



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

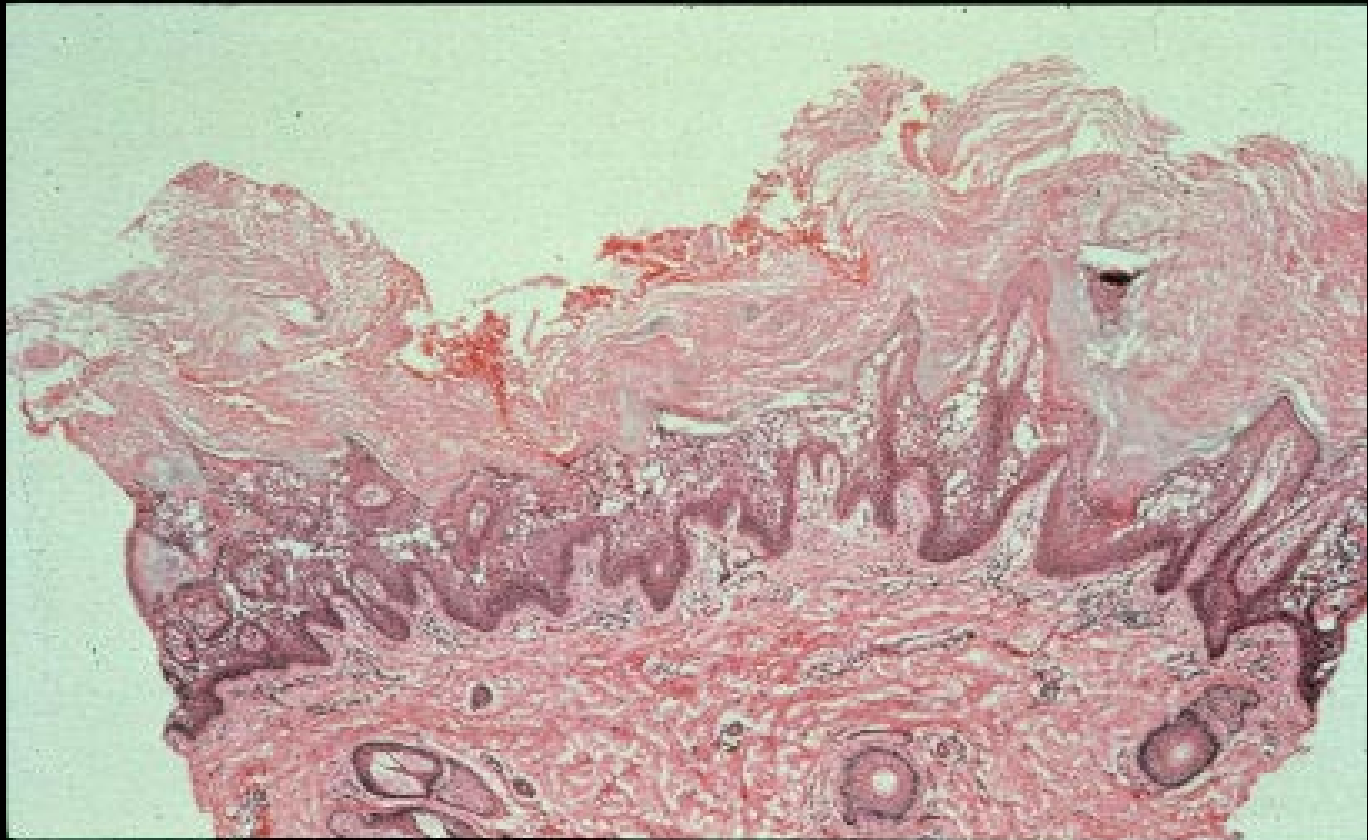
Disorders due to mutation in a Keratin Gene (s)

- *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



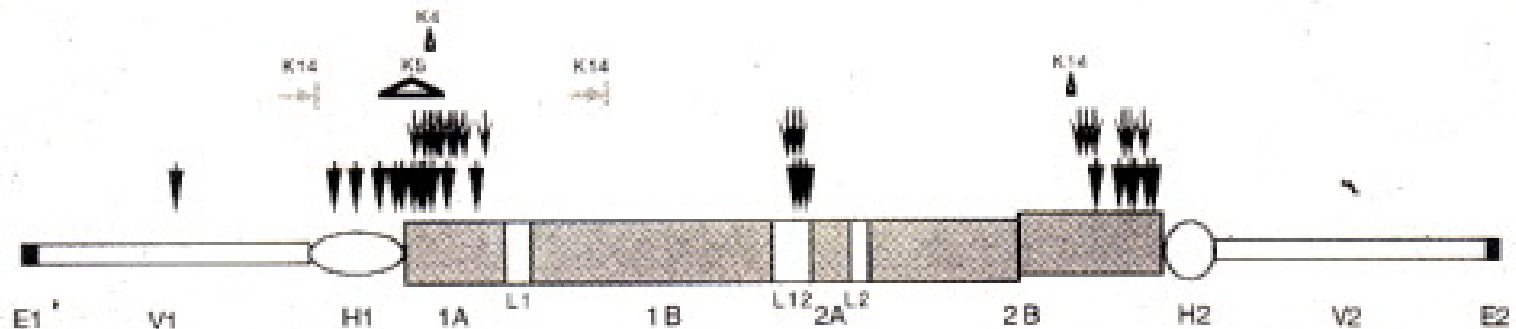
KRT 10 mutation



KRT 1 mutation

Mutation Distribution in KRT disorders

Locations of Mutations in Keratin Chains In
EH, EBS, IBS, EPPK, NEPPK, PC,
SM and WSN



- ↓ 47 mutations in type I genes in K9,K10,K13,K14,K16,K17
- ↓ 29 mutations in type II genes in K1,K2e,K4,K5
- △ 3 deletions in K4, K5, K14
- 2 truncations



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)

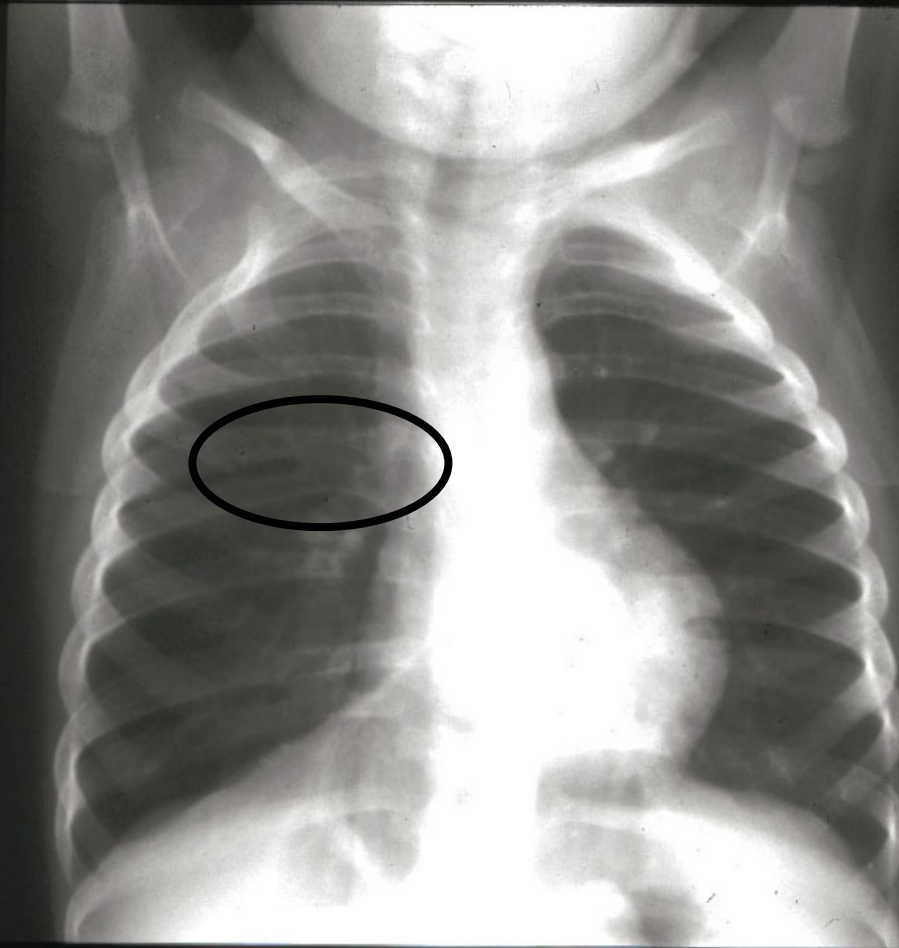
- **Autosomal Dominant**
 - **Major Features:**
 - Multiple basal cell carcinomas
 - Palmar and plantar pits
 - Jaw cysts
 - **Minor Features:**
 - Skeletal anomalies
 - Typical facies (CL/P in ~5%)
 - Medulloblastoma, ovarian fibroma
 - **Frequency, ~1:100,000?**

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:

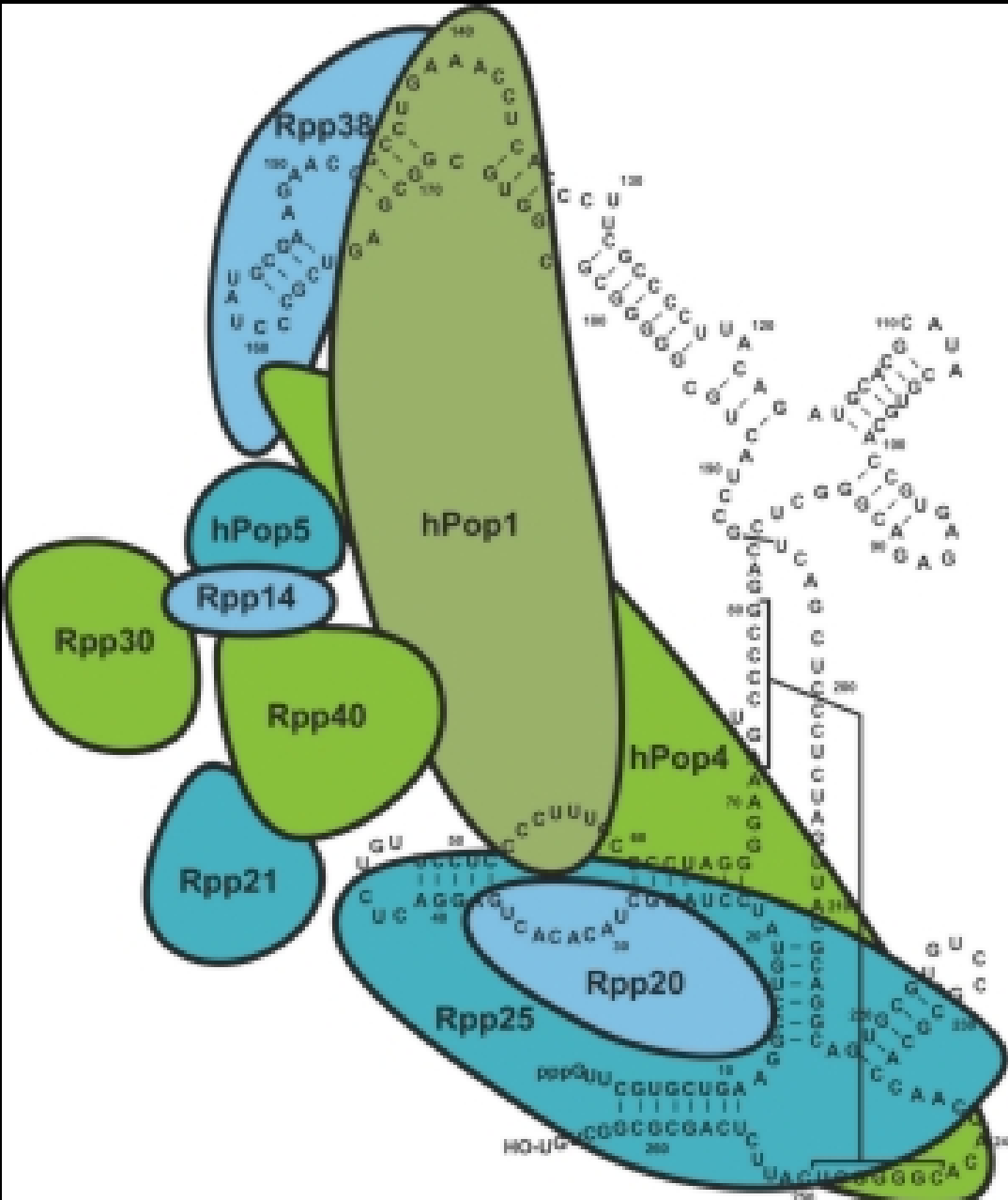
HR Pufnstuf

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*