Genetic Testing of the ALOX12B, ALOXE3, NIPAL4 (ICHTHYIN), and CYP4F22 Genes in Autosomal Recessive Congenital Ichthyosis (ARCI)

Clinical Features:
Autosomal recessive congenital ichthyoses (ARCI) form a heterogeneous group of disorders characterized by generalized scaling and variable degree of redness of the skin. ARCI manifests at birth or infancy, generally without primary involvement of other organ systems (non-syndromic). The skin features of ARCI may overlap considerably with various types of syndromic ichthyoses (see our website www.genedx.com for information on other types of ichthyoses). Most neonates with ARCI present as collodion babies with a taut, translucent or opaque membrane that encases the entire body and lasts for days to two weeks. In severe cases, ectropion, eclabium, and scarring alopecia of the scalp and eyebrows may be present. After shedding the collodion membrane, the presentation and severity of ARCI between individuals can vary significantly.

The 3 major types of non-syndromic ichthyoses include Harlequin ichthyosis (HI), lamellar ichthyosis (LI) and congenital ichthyosiform erythroderma (CIE). At one end of the spectrum is severe ‘classic’ lamellar ichthyosis (LI), which is characterized by large, dark brown, plate-like scale without underlying erythroderma. At the other end is severe ‘classic’ CIE, with fine, whitish scale and intense redness (erythroderma) of the skin. The clinical features of CIE can be milder than in LI and demonstrate a greater variability in the intensity of redness, scale, and involvement of palms and soles. However, CIE may cause substantial metabolic stress in young children and growth delay. There are also cases of (almost) complete resolution of the skin disorder, so-called ‘self-healing collodion ichthyosis’.

Distinguishing between these disorders on clinical grounds can be useful for clarifying prognosis and management and, to some extent, to choose which genes to analyze. A skin biopsy is not necessary to establish the diagnosis of ARCI and is usually not helpful in differentiating among the different clinical disorders along the spectrum. However, a skin biopsy is useful to differentiate ARCI from the bullous forms of ichthyosis (epidermolytic ichthyosis, also known as epidermolytic hyperkeratosis).

Genetics:
Harlequin ichthyosis is the most severe form of ARCI. Pathogenic variants in the ABC transporter gene ABCA12 account for approximately 95% of cases of HI and are also responsible for a rare form of lamellar ichthyosis seen in Northern Africa.
Lamellar ichthyosis is the most common presentation of ARCI. Pathogenic variants in TGM1 account for approximately 32-55% of all ARCI cases.

Congenital ichthyosiform erythroderma (non-bullous) is due to pathogenic variants in the ALOXE3, ALOX12B, and NIPAL4 (aka ICHTHYIN) genes. Patients with lamellar ichthyosis, hyperlinearity of the palms and soles, and no colloidion membrane at birth (LI type 3) have been found to harbor variants in the CYP4F22 gene. The genes ALOX12B and ALOXE3 encode the lipid processing enzymes 12R-LOX and eLOX, respectively. They both function in the 12(R)-lipoxygenase pathway, which is crucial for formation of the epidermal lipid barrier. While 12R-LOX is responsible for generating fatty acid hydroperoxide, eLOX functions as hydroperoxide isomerase to generate epoxy alcohols. Pathogenic variants in the epidermal ALOX genes are predicted to interfere with the normal structure and/or function of these enzymes, thus disturbing the skin barrier. The precise function of the protein product of NIPAL4 (ICHTHYIN) is currently unknown. CYP4F22 encodes a member of the CYP superfamily of heme-thiolate enzymes, which is thought to play a role in the 12(R) lipoxygenase (hepoxilin) pathway involved in arachidonic acid metabolism and eicosanoid synthesis.

Test Methods: (12 pt bold)
Bi-directional DNA sequencing of the ABCA12, TGM1, ALOX12B (exons 1-15), ALOXE3 (exons 1-15), NIPAL4 (ICHTHYIN) (exons 1-6), and CYP4F22 (exons 1-12) genes are offered as separate tests. In most cases of ARCI, TGM1 variants should be ruled out first (see separate info sheet). Then the clinical phenotype should dictate the order of other gene tests (see Table below).

Test Sensitivity:

<table>
<thead>
<tr>
<th>Gene</th>
<th>Sensitivity</th>
<th>Phenotype and Distinguishing Features</th>
<th>Geographic region</th>
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<tbody>
<tr>
<td>TGM1[^6,^7,^8]</td>
<td>32-55% of all ARCI; &gt;90% of severe LI</td>
<td>Colloidion membrane; CIE; mild to severe LI</td>
<td>Pan-ethnic</td>
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<tr>
<td>ABCA12[^6]</td>
<td>5% of all ARCI; &gt;95% of Harlequin ichthyosis</td>
<td>Most severe form of ichthyosis; ‘Harlequin baby’ presentation at birth</td>
<td>Pan-ethnic</td>
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<tr>
<td>ALOX12B[^1,^2,^6,^7]</td>
<td>12% of all ARCI; 7% of TGM1 negative patients</td>
<td>CIE; often colloidion membrane; mild LI; keratoderma present</td>
<td>Europe, India, Mediterranean</td>
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<tr>
<td>ALOXE3[^1,^2,^6,^7]</td>
<td>5% of all ARCI; 7% of TGM1 negative patients</td>
<td>CIE; often colloidion membrane; mild LI; keratoderma absent</td>
<td>Europe, India, Mediterranean</td>
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<tr>
<td><strong>NIPAL4</strong> <em>(ICHTHYIN)</em>[^3,4,6]</td>
<td>Up to 16% of all ARCI in one study, likely less in other populations</td>
<td>CIE; +/- collodion membrane; +/- LI; specific electron microscopy features (EM type III: abnormal lamellar bodies, elongated membranes in stratum granulosum)</td>
<td>Norway, Sweden, Mediterranean, South American</td>
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<td><strong>CYP4F22</strong>[^5,6]</td>
<td>Uncommon; in one study up to 8% of all ARCI</td>
<td>No collodion membrane at birth; erythroderma with hyperlinearity of palms/soles</td>
<td>Mediterranean families</td>
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References: