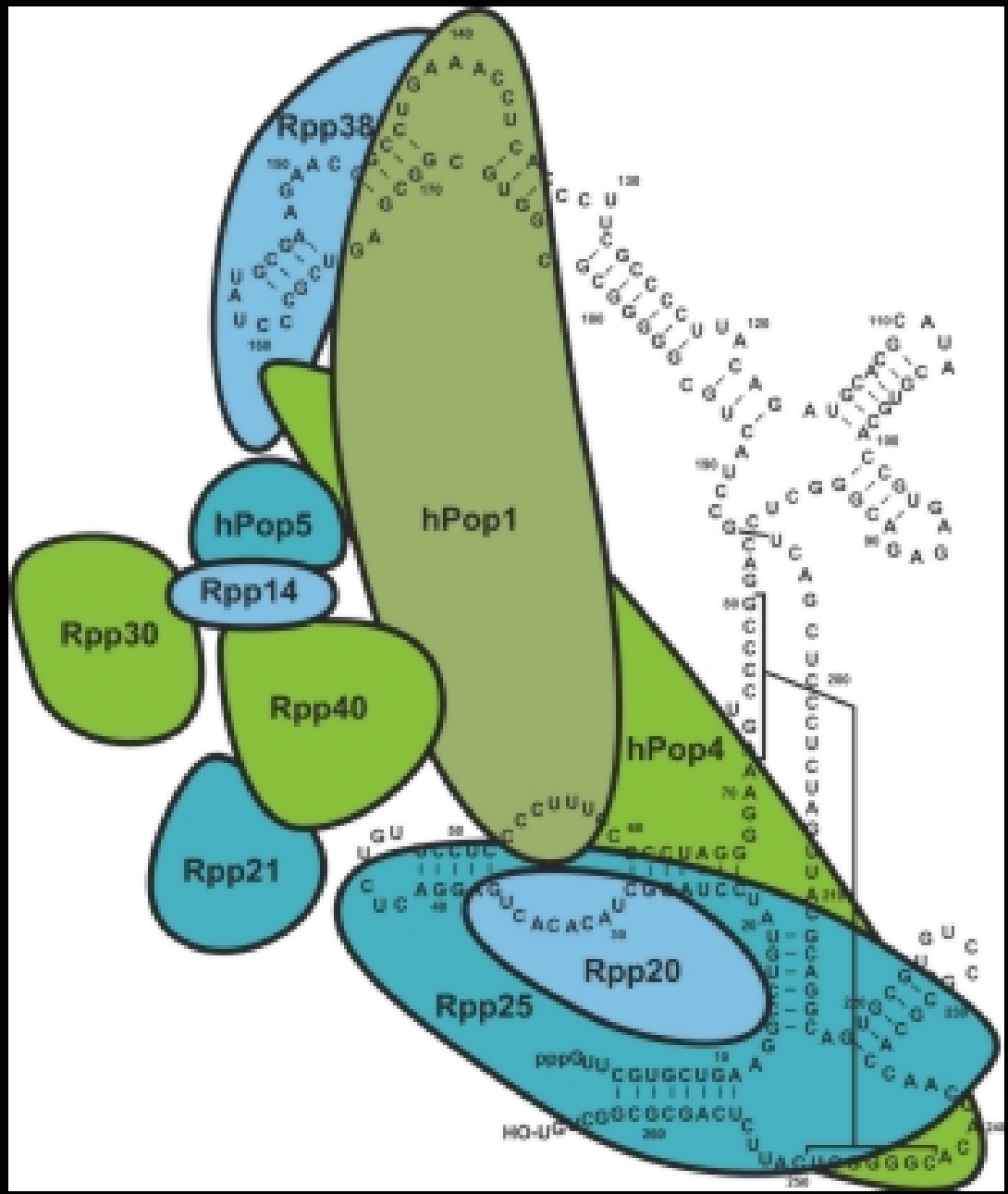
Film credits:
1930s Nothing Sacred
Alice in Wonderland
The Undead

TV:
HR Pufnstuf
Sigmund & the Sea Monsters

Cartilage-Hair Hypoplasia

- Mutation in the RMRP gene
  - Nuclear gene
  - Codes for the RNA component of ***R***ibonuclease (RNase) ***M***itochondrial ***R***NA ***P***rocessing (MRP) enzyme

RNase MRP Complex



Cartilage-Hair Hypoplasia

- Function of the RNase MRP complex
  - Active in both nucleus and mitochondria
    - Mitochondria – generation of RNA primers for mitochondrial DNA replication
    - Nucleolus – involved in processing of pre-rRNA
  - Possibly – functions in cell cycle regulation, particularly late stage. Cells defective in MRP function arrest in telophase and die.

Cartilage-Hair Hypoplasia: The RMRP Gene

- Untranslated (e.g. encodes an RNA, not a protein)
- Mutation distribution:
  - Finnish mutation, nt70 A→G
    - Arose ~4500 years ago
    - Detected in 1:120 Finnish controls
    - Contributes to 92% of mutations in Finnish patients
    - Accounts for 48% of CHH patients from elsewhere
  - >40 other mutations described

Issues

- Primary genodermatoses
  - Generalized (like lamellar ichthyosis, EHK)
  - Localized (like PC, EPPK)
  - *How to target the entire integument?*
- "Secondary" genodermatoses -- affecting multiple organ systems
  - CHH, X-linked HED, Gorlin Syndrome
  - *Selection of target for therapy?*
- Congenital genodermatoses vs. Delayed onset disorders
  - LI, EHK vs. Gorlin Syndrome
  - *When to treat?*
- Types of genes:
  - Structural proteins, Enzymes, RNAs
  - *No single answer to how to treat or deliver*