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Autosomal Recessive Congenital Ichthyosis

Gabriele Richard, MD, FACMG[1]

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Summary

The purpose of this overview is to increase the awareness of clinicians regarding autosomal recessive congenital ichthyosis (ARCI), related genetic counseling issues, and management.

The following are the goals of this overview.

Goal 1

Briefly describe the clinical characteristics of ARCI.

Goal 2

Review the genetic causes of ARCI.

Goal 3

Review the differential diagnosis of ARCI with a focus on genetic conditions.

Goal 4

Provide an evaluation strategy to identify the genetic cause of ARCI in a proband (when possible).

Goal 5

Inform genetic counseling of family members of an individual with ARCI.

Goal 6

Review management of ARCI.

Author Affiliation: 1 Medical Director, GeneDx, Inc, Gaithersburg, Maryland; Email: grichard@genedx.com.

1. Clinical Characteristics of Autosomal Recessive Congenital Ichthyosis

Autosomal recessive congenital ichthyoses (ARCI) are lifelong skin disorders with generalized scaling and variable erythema that typically manifest at birth or early infancy. ARCI encompass several forms of nonsyndromic ichthyosis, which vary significantly in clinical presentation and severity, including the most severe and sometimes fatal form, harlequin ichthyosis; lamellar ichthyosis (LI); (nonbullous) congenital ichthyosiform erythroderma (CIE); and intermediate phenotypes with variable degrees of erythema and size and quality of scale. While these phenotypes fall on a continuum, the phenotypic descriptions are clinically useful for clarifying prognosis and management for affected individuals.

Presentation at Birth

Children with ARCI are often born prematurely encased in a **collodion membrane**, a taut, shiny, transparent membrane formed by the thickened cornified layers of the skin, resembling plastic wrap. They can experience high levels of transepidermal water loss with resultant dehydration and hypernatremia. They are at increased risk for skin infections and sepsis during the neonatal period. Tautness of collodion membrane often leads to ectropion, eclabium, and underdeveloped nasal and auricular cartilage. Impaired sucking and pulmonary ventilation may lead to dehydration, malnutrition, hypoxia, and pneumonia. Gradually, within two to four weeks, the collodion membrane dries and peels off, transitioning to generalized scaling and erythema characteristic of the underlying form of ARCI, predominantly LI and CIE.

In the rarest form of ARCI, **harlequin ichthyosis**, babies are born prematurely covered in thick, hard, armor-like plates of cornified skin separated by deep fissures. The taut skin results in deformation of facial features, microcephaly, lack of eyelashes and eyebrows, and sometimes alopecia. Circular bands of hardened skin can lead to vascular constriction, ischemia, and distal edema with a mitten-like casing of hands and feet. Babies are at risk for life-threatening complications in the neonatal and postnatal period, including respiratory insufficiency, dehydration, electrolyte imbalance, temperature instability, feeding issues, bacterial infections, and sepsis, potentially with fatal consequences. A survival rate of 56% has been reported, although that is expected to further increase with improved neonatal intensive care and treatment options, such as early topical and/or systemic retinoids [Ahmed & O'Toole 2014, Glick et al 2017].

Babies with **ichthyosis-prematurity syndrome** (IPS) are born prematurely between 29 and 35 weeks' gestation. Polyhydramnios is common, and fetal ultrasound may reveal echogenic sediment in the amniotic fluid. The skin at birth is erythrodermic, swollen, and massively thickened with a vernix-like appearance. The most severely affected skin is the scalp, often with cobblestone-like hyperkeratosis. Neonates suffer from severe, sometimes fatal asphyxia due to reduced lung function from intrauterine amniotic fluid aspiration. They have poor Apgar scores and require intensive care and prolonged hospitalization. Nevertheless, the prognosis of IPS is generally excellent. After a few days, the skin sheds and improves significantly, regressing to a mild ichthyosis with underlying erythema that eventually resolves [Khnykin et al 2012].

Postnatal Features

Lamellar ichthyosis (LI). LI Typically presents at birth with a collodion membrane, which is replaced by large, whitish, and later brown, plate-like scales in a generalized distribution. Erythroderma (generalized redness of the skin) may be present but is usually mild and not a predominant feature. Other frequent findings are ectropion, eclabium, and scarring alopecia involving the scalp and eyebrows. Built-up scale leads to sweat duct constriction and severe heat intolerance. Accumulation of scale in the external ear canals can lead to occlusion, bacterial colonization, and recurrent infections. Thickening and fissuring of the skin on palms and soles (palmoplantar

keratoderma) and curved nails are common. Whole-body scaling and other associated features persist throughout life.

Congenital ichthyosiform erythroderma (CIE). At birth, more than 90% of infants with CIE present with a collodion membrane, which gives way to prominent generalized erythroderma and fine, white, semiadherent scales. Palms and soles are often severely thickened (palmoplantar keratoderma), with painful fissures and digital contractures. Ectropion, eclabium, scalp involvement, and loss of eyebrows can occur, although less frequently than in LI. Severe exfoliative erythroderma causes significant metabolic stress through very high caloric loss from inflammation and scaling of the skin, often leading to poor weight gain and growth deficiency if the caloric needs cannot be adequately met [Moskowitz et al 2004]. Similar to LI, scaling, hypohidrosis, and heat intolerance may persist lifelong.

Intermediate and rare phenotypes. Many affected individuals with ARCI fall between the LI-CIE spectrum and may be classified as having mild LI or mild CIE, or have overlapping, variable features. In a rare form of congenital ichthyosis, skin involvement may be limited to the trunk and scalp ("bathing suit ichthyosis") due to a temperature-sensitive effect [Marukian et al 2017].

In about 10% of babies with a collodion membrane, a milder "self-healing" phenotype known as "self-improving collodion ichthyosis" occurs [Traupe et al 2014]. Residual skin findings after infancy include generalized dry skin (xerosis), mild or focal scaling, hyperlinear palms, red cheeks, or anhidrosis [Raghunath et al 2003, Vahlquist et al 2010]. Individuals with ARCI born with erythroderma but mostly without collodion membrane who later develop generalized LI and hyperlinear palms and soles have been reported as having LI type 3 [Lefèvre et al 2006].

Harlequin ichthyosis is the most severe form of ARCI. Morbidity and mortality in neonates are high, which can be improved by intensive neonatal care and oral/topical retinoid therapy. However, harlequin ichthyosis remains a serious and chronic skin disorder throughout life. Surviving children gradually shed the armor-like skin plates and develop generalized scaling and intense redness and inflammation of the skin (erythroderma), with a very severe CIE phenotype. Significant growth delay, hypohidrosis and anhidrosis, heat intolerance, and vitamin D deficiency are common. Other features include ocular issues related to persistent severe ectropion, alopecia, palmoplantar keratoderma with painful fissures and digital contractures, chronic constipation, anemia, arthralgia or arthritis, and joint contractures [Ahmed & O'Toole 2014].

Skin cancer. Atypical melanocytic nevi, malignant melanoma, squamous cell carcinoma, and basal cell carcinoma have been reported [Fernandes et al 2010, Natsuga et al 2011]. Albeit the true incidence of skin malignancies among individuals with ARCI has not been established, several case reports indicate that adults with ARCI are at increased risk to develop multiple squamous cell carcinoma and basal cell carcinoma at an unusually young age (between age 25 and 51 years). Other skin malignancies, such as malignant melanoma, malignant fibrous histiocytoma, and cutaneous lymphoma, were rarely observed.

Skin biopsy

- Histologic findings in ARCI are mostly nonspecific, showing epidermal hyperplasia and ortho-hyperkeratosis (thickened stratum corneum, the uppermost layer of the epidermis) with an underlying acanthosis.
- Harlequin ichthyosis is characterized by extreme hyperkeratosis and follicular plugging. Electron microscopy shows absence of lamellar bodies and lipid bilayers.

2. Genetic Causes of Autosomal Recessive Congenital Ichthyosis

Table 1. Autosomal Recessive Congenital Ichthyosis: Genes and Distinguishing Clinical Features

Gene [1]	% of All ARCI [2]	Distinguishing Clinical Features	Other	Selected OMIM Links / References
ABCA12	3%-12%	• Accounts for >93% of HI; biallelic complete loss-of-function variants were assoc w/most severe HI. • CIE or LI presented in those w/variants w/partial function; often assoc w/severe erythroderma & PPK. • Albeit extremely rare, a mosaic form of CIE due to postzygotic somatic mosaicism has been observed.	• ~4% of distinct variants are large deletions/duplications. [3] • Missense variants in the region coding for the 1st nuclear binding fold were assoc w/LI & predicted to interfere w/specific functions of this protein domain.	OMIM 601277; OMIM 242500; Sakai et al [2009], van Leersum et al [2020]
ALOX12B	9%-21%	• >75% of affected persons w/ *ALOX12B* variants were born w/collodion membrane & later had mild-to-moderate CIE w/fine scaling & erythema. • Persons w/self-improving collodion ichthyosis	• ~2% of distinct variants are large deletions/duplications. [3] • The variant p.Tyr521Cys accounts for 22% of disease alleles.	OMIM 242100; Hotz et al [2021]
ALOXE3	3%-10%	• >33% of affected persons w/ *ALOXE3* variants were born w/collodion membrane & later had mild-to-moderate CIE w/fine scaling & erythema. • Intermediate phenotypes • Persons w/self-improving collodion ichthyosis	• More common in Austria • ~10% of distinct variants are large deletions/duplications. [3] • The variant p.Pro630Leu accounts for 40% of disease alleles & p.Arg234Ter accounts for 21%.	OMIM 606545; Harting et al [2008], Hotz et al [2021]
CASP14	Rare	No collodion membrane at birth, generalized fine, whitish scales, & no erythema	• 1 homozygous frameshift variant was observed in 2 Algerian families. • To date, no large deletions/ duplications have been reported. [3]	OMIM 617320
CERS3	<1%-3%	• Collodion membrane at birth, erythema & fine scales on face & trunk, larger, gray-brown scales on lower limbs, & hyperlinear palms/soles • A distinct feature is keratotic lichenification w/prematurely aged appearance of skin.	• More common in Iran (5.6% of variants) • 1 multigene deletion reported incl *CERS3* assoc w/syndromic ichthyosis. • See also footnote 4.	OMIM 615023

Table 1. continued from previous page.

Gene [1]	% of All ARCI [2]	Distinguishing Clinical Features	Other	Selected OMIM Links / References
CYP4F22	3%-10%	• Typically, erythroderma at birth but w/o collodion membrane & later in life present w/LI w/larger, white-gray scales & hyperlinear palms/soles • Persons w/self-improving collodion ichthyosis	• ~3% of distinct variants are large deletions/duplications. [3] • Less common in northern Europeans	OMIM 604777; Scott et al [2013], Bučková et al [2016], Diociaiuti et al [2016], Noguera-Morel et al [2016]
LIPN	<1%	Childhood onset w/generalized fine, white scaling & minimal erythema	• 5% of variants in Middle Eastern populations • To date, no large deletions/ duplications have been reported. [3]	OMIM 613943
NIPAL4	5%-9%	• <30% of persons w/*NIPAL4* variants have collodion membrane at birth. • Congenital ichthyosis w/ coarse, gray-white scales, mild-to-moderate erythroderma, & sparing of face • Yellowish PPK & hypohidrosis • Specific electron microscopic (EM) abnormalities (classified as ARCI EM type 3) w/abnormal lamellar bodies & elongated perinuclear membranes in granular layer	• More common in Scandinavia (12.5%) • Higher prevalence in Sweden, Denmark, & Norway, where *NIPAL4*-related ARCI accounts for ~90% of ARCI w/o collodion membrane presentation in those w/o *TGM1* variants. • The variant p.Asn176Asp is a mutation hot spot, observed in 87% of disease alleles & 70% of persons tested. • To date, no large deletions/ duplications have been reported. [3]	OMIM 612281; Dahlqvist et al [2007], Scott et al [2013], Bučková et al [2016], Ballin et al [2019]
PNPLA1	≤5%	• Typically, collodion membrane at birth & then transition to CIE phenotype w/scalp involvement & hyperlinear palms/soles • Mild disease w/generalized fine exfoliation & hyperkeratotic plaques over knees resembling progressive symmetric erythrokeratoderma • Ectropion, eclabium, & alopecia are lacking.	• More common in Iran (15% of variants) • Higher prevalence in northern Africa, Spain, & Iran, likely due to founder variants • To date, no large deletions/ duplications have been reported. [3]	OMIM 615024; Vahidnezhad et al [2017], Zimmer et al [2017]
SDR9C7	1%	CIE & intermediate phenotypes w/PPK & frequent fungal infections of skin & nails.	• More common in Austria (6% of variants) • To date, no large deletions/ duplications have been reported. [3]	OMIM 617574

Table 1. continued from previous page.

Gene [1]	% of All ARCI [2]	Distinguishing Clinical Features	Other	Selected OMIM Links / References
SLC27A4	Rare; 4%-5% in Scandinavia & northern Europe	• IPS: polyhydramnios & premature birth • Severe perinatal presentation w/respiratory asphyxia & thick, vernix caseosa-like scale or cobblestone-like hyperkeratosis on scalp, forehead, & trunk • Skin findings resolve over several weeks, transitioning to mild generalized follicular hyperkeratosis	• Mainly in persons from Scandinavia & northern Europe • The variant c.504C>A (p.Cys168Ter) is a founder variant in persons of Scandinavian ancestry. • A deletion of exon 3 has been reported. [3]	OMIM 608649; Sobol et al [2011], Lwin et al [2016]
SULT2B1	<1%	Collodion membrane at birth in most affected persons; later, LI-like phenotype w/milder scaling in large skin folds	Reported in few consanguineous families from North Africa, Middle East, & South Asia	Heinz et al [2017]
TGM1	24%-34%	• ~70%-90% of persons w/LI phenotype have *TGM1* variants. • *TGM1* variants also reported in many persons w/much milder non-erythrodermic phenotypes. • Persons w/"bathing suit ichthyosis" • Persons w/self-improving collodion ichthyosis	• More common in Scandinavia & Galicia • The variant c.877-2A>G is a Norwegian/German founder variant & is common in Norway, Finland, & North America. • The variants c.2278C>T (p.Arg760Ter) & c.1223_1227delACACA are founder variants in Galician population of Spain. • <1% of variants are large deletions/duplications. [3]	OMIM 242300; Shevchenko et al [2000], Raghunath et al [2003], Mazereeuw-Hautier et al [2009], Hackett et al [2010], Rodríguez-Pazos et al [2011], Fachal et al [2014]
Unknown [5]	7%-17%			

ARCI = autosomal recessive congenital ichthyosis; CIE = congenital ichthyosiform erythroderma; HI = harlequin ichthyosis; IPS = ichthyosis-prematurity syndrome; LI = lamellar ichthyosis; PPK = palmoplantar keratoderma

1. Genes are listed alphabetically.

2. Israeli et al [2013], Pigg et al [2016], Youssefian et al [2019], Seidl-Philipp et al [2020], Simpson et al [2020], Sun et al [2022]

3. Does not represent the overall percentage of deletions/duplications among probands/families; data derived from the subscription-based professional view of Human Gene Mutation Database [Stenson et al 2020]

4. Large contiguous deletions reported including *CERS3* and *ADAMTS1*

5. Based on several studies using multigene testing, 7%-17% of individuals with congenital ichthyosis do not have pathogenic variants in any of the known genes [Israeli et al 2013, Pigg et al 2016, Youssefian et al 2019, Seidl-Philipp et al 2020, Simpson et al 2020, Sun et al 2022]. Pathogenic variants have not been identified in any of the following situations: (1) one or more variants were identified in one of the known ichthyosis genes but are of uncertain clinical significance [Youssefian et al 2019]; (2) linkage of congenital ichthyosis has been suggested to two other loci on chromosome 19 [Fischer et al 2000, Virolainen et al 2000]; (3) homozygosity mapping in two consanguineous families identified a region on chromosome 12 (ARCI7) [Mizrachi-Koren et al 2005]; and (4) linkage to a locus on 15q26.3 - possibly identical to the location of *CERS3* - has been suggested in an aboriginal family from Taiwan [Wu & Lee 2011].

3. Differential Diagnosis of Autosomal Recessive Congenital Ichthyosis

Birth. The differential diagnosis of autosomal recessive congenital ichthyosis (ARCI) includes the disorders summarized in Table 2.

Table 2. Differential Diagnosis of Autosomal Recessive Congenital Ichthyosis: Genetic Disorders with Ichthyosis Present at Birth

Gene	Disorder	MOI	Skin Findings	Other Findings / Comment
AARS1 *ERCC2* *ERCC3* *GTF2E2* *GTF2H5* *MARS1* *MPLKIP* *RNF113A* *TARS1*	Trichothiodystrophy w/ ichthyosis (OMIM PS601675)	AR XL [1]	Generalized CIE; less frequent collodion membrane at birth; later generalized ichthyosis w/variable size & color of scale; follicular hyperkeratosis reported	• IUGR & prematurity • ≥1 of the following: brittle sulfur-deficient hair, nail dystrophy, photosensitivity (*ERCC2*, *ERCC3*, *GTF2H5*), infertility, DD, microcephaly, ataxia, abnormal brain MRI, short stature
ABHD5	Chanarin-Dorfman syndrome (neutral lipid storage disease) (OMIM 275630)	AR	Mostly resembling CIE; very rarely ectropion, alopecia	• Widespread lipid deposits result in hepatomegaly & fibrosis, cataracts, & sensorineural hearing loss. • DD is common. • Variable findings incl microcephaly, ataxia, short stature, splenomegaly, & renal insufficiency. • Lipid vacuoles in circulating granulocytes & monocytes on fresh peripheral blood smear
ALDH3A2	Sjögren-Larsson syndrome (OMIM 270200)	AR	Generalized ichthyosis w/accentuated skin markings, PPK, mild/variable erythema, & pruritus	Premature birth; spastic di- or tetraplegia; ID; white matter disease on MRI; juvenile macular dystrophy
EBP	X-linked chondrodysplasia punctata 2	XL	In females, erythroderma & patchy, linear, or diffuse ichthyosis w/adherent scales that may resolve into atrophoderma, hyperpigmentation, & alopecia	• In females, punctuate calcification in epiphyseal cartilage, asymmetric rhizomelic limb shortening, short stature, cataracts, & sensorineural hearing loss • Early gestational male lethality
EDA *EDAR* *EDARADD* *WNT10A* [2]	Hypohidrotic ectodermal dysplasia (HED)	AD AR XL [3]	• Neonates may be diagnosed because of peeling skin (like that of "postmature" babies) & periorbital hyperpigmentation. • Later, persons develop dry skin & chronic eczema.	• ↓ ability to sweat; sparse scalp & body hair, & congenital absence of teeth • Cardinal features of classic HED become obvious during childhood.
GBA1 (*GBA*)	Gaucher disease (perinatal-lethal form)	AR	May be assoc w/collodion membrane or generalized ichthyosis at birth	Nonimmune hydrops fetalis, akinesia & arthrogryposis, hepatosplenomegaly, pancytopenia, & facial dysmorphism (low-set & dysplastic ears, hypertelorism, & flat nasal bridge w/small, upturned nose)
GJB2	Keratitis-ichthyosis-deafness syndrome (OMIM 148210)	AD	May present w/transient erythroderma at birth; symmetrical hyperkeratotic plaques & palmoplantar keratoderma develop later.	Sensorineural hearing loss & progressive vascularizing keratitis; ↑ susceptibility to develop squamous cell carcinoma

Table 2. continued from previous page.

Gene	Disorder	MOI	Skin Findings	Other Findings / Comment
KRT1 *KRT10*	Epidermolytic ichthyosis (EI) (formerly epidermolytic hyperkeratosis) (OMIM 113800)	AD AR [4]	• Skin fragility, blistering, & erythema at birth & during infancy; transitions to pronounced ridged or cobblestone-like hyperkeratosis • Severe PPK is common in *KRT1*-related EI. • *KRT2*-related SEI is milder w/ superficial "molting" of small areas of skin. • No collodion membrane at birth	• Life-threatening complications in neonates are sepsis & fluid & electrolyte imbalances. • Later complications incl recurrent blistering & skin infections, heat intolerance, body odor, & gait abnormalities.
KRT2	Superficial epidermolytic ichthyosis (SEI) (formerly ichthyosis bullosa of Siemens) (OMIM 146800)	AD		
SPINK5	Netherton syndrome (OMIM 256500)	AR	• CIE often w/continuous skin peeling • Atopic manifestations	• Hair shaft anomalies & poor weight gain • Life-threatening complications during infancy incl temperature & electrolyte imbalance, recurrent infections, & sepsis.
ST14	Autosomal recessive ichthyosis w/hypotrichosis (OMIM 602400)	AR	• Congenital ichthyosis w/white, fine scale & scalp involvement & possibly sparing of flexures • Follicular atrophoderma w/pitted ("orange peel") appearance of skin in face & dorsal hands	• Generalized, diffuse, non-scarring hypotrichosis that improves w/age • Scalp hair is light colored, sparse, lusterless, & curly. • Hypohidrosis; eye involvement incl photophobia &/or inflammation of eyelids
ELOVL4	Ichthyosis, spastic quadriplegia, & impaired intellectual development (OMIM 614457)	AR	May have collodion membrane at birth; generalized ichthyosis, variable erythema, & PPK	Profound DD, poor weight gain, spastic quadriplegia, epilepsy, hypotonia, & severely delayed myelination on brain MRI

AD = autosomal dominant; AR = autosomal recessive; CIE = congenital ichthyosiform erythroderma; DD = developmental delay; ID = intellectual disability; IUGR = intrauterine growth restriction; MOI = mode of inheritance; PPK = palmoplantar keratoderma; XL = X-linked

1. Trichothiodystrophy is inherited in an autosomal recessive manner with the exception of *RNF113A*-related trichothiodystrophy, which is inherited in an X-linked manner.

2. WNT10A pathogenic variants are also associated with odontoonychodermal dysplasia (OMIM 257980) and Schöpf-Schultz-Passarge syndrome (OMIM 257980), disorders in which hypohidrotic ectodermal dysplasia is a finding.

3. EDA-related hypohidrotic ectodermal dysplasia (HED) is inherited in an X-linked manner. *EDAR*-, *EDARADD*-, and *WNT10A*-related HED are inherited in an autosomal recessive or an autosomal dominant manner.

4. KRT1-related epidermolytic ichthyosis (EI) is inherited in an autosomal dominant manner; *KRT10*-related EI is inherited in autosomal dominant or rarely in an autosomal recessive manner.

Infancy. Other ichthyoses that may not be evident at birth but appear soon after include the following:

- **Ichthyosis vulgaris** (OMIM 146700) usually presents within the first year of life; it is characterized by mild ichthyosis/xerosis, keratosis pilaris, and hyperlinear palms and soles, and is often associated with atopy. Individuals with typical mild features are heterozygous for a loss-of-function pathogenic variant in *FLG*, while homozygous or compound heterozygous individuals show a more severe phenotype reminiscent of lamellar ichthyosis [Smith et al 2006; Thyssen et al 2013; Author, unpublished data].
- **X-linked ichthyosis** (steroid sulfatase deficiency; OMIM 308100) is characterized in infancy by white, adherent scales that darken over time (especially affecting the flexures), asymptomatic corneal opacities, and occasionally cryptorchidism. High plasma cholesterol sulfate concentration identifies affected males.

X-linked ichthyosis is caused by recurrent genomic deletions including *STS* on Xp22.31 in more than 90% of affected males. Larger deletions may result in a more complex phenotype that may include intellectual disability, autism spectrum disorder, anosmia (Kallmann syndrome), and other features [Cañueto et al 2010]. Intragenic *STS* pathogenic variants have been rarely reported as well.

4. Evaluation Strategies to Identify the Genetic Cause of Autosomal Recessive Congenital Ichthyosis in a Proband

Establishing a specific genetic cause of autosomal recessive congenital ichthyosis (ARCI):

- Can aid in discussions of prognosis (which are beyond the scope of this *GeneReview*) and genetic counseling;
- Usually involves a medical history, physical examination, family history, and molecular genetic testing.

Medical history. Assess for history of a collodion membrane with ectropion and/or eclabium, generalized scaling, exfoliative erythroderma, or harlequin baby presentation; premature birth and temperature and electrolyte imbalances, skin infections, sepsis or digital constriction bands during the neonatal period; skin manifestations during infancy and early childhood; and heat intolerance and recurrent skin infections (see Table 1 for genotype-phenotype correlations).

Physical examination. Skin examination should include assessment of scale pattern, quality, and color; presence of a collodion membrane at birth; presence of erythroderma; erosions or blistering; presence of xerosis (dry skin), alopecia of the scalp and eyebrows, scarring, and hypohidrosis or anhidrosis; evaluation of the extremities for presence of palmoplantar keratoderma with fissures, tapering of digits, and/or flexural joint contractures and assessment of nail shape abnormalities or nail dystrophy; assessment of facial features including ears, eye exam for ectropion, dry eyes, or corneal defects, and for eclabium; and assessment for growth deficiency. (The shape, color, and appearance of scales and degree of erythema varies between the different types of ARCI based on their underlying genetic causes; see Table 1 for genotype-phenotype correlations.)

Family history. A three-generation family history should be taken, with attention to relatives with manifestations of ARCI and documentation of relevant findings through direct examination or review of medical records, including results of molecular genetic testing. Absence of a known family history does not preclude the diagnosis.

Molecular genetic testing approaches can include a combination of **gene-targeted testing** (multigene panel, serial single-gene testing) and **comprehensive genomic testing** (exome sequencing, genome sequencing). Gene-targeted testing requires the clinician to hypothesize which gene(s) are likely involved, whereas genomic testing does not.

- **A multigene panel** that includes the genes in Table 1 and other genes of interest (see Differential Diagnosis) is the **diagnostic test of choice**, as it offers the possibility to evaluate concurrently for syndromic forms of congenital ichthyosis, which may not be distinguishable based on clinical grounds prior to onset of specific symptoms. Note: (1) The genes included and the sensitivity of multigene panels varies by laboratory and are likely to change over time. (2) Some multigene panels may include genes not associated with the condition discussed in this *GeneReview*; thus, clinicians need to determine which multigene panel is most likely to identify the genetic cause of the condition while limiting identification of variants of uncertain significance and pathogenic variants in genes that do not explain the underlying phenotype. (3) In some laboratories, panel options may include a custom laboratory-designed panel and/or custom phenotype-focused exome analysis that includes genes specified by the clinician. (4) Methods used in a panel may include sequence analysis, deletion/duplication analysis, and/or other non-sequencing-based tests.

For an introduction to multigene panels click here. More detailed information for clinicians ordering genetic tests can be found here.

- **Serial single-gene testing** can be considered if multigene panel testing is not available; the order of testing is determined by the genes in which pathogenic variants most commonly occur for a given phenotype. Sequence analysis of the gene of interest is performed first, followed by gene-targeted deletion/duplication analysis if only one or no pathogenic variant is found.
  - In individuals with harlequin ichthyosis, analysis of *ABCA12* should be performed first.
  - In individuals with ARCI and without harlequin presentation at birth, analysis of *TGM1* should be performed first.
  - In individuals with ichthyosis-prematurity syndrome, molecular genetic testing should start with *SLC27A4*.
- **Comprehensive genomic testing** (which does not require the clinician to determine which gene[s] are likely involved) may be considered especially in individuals with ARCI who also have other organ manifestations (syndromic presentation). **Exome sequencing** is most commonly used; **genome sequencing** is also possible.

  For an introduction to comprehensive genomic testing click here. More detailed information for clinicians ordering genomic testing can be found here.

5. Genetic Counseling

Genetic counseling is the process of providing individuals and families with information on the nature, mode(s) of inheritance, and implications of genetic disorders to help them make informed medical and personal decisions. The following section deals with genetic risk assessment and the use of family history and genetic testing to clarify genetic status for family members; it is not meant to address all personal, cultural, or ethical issues that may arise or to substitute for consultation with a genetics professional. —ED.

Mode of Inheritance

By definition, autosomal recessive congenital ichthyosis (ARCI) is inherited in an autosomal recessive manner.

Risk to Family Members

Parents of a proband

- The parents of an affected child are presumed to be heterozygous for an ARCI-related pathogenic variant.
- If a molecular diagnosis has been established in the proband, molecular genetic testing is recommended for the parents of the proband to confirm that both parents are heterozygous for an ARCI-related pathogenic variant and to allow reliable recurrence risk assessment.
- If a pathogenic variant is detected in only one parent and parental identity testing has confirmed biological maternity and paternity, it is possible that one of the pathogenic variants identified in the proband occurred as a *de novo* event in the proband or as a postzygotic *de novo* event in a mosaic parent [Jónsson et al 2017]. If the proband appears to have homozygous pathogenic variants (i.e., the same two pathogenic variants), additional possibilities to consider include:
  - A single- or multiexon deletion in the proband that was not detected by sequence analysis and that resulted in the artifactual appearance of homozygosity;
  - Uniparental isodisomy for the parental chromosome with the pathogenic variant that resulted in homozygosity for the pathogenic variant in the proband.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Sibs of a proband

- If both parents are known to be heterozygous for an ARCI-related pathogenic variant, each sib of an affected individual has at conception a 25% chance of being affected, a 50% chance of being an asymptomatic carrier, and a 25% chance of being unaffected and not a carrier.
- Heterozygotes (carriers) are asymptomatic and are not at risk of developing the disorder.

Offspring of a proband. Unless an affected individual's reproductive partner also has ARCI or is a carrier, offspring will be obligate heterozygotes (carriers) for an ARCI-related pathogenic variant (see **Family planning**).

Other family members. Each sib of a proband's parents is at a 50% risk of being a carrier of an ARCI-related pathogenic variant.

Carrier Detection

Carrier testing for at-risk relatives requires prior identification of the ARCI-related pathogenic variants in the family.

Related Genetic Counseling Issues

Family planning

- The optimal time for determination of genetic risk and discussion of the availability of prenatal/preimplantation genetic testing is before pregnancy.
- It is appropriate to offer genetic counseling (including discussion of potential risks to offspring and reproductive options) to young adults who are affected, are carriers, or are at risk of being carriers.
- Gene-targeted testing for the reproductive partners of known carriers, and for the reproductive partners of individuals affected with ARCI should be considered, particularly if both partners are of the same ethnic background. ARCI-related founder variants have been identified in individuals of Scandinavian, Norwegian/German, and Galician heritage (see Table 1).

DNA banking. Because it is likely that testing methodology and our understanding of genes, pathogenic mechanisms, and diseases will improve in the future, consideration should be given to banking DNA from probands in whom a molecular diagnosis has not been confirmed (i.e., the causative pathogenic mechanism is unknown). For more information, see Huang et al [2022].

Prenatal Testing and Preimplantation Genetic Testing

Molecular genetic testing. Once the ARCI-related pathogenic variants have been identified in an affected family member, prenatal and preimplantation genetic testing are possible.

3D or 4D ultrasound examination may be helpful in identifying fetuses with harlequin ichthyosis as early as the second trimester in families with a known history of harlequin ichthyosis. Reported findings include polyhydramnios, dense floating particles in amniotic fluid ("snowflake sign"), atypical facial morphology (O-shaped mouth, eclabium, ectropion), and flexion contractures [Rathore et al 2015, Zhou et al 2021]. Echogenic sediment in the amniotic fluid has been described on fetal ultrasound in pregnancies of a fetus with ichthyosis-prematurity syndrome [Blaas et al 2012, Dereksson et al 2012].

Differences in perspective may exist among medical professionals and within families regarding the use of prenatal testing. While most centers would consider use of prenatal testing to be a personal decision, discussion of these issues may be helpful.

Resources

GeneReviews staff has selected the following disease-specific and/or umbrella support organizations and/or registries for the benefit of individuals with this disorder and their families. GeneReviews is not responsible for the information provided by other organizations. For information on selection criteria, click here.

- **Foundation for Ichthyosis and Related Skin Types, Inc. (FIRST)**
  Phone: 215-997-9400; 800-545-3286
  www.firstskinfoundation.org
- **MedlinePlus**
  Harlequin ichthyosis
- **European Network for Ichthyosis**
  https://ichthyosis.info/
- **National Organization for Rare Disorders (NORD)**
  Phone: 617-249-7300
  Living with a Rare Disease
- **National Registry for Ichthyosis and Related Skin Disorders**
  Email: ichthyosisregistry@yale.edu
  www.firstskinfoundation.org/national-registry-for-ichthyosis-and-related-disorders

6. Management

Guidelines for the management of congenital ichthyosis have been published [Mazereeuw-Hautier et al 2019a, Mazereeuw-Hautier et al 2019b, Zaenglein et al 2021].

Evaluations Following Initial Diagnosis

To establish the extent of disease and needs in an individual diagnosed with autosomal recessive congenital ichthyosis (ARCI), the evaluations summarized in Table 3 (if not performed as part of the evaluation that led to the diagnosis) are recommended.

Table 3. Recommended Evaluations Following Initial Diagnosis in Individuals with Autosomal Recessive Congenital Ichthyosis

System/Concern	Evaluation	Comment
Complications due to prematurity	Eval for issues relating to prematurity & impaired skin barrier function (e.g., respiratory distress, temperature instability, electrolyte imbalances, skin infections, sepsis)	
Pulmonary	Eval for chest constriction, suppressed ventilation & respiratory distress, & aspiration of amniotic fluid containing scales	In neonates w/HI & IPS
Vascular manifestations in extremities	Eval of hands & feet for constriction bands, ischemia, & contractures	In neonates w/HI & collodion membrane
Dermatologic	Eval by dermatologist familiar w/congenital ichthyosis	All neonates w/collodion membrane or generalized erythroderma/scaling
Fluids/Nutrition	• Assessment of transepidermal water loss & hydration status • Assessment of feeding & nutrition status	
Infectious disease	Exam for evidence of infection	

Table 3. continued from previous page.

System/Concern	Evaluation	Comment
Ophthalmologic	Eval by ophthalmologist	To assess for eyelid closure & corneal dryness in infants w/ectropion
ENT	Eval by ENT	Assessment of external ear canals for blockage w/scale & detritus
Genetic counseling	By genetics professionals [1]	To inform affected persons & their families about nature, MOI, & implications of ARCI to facilitate medical & personal decision making
Family support & resources	Assess need for: • Community or online resources such as Parent to Parent &/or patient advocacy groups; • Social work involvement for parental support; • Home nursing referral.	

ARCI = autosomal recessive congenital ichthyosis; HI = harlequin ichthyosis; IPS = ichthyosis-prematurity syndrome; MOI = mode of inheritance

1. Medical geneticist, certified genetic counselor, certified advanced genetic nurse

Treatment of Manifestations

Treatment of ARCI is mainly symptomatic, as no curative therapies exist.

Supportive care to improve quality of life, maximize function, and reduce complications is recommended. This ideally involves multidisciplinary care by specialists in relevant fields (see Table 4). For a detailed review, see also Paller & Butala [2022].

Table 4. Treatment of Manifestations in Individuals with Autosomal Recessive Congenital Ichthyosis

Manifestation/ Concern	Treatment	Considerations/Other
Complications due to prematurity	• Provide moist environment in highly humidified incubator (50%-70% humidity). • Prevent infection using hygienic standard precautions. • Perform regular bacteriologic samplings to monitor for skin & systemic infections. • Monitor & maintain body temperature to avoid hypothermia or overheating. • Monitor & maintain weight & water & electrolyte balance to avoid hypernatremia or dehydration. • Manage pain as needed.	• Admission to NICU • Interdisciplinary approach w/involvement of parents in care • Avoidance of invasive procedures (due to ↑ risk of infections)
Pulmonary	If pulmonary ventilation is suppressed due to skin constriction or nasal occlusion, endotracheal intubation may be required.	Mostly limited to infants w/severe HI

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Vascular manifestations in extremities	**In neonates & infants:** massaging of constriction bands w/emollients may soften skin & improve vascular circulation; if ischemia is evident, topical retinoids or surgical linear band incisions may be considered.	
	In older children & adults: physical therapy for contractures, arthritis, pain	
Dermatologic (topical therapy)	**In neonates & infants:** frequent daily application of bland emollients, such as petrolatum-based creams & ointments to keep skin soft, supple, & hydrated	
	In older children & adults: humidification w/long baths, lubrication & keratolytic agents (e.g., alpha-hydroxy acid, urea preparations; vitamin D3 derivatives) to promote peeling & thinning of stratum corneum	• In young children, topical salicylic acid preparations should be avoided because of absorption through skin leading to toxicity. • Topical use of tacrolimus or vitamin D should be considered w/caution due to skin absorption. • Skin irritation may limit use of keratolytics.
	Topical retinoids (tazarotene, tretinoin, & adapalene) to ↓ scaling, reverse ectropion, & digital contractures	Systemic laboratory monitoring is not recommended for topical use.
Dermatologic (systemic therapy)	**In neonates:** treatment w/systemic retinoids usually unnecessary, but may be considered in neonates w/ severe HI	• For long-term use of systemic retinoids, important safety & health concerns must be considered. • Treatment requires careful risk vs benefit assessment & monitoring, & should be performed by dermatologist familiar w/ congenital ichthyosis. • Oral retinoid therapy should be used w/ caution in women of child-bearing age because of teratogenicity (see Pregnancy Management). • Additional side effects of retinoids incl hypertriglyceridemia, hepatotoxicity, bone toxicity & ligamentous calcifications, dry eyes, night blindness, & retinal dysfunction from long-term use. • For a detailed review of choice of retinoid, dosage, treatment duration, toxicity, monitoring, & disease-specific considerations for ARCI, see Zaenglein et al [2021].
	In children & adults: • Moderate to severe ARCI often necessitates systemic (oral) retinoid therapy. • Oral retinoids (isotretinoin, etretinate) can effectively ↓ hyperkeratosis & scaling but are less beneficial in suppressing erythroderma.	
Temperature stability	Frequent fluid intake & moistening of skin w/water (e.g., spray bottle) or use of cooling vests, air conditioning, & humidifiers may prevent overheating & heat intolerance.	Avoidance of extreme temperatures

Table 4. continued from previous page.

Manifestation/ Concern	Treatment	Considerations/Other
Fluids/Nutrition	**In neonates:** • Monitor weight daily as indicator for sufficient fluid & nutrient intake. • High-calorie diet; nutritional support via oro- or nasogastric tube may be necessary due to high caloric demand, &/or complications from eclabium. • Prevent dehydration.	
	In children & adults: ↑ intake of high-calorie foods, fluids, & protein is necessary, esp for persons w/severe erythroderma.	
Infectious disease	• Antiseptics, antifungal topicals in macerated skin areas • Prompt treatment of skin or systemic bacterial infection according to antibiotic sensitivity profile	Prophylactic antibiotic treatment may be considered for neonates w/HI.
Ophthalmologic	Lubrication of cornea w/artificial tears or prescription ophthalmic ointments, esp at night, is helpful in preventing desiccation of cornea.	In persons w/ectropion
ENT	Regular removal of built-up scale in external ear canals; regular hearing eval	
Skin cancer	Standard treatments for skin cancers	
Family support & resources	• Patient advocacy groups to provide family support & other resources • Disability resources & information • Financial aid programs • Children's camps (Camp Discovery, Camp Wonder)	

HI = harlequin ichthyosis; NICU = neonatal intensive care unit

Surveillance

To monitor existing manifestations, the individual's response to supportive care, and the emergence of new manifestations, the evaluations summarized in Table 5 are recommended.

Table 5. Recommended Surveillance for Individuals with Autosomal Recessive Congenital Ichthyosis

System/Concern	Evaluation	Frequency
Dermatologic	Assess skin involvement	Annually or as needed
	Assessment for skin cancer	Annually in adults w/prior non-melanoma skin cancer
Infectious disease	Asses for evidence of infection	As needed
Ophthalmologic	Assess for dry eye & corneal health	Annually or as needed in persons w/ectropion
	Eye eval	• Every 4-6 mos after starting systemic retinoid therapy • Every 6-12 mos in persons on long-term systemic retinoid therapy

Table 5. continued from previous page.

System/Concern	Evaluation	Frequency
ENT	Eval for & removal of excess scale & skin detritus from external ear canals	As needed
Family/Community	Assess family need for social work support (e.g., palliative/respite care, home nursing, other local resources), care coordination, or follow-up genetic counseling if new questions arise (e.g., family planning).	At each visit

Agents/Circumstances to Avoid

Invasive procedures in infants with complications related to prematurity should be avoided because of increased risk of infections related to such procedures.

Skin irritants and overheating should be avoided.

Topical salicylic acid preparations in children should be avoided because of absorption through the skin leading to toxicity.

Topical use of tacrolimus or vitamin D should be considered with caution due to skin absorption.

Evaluation of Relatives at Risk

See Genetic Counseling for issues related to testing of at-risk relatives for genetic counseling purposes.

Pregnancy Management

Affected mothers are at no specific disease-related risks during pregnancy, but overheating should be avoided during pregnancy.

Systemic retinoids are known to be teratogenic to a developing fetus and pose a high risk for birth defects. Therefore, women who are using systemic retinoids should be appropriately counseled about pregnancy risks and the need for highly effective contraception; regular monitoring with pregnancy tests is indicated. Systemic retinoids should be administered only by physicians who are knowledgeable regarding their risks and benefits. To access isotretinoin in the US, women and their prescribing providers must be enrolled in the iPLEDGE program to minimize the potential for fetal exposure. Pregnancy avoidance is initiated before therapy, continues during therapy, and extends post treatment until the drug is cleared from the body. While both isotretinoin and acitretin may be effective in preventing skin cancers, acitretin may take longer to be eliminated from the body, requiring an extended period (3 years) of post-therapy pregnancy avoidance to minimize teratogenic risk.

See MotherToBaby for further information on medication use during pregnancy.

Therapies Under Investigation

Advances in understanding the genetics and pathophysiology of ichthyosis paired with new biotechnology approaches have led to the exploration and development of pathogenesis-based therapies for ichthyoses. Among those are enzyme replacement therapy (ERT) and lipid replacement therapy (LRT); repurposing of biologic therapeutics; and gene replacement and gene editing therapies. It can be expected that some of these new therapies will prove their efficacy and will be incorporated in the treatment of ichthyosis. Nevertheless, there are only a few ongoing, registered clinical trials for treatment of ARCI. Results have not been published, and no conclusions regarding the long-term safety and efficacy can be made at this time. For a detailed review, see Joosten et al [2022] and Paller & Butala [2022].

Gene replacement. Phase II dose studies are ongoing for KB105, a gel applied to the skin to correct transglutaminase-1 (TG1) deficiency (NCT04047732). This is a preclinical gene therapy trial for ARCI. The approach is based on a successful transfer of the wild type TGM1 into keratinocytes of individuals with lamellar ichthyosis (LI) using a retroviral vector, which was effective in vitro [Choate et al 1996]. The approach was then adapted for in vivo use with a modified herpes simplex virus-1 (HSV1) vector (KB105), which is non-integrating, non-replicating, and can accommodate multiple gene copies. It was formulated into a gel, and in a Phase I placebo-controlled trial, KB105 gel was tested in four individuals with LI and showed a significant increase in TGM1 expression and functional activity based on quantitative real-time PCR, immunofluorescence, and in situ enzymatic assays performed on skin biopsies [Agarwal et al 2020]. Over the 30-day dosing period, this correlated with improvement of scaling in the KB105-treated areas based on the Investigator's Global Assessment (IGA) scale compared to placebo. Treatment was well tolerated with no adverse events and with no evidence of immune response reported.

Repurposing of FDA-approved biological therapeutic drugs and related biologics for congenital ichthyoses. Several clinical trials are ongoing to repurpose biologics successfully used to treat inflammatory skin disorders such as psoriasis and atopic dermatitis for the treatment of congenital ichthyoses:

- Phase I open-label and long-term extension study using subcutaneous injection of human monoclonal antibody targeting IL-12/IL-23 (ustekinumab) (NCT04549792)
- Phase II multicenter, randomized, double-blind, placebo-controlled dosage study using subcutaneous injection of humanized monoclonal antibody ANB019 targeting IL-36 receptor (imsidolimab) (NCT04697056)
- Phase IV experimental non-randomized clinical study comparing the effect of subcutaneous injections with either secukinumab, ustekinumab, or dupilumab with symptomatic treatment in children with congenital ichthyosis (NCT04996485)

These trials are based on the pivotal finding that congenital ichthyoses demonstrate an interleukin 17-dominant immune profile with marked elevations in Th17/IL-23 pathway cytokines and chemokines reminiscent of the inflammatory pattern of psoriasis [Paller et al 2017]. Further case reports indicated that individuals with ARCI, when treated with injections of recombinant human monoclonal antibodies targeting the cytokines IL-17, IL12/IL23 (ustekinumab or secukinumab), showed improvement of the inflammatory disease components (erythema, joint arthropathy) with minor effects on hyperkeratosis and scaling [Haiges et al 2019, Poulton et al 2019]. Ustekinumab or secukinumab also led to considerable improvements for other genetic inflammatory skin disorders due to pathogenic variants in *SPINK5* (Netherton syndrome), *CARD14* (pityriasis rubra pilaris), and *DSP* (SAM syndrome), suggesting that inhibitors of the TH17/IL-23 pathway may also ameliorate the clinical manifestations of ARCI [Paller 2020].

In a subsequent double-blind placebo-controlled Phase II trial with secukinumab (NCT03041038), 20 adults with different subtypes of congenital ichthyosis (congenital ichthyosiform erythroderma, LI, Netherton syndrome, and epidermolytic ichthyosis) received subcutaneous secukinumab injections or placebo every four weeks for 16 weeks in total, followed by a 16-week open-label phase and a 20-week extension for safety [Lefferdink et al 2023]. Overall, there was no significant improvement of severity of ichthyosis or reduction of Th17-related biomarkers. While participants with LI showed no response at all time points, some other participants receiving secukinumab showed a significant decrease in erythema and transepidermal water loss after prolonged treatment (weeks 32 and 52). These findings suggest that use of biological therapies influencing the overactive Th17 pathway in ARCI could be beneficial for certain types of ichthyoses with a more prominent inflammatory component. To pursue this approach further, the ongoing clinical trials for congenital ichthyosis listed above focus on the inhibition of IL-12/IL-23 with ustekinumab (NCT04549792, NCT04996485), IL4/IL13 with dupilumab (NCT04996485), and IL36 with imsidolimab (NCT04697056) to determine which of these biologics might reduce severity and yield lasting improvement of ichthyosis. If any are proven effective, it may

soon be feasible to integrate biologics into the treatment regimen for certain congenital ichthyoses, as these biologics and their safety profile have been well studied previously.

Gene editing. In a recent study, an adenine base editor (ABE) system was developed to introduce a targeted single-nucleotide variant in DNA or RNA with the help of a single guide RNA that would correct a disease-causing variant in *TGM1* identified in a couple who were heterozygous for an LI-associated variant [Dang et al 2022]. First, in vitro, different ABEs were screened for efficacy in cultured cells with a biallelic pathogenic *TGM1* nonsense variant (c.607C>T) and were found to be effective in correcting this nucleotide change. Then these ABEs were injected into heterozygous human embryos in vitro generated by intracytoplasmic sperm injection into matured oocytes. The ABEs were able to correct the specifically targeted pathogenic variant and restore the wild type sequence in two of seven or in five of eight embryos, respectively. From a safety perspective, there was no evidence for editing of other (off-site) DNA nucleotides by whole-genome sequencing, but RNA sequencing revealed a high rate of RNA single-nucleotide variations that were spontaneously introduced by the deaminase (ABEs). This is the first study to demonstrate the feasibility of correcting a *TGM1* pathogenic variant in an embryo in vitro with the ABE gene editing system. Nevertheless, it also highlights the need for further improvements of safety and efficacy before any clinical application is considered.

ERT and LRT. ARCI is associated with biallelic variants in at least 13 epidermally expressed genes (see Table 1), which result in deficiency of enzymes and cofactors involved in epidermal lipid metabolism and transport and formation of the skin barrier. A series of preclinical in vitro studies have aimed to directly replace either the missing enzyme or the missing epidermal lipids (e.g., omega-O-acylceramides) to restore normal skin barrier function. An example is the application of thermo-responsive nanogels containing tranglutaminase-1 on cultured full-thickness skin equivalents derived from fibroblasts and keratinocytes of individuals with *TGM1*-related ARCI [Plank et al 2019]. While these topical ERT/LRT studies yielded some promising results, these approaches are still hampered by several challenges, foremost by the cytotoxicity of the enzymes and/or accumulation of free fatty acids or other proximal metabolites. No clinical trials are registered at present.

Search ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe for access to information on clinical studies for a wide range of diseases and conditions.

Chapter Notes

Author Notes

Dr Gabriele Richard, a trained dermatologist and PhD medical geneticist, has more than 20 years' experience in clinical and molecular genetic studies of ichthyoses and other disorders of cornification. Her prior research studies helped elucidate the molecular basis of numerous inherited ichthyoses and other skin disorders, and she is now dedicated to the rapid molecular diagnosis of these conditions in a diagnostic laboratory, using next-generation sequencing panels and exome and genome sequencing. She has contributed to more than 100 scientific publications, review articles, and book chapters.

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Author History

Sherri J Bale, PhD, FACMG; GeneDx (2001-2017)
Gabriele Richard, MD, FACMG (2001-present)

Revision History

- 20 April 2023 (sw) Comprehensive update posted live; scope changed to overview
- 18 May 2017 (ha) Comprehensive update posted live
- 28 August 2014 (me) Comprehensive update posted live
- 13 September 2012 (cd) Revision: sequence analysis, deletion/duplication analysis and prenatal diagnosis for *PNPLA1* mutations available clinically
- 19 April 2012 (me) Comprehensive update posted live
- 19 November 2009 (cd) Revision: gene *ICHTHYIN* changed to *NIPAL4*
- 11 December 2008 (cd) Revision: deletion/duplication analysis available for *ABCA12*
- 30 June 2008 (cd) Revision: sequence analysis and prenatal testing available for *NIPAL4* mutations
- 29 October 2007 (me) Comprehensive update posted live
- 7 September 2005 (gr) Revision: testing for *ALOX12B*, *ALOXE3*, and *ABCA12* clinically available
- 29 December 2004 (me) Comprehensive update posted live
- 30 January 2003 (me) Comprehensive update posted live
- 10 January 2001 (me) Review posted live
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