Title: Autosomal Recessive Congenital Ichthyosis *GeneReview* – Less Common Genetic Causes
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CERS3

Gene structure. *CERS3* encodes ceramide synthase 3. The gene spans 143.9 kb; it has two isoforms and four known transcript variants. The longest transcript (NM_001290341.1) encodes isoform 1 and includes 14 exons (11 are coding); a shorter transcript variant 4 (NM_001290343.1) encodes isoform 2 and has 13 exons (10 coding).

Pathogenic variants. Homozygous pathogenic sequence variants (1 splice site and 1 missense change) have been identified in two patients with ARCI. Both patients had collodion membranes at birth with ectropion and eclabium, and later generalized scaling and mild erythroderma, including scalp and palms and soles (hyperlinearity) [Eckl et al 2013, Radner et al 2013]. One patient had pruritus, pronounced keratotic lichenification with a prematurely aged appearance, and recurrent skin infections [Eckl et al 2013]. However, this gene does not seem to play a prominent role for ARCI in Scandinavia as no pathogenic *CERS3* variants were identified in 132 unrelated ARCI families from this geographic region [Pigg et al 2016].

Nevertheless, three consanguineous Tunisian families with congenital ichthyosis and eye, heart, and skeletal anomalies were found to have a contiguous gene deletion encompassing *ADAMTS17* (suggested to account for all extracutaneous features reminiscent of Weill-Marchesani syndrome), *FLJ42289*, and *CERS3* (shown to account for congenital ichthyosis) [Radner et al 2013].

Normal gene product. CERS3 encodes a protein of 394 amino acids that belongs to the family of ceramide synthases, which form dihydroceramide from sphinganine by N-acylation of the sphingoid base. Ceramide synthase 3 contains two common motifs, a homeobox (Hox) domain (residues 83-127) and a TRAM, LAG1, and CLN8 (TLC) domain (residues 130-331), which also contains the active site. Ceramide synthase 3 is one of the main ceramide synthases of the skin, expressed in the stratum granulosum and stratum corneum, and uniquely able to metabolize an extended spectrum of very long acyl chains (C26 to C34). The synthesis of very long chain ceramides by ceramide synthase 3 is a crucial early step for the formation of the skin barrier [Eckl et al 2013].

Abnormal gene product. Pathogenic sequence variants in *CERS3* have been linked to abnormal sphingolipid metabolism and epidermal lipid architecture of the skin. A missense variant, NM_001290343.1:c.43T>C (NP_001277272.1:p.Trp15Arg), was shown to mildly reduce mRNA expression and immunostaining for ceramide synthase 3 in affected skin, but significantly induced expression of ALOX12B and ALOXE3 and other terminal differentiation-specific epidermal proteins [Eckl et al 2013]. Presence of the mutated protein in vitro and in patient keratinocytes resulted in loss of free and protein-bound very long-chain ceramides (C26-C34). There was evidence for an immature cornification process leading to cleft-like inclusions in the stratum corneum

due to improperly processed neutral lipids, and an impaired epidermal barrier function. These abnormalities are consistent with findings in Cers3 knockout mice, which die shortly after birth due to a severe skin barrier defect with increased transepidermal water loss [Eckl et al 2013].

A splice site pathogenic variant in *CERS3* (NM_178842.3: c.609+1G>T) resulted in skipping of exon 9 and in-frame deletion of 93 bp in the *CERS3* coding transcript, and loss of protein expression in affected skin [Radner et al 2013]. A massive reduction of ceramides in the upper epidermis and a distorted sphingolipid profile with marked decrease of very long-chain (VLC, >C20) ceramides (sphingosine, phytosphingosine, acylceramides, glucosylacylceramides) and slight increase of medium- to long-chain acyl ceramides (C16–20) were observed by TLC analysis of lipid extracts [Radner et al 2013].

LIPN

Gene structure. *LIPN* encodes a lipase able to withstand acid conditions. The gene (NM_001102469.1) includes nine coding exons and the cDNA spans 16.8 kb in length.

Pathogenic variants. A homozygous 2-bp deletion predicted to lead to a frameshift and premature termination of translation has been reported in a single consanguineous family with 7 affected individuals. Clinical features in this family were childhood-onset ichthyosis with generalized fine, white scale and slight erythema. Histologic abnormalities of the epidermis were nonspecific, including hyperkeratosis and acanthosis [Israeli et al 2011].

Normal gene product. *LIPN* encodes a lipase, family member N, of 398 amino acids. It is exclusively expressed in the granular layer of the epidermis and upregulated during epidermal differentiation, albeit the exact function of lipase N is currently unknown. It is speculated to be critically important for triglyceride metabolism of the skin, and might be part of a pathway including *ABHD5*, the gene involved in neutral lipid storage disease (Chanarin-Dorfman syndrome) [Israeli et al 2011].

Abnormal gene product. The only *LIPN* pathogenic variant reported to date results in a frameshift and has been demonstrated to lead to mRNA decay and significantly decreased mRNA levels in affected skin [Israeli et al 2011].

References

Eckl KM, Tidhar R, Thiele H, Oji V, Hausser I, Brodesser S, Preil ML, Onal-Akan A, Stock F, Müller D, Becker K, Casper R, Nürnberg G, Altmüller J, Nürnberg P, Traupe H, Futerman AH, Hennies HC. Impaired epidermal ceramide synthesis causes autosomal recessive congenital ichthyosis and reveals the importance of ceramide acyl chain length. J Invest Dermatol. 2013;133:2202-11.

Israeli S, Khamaysi Z, Fuchs-Telem D, Nousbeck J, Bergman R, Sarig O, Sprecher E. A mutation in LIPN, encoding epidermal lipase N, causes a late-onset form of autosomal-recessive congenital ichthyosis. Am J Hum Genet 2011;88:482-7.

Pigg MH, Bygum A, Gånemo A, Virtanen M, Brandrup F, Zimmer AD, Hotz A, Vahlquist A, Fischer J. Spectrum of autosomal recessive congenital ichthyosis in Scandinavia: clinical characteristics and novel and recurrent mutations in 132 patients. Acta Derm Venereol 2016;96:932-7.

Radner FP, Marrakchi S, Kirchmeier P, Kim G-J., Ribierre F, Kamoun B, Abid L, Leipoldt M, Turki H, Schempp W, Heilig R, Lathrop M, Fischer J. Mutations in CERS3 cause autosomal recessive congenital ichthyosis in humans. PLoS Genet 2013;9:e1003536.