Syndromic and nonsyndromic ichthyoses: What’s new?

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2010: Classification of Ichthyoses

• Largely based on clinical features and genetic basis

• Most important changes:
  – Keratinopathic as new category with $KRT1/KRT10$ (epidermolytic, Curth-Macklin, ichthyosis en confetti) and $KRT2$ (superficial epidermolytic) gene mutations
  – Lamellar and CIE as clinical manifestations within the Autosomal Recessive Congenital Ichthyosis (ARCI) spectrum; harlequin a severe form of CIE (at least 10 underlying gene defects with $TGM1$ most common and usually LI)
  – Syndromic vs nonsyndromic

Oji et al. JAAD 2010; 63:607
What’s happened since 2010?

• Careful clinical observation of scaling to help distinguish among subtypes
  – Most common:
    • Nonsyndromic: Ichthyosis vulgaris, ARCI (autosomal recessive congenital ichthyosis), epidermolytic ichthyosis
    • Nonsyndromic or syndromic: Recessive X-linked ichthyosis
    • Syndromic: Netherton

• Use of new technology to discover new subtypes of ichthyosis

• Immunophenotyping to understand the clinical phenotype that characterizes the ichthyosis: new therapeutic directions
Nonsyndromic Ichthyosis vulgaris

- Recognized to be related to having 1 or 2 alleles with FLG mutation in 2006
  - Minority of Blacks with ichthyosis vulgaris have a FLG mutation: cause of IV undefined
- Semi-dominant, not autosomal dominant
- Most common (up to 1:10 of individuals)
- Strong association with AD

Smith et al. Nat Genet. 2006;38:337
Tips on Ichthyosis vulgaris

- If present at birth, it is not Ichthyosis vulgaris!
- Manifestation depends on climate/humidity
- Bran-like, adherent scales most prominent on lower legs
- Usually mild palmoplantar keratoderma defined by hyperlinearity
Scales of Ichthyosis vulgaris
Tips for epidermolytic ichthyosis

• Most commonly misdiagnosed as a blistering disorder at birth (esp EB vs staph scalded skin) – may be erythematous and tender

• Hyperkeratosis, scaling in first few months; often subtle and on elbows, knees at first
Progressive development of “verrucous” scales, particularly at flexural areas

More severe palmoplantar thickening is clue to KRT1 mutations (*KRT9* compensates for *KRT10*)
Berber carpeting
Collodion Baby

- Thick “collodion” membrane but poor barrier: needs emollient
- Careful observation for first week (water and electrolyte loss, temperature instability, infection)
- Sheds during first month
- 65% of collodion babies reveal ARCI phenotype after shedding
- Cannot distinguish outcome of babies with collodion phenotype
The spectrum of ARCI

- Severe lamellar
- CIE
- Harlequin

Usually \textit{TGM1}

Scaling

Erythema
Lamellar ichthyosis

- Mildest forms can be hard to distinguish from RXLI
- Larger lamellar plates typical

Dermoscopy
Nonbullous congenital ichthyosiform erythroderma (CIE)

- More prominent erythroderma
- Fine white scales on face, scalp, and trunk, although sometime larger (platelike) scales overlying redness
Harlequin ichthyosis
Is this CIE?

What are these white spots?

Hyperkeratotic plaques on the knee

Ichthyosis with confetti

Father

Daughter

KRT10 mutation and revertant mosaicism
Onset by age 3 and progressive; widespread
KRT1: onset ~20 y/o
C-terminal frameshift mutations to correct

Choate et al. Science 2010;330:94; Choate et al. JCI 2015;125:1703
Whole exome sequencing

• Exome includes ~1% of genome but 90% of the pathogenic mutations

• WES costs 10% of WGS ~ $500

• Unbiased approach to discovery
  - Simultaneous analysis of all candidate genes and others
  - Low frequency mutations in known genes
  - Mutations in newly associated genes, incl. regulator genes

Genotyping: Faster and less costly
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- Ichthyosis
  - Ichthyosis gene screen: targeted amplification and high throughput sequencing for 48 genes
  - Cost: $50 per patient (Yale)
Use of WES for gene discovery

750 kindreds with ichthyosis
15% without a known genetic mutation: WES for gene discovery

Courtesy of Dr. K. Choate
X-linked recessive ichthyosis

- X-linked: 1:1500 males (carriers escape X-chromosome inactivation)
- Commonly suspected prenatally based on high levels of maternal estriol and FISH analysis/microarrays
- Usually deletion in ARSC1, encodes arylsulfatase C = steroid sulfatase; placental deficiency leads to failure to progress at delivery
- Accumulated cholesterol sulfate inhibits normal degradation of stratum corneum desmosomes and leads to corneocyte retention
Tips for recessive X-linked ichthyosis

- Begins in 1st 3 months; ~17% with scaling at birth
- Small to large, brown scale
- Often accentuation on neck (“dirty neck”), abdomen, back, legs, feet
- Typical sparing of flexurals
- Nonsyndromic if skin only
- Syndromic if other features (undescended testes to contiguous gene deletions: e.g., retardation, anosmia)
Tips for Netherton syndrome

• Premature delivery; early erythroderma; issues with hyponatremic dehydration and failure to thrive may early clue to diagnosis

• May be misdiagnosed as atopic dermatitis
  – Itchy skin; often erythrodermic
  – Can have associated food and other allergies
Tips for Netherton syndrome

- Associated fragile hair, including of eyebrows, can be clue: may need many hairs to find the characteristic trichorrhexis invaginata
Tips on Netherton syndrome

- Some retain erythroderma throughout adulthood
• Some retain erythroderma
• Others progress to the ichthyosis linearis circumflexa pattern (migratory, peripheral double-edged scale), especially after 2 y/o
The ichthyoses

- Despite knowing causative DNA mutations, no pathogenesis-based therapy available
- Treatment largely peeling agents for scaling and retinoids

- How do these DNA and protein changes translate into inflammation and scaling?

Is there a shared immune phenotype among these types of ichthyosis that could amenable to targeted therapy?
Strong Th17 skewing

Paller et al. JACI 2017;139:152
Why is the IL-17 pathway expression so high in ichthyoses?

• Merely a response to increase the antimicrobial innate immune defense in the face of epidermal barrier impairment?

• Does the IL-17 skewing drive the inflammation of ichthyosis, as for psoriasis?

Paller et al. JACI 2017;139:152
Why is the IL-17 pathway expression so high in ichthyoses?

- Trial of secukinumab in adults with ichthyosis (LI, CIE, EI, NS)
  - Test therapeutic relevance
  - Increase understanding of the role of inflammation in ichthyosis

- If successful, will advance therapeutic approach to affected children with ichthyosis

Trial sites: Chicago and NY (Mt Sinai) – have any eligible patient email me at apaller@northeastern.edu
In summary....

- The extent of erythema, severity of scaling, and morphology of scales help us to classify ichthyoses among the various syndromic and nonsyndromic forms.

- New technology has dramatically altered our ability to genotype patients, including discovery of new genes associated with ichthyosis.

- Immunophenotyping has shown a shared pattern of Th17/IL23 skewing, suggesting that we may repurpose targeted therapy for psoriasis towards ichthyosis.

  - Please feel free to provide my email to patients with ichthyosis who might benefit: apaller@northwestern.edu