Genetics of Lamellar Ichthyosis

by Ziske Maritska

Submission date: 03-Jun-2024 06:39PM (UTC+0700)
Submission ID: 2185492025
File name: Genetics_of_Lamellar_Ichthyosis.pdf (654.25K)
Word count: 2610
Character count: 15393

Genetics of lamellar ichthyosis

Ziske Maritska[a], Sandria Sandria[b], Nunung Noviyanti[b], Ulfa M. Lubis[c], Maretha W. Astria[c], Merta A. Prastika[c], Priya A. Chandra[c], Raden Satria Surya Chandra[c]

Departments of [a]Biology Medicine, [b]Pathology Anatomy, [c]Dermatovenereology, Faculty of Medicine, Universitas Sriwijaya, Sriwijaya, Indonesia

Correspondence to Ziske Maritska, M. Si.Med, Jl. Dr. Mohammad Ali, Palembang, South Sumatera 30126, Indonesia. Tel: +62 812 2480 1100; fax: (0711)373438; e-mail: ziske _maritska@unsri.ac.id

Received: 6 October 2022
Revised: 1 December 2022
Accepted: 20 December 2022
Published: 18 April 2024

Egyptian Journal of Dermatology and Venereology 2024, 44:69–72

Ichthyosis is a dermatological condition that causes the skin in a wide range of integumentary regions of the body to become dry, rough, and scaly. Ichthyosis affect 5–10/100 000 people worldwide. Lamellar ichthyosis (LI) is part of autosomal recessive congenital ichthyosis and is a significant type of inherited ichthyosis in nonsyndromic form. Patients with LI are susceptible to depression and low quality of life. TGM1 gene is the primary gene affected in LI. Clinical manifestations of LI are large scales on lower extremities; hence, the management of LI would consist of hydration, keratolytic, and oral retinoid. Genetic counseling are also recommended for patients with LI and their families. This review provides a brief discussion on the genetics of LI.

Keywords:
genetics, ichthyosis, lamellar ichthyosis

Egypt J Dermatol Venereol 44:69–72

1110-6530

Introduction

Ichthyosis is a dermatological condition that causes the skin in a wide range of integumentary regions of the body to become dry, rough, and scaly. The term ichthyosis refers to dermatosis with scaly features, which could also be found with or without erythema [1]. The classification for ichthyosis could be grouped into inherited and acquired. Inherited ichthyosis could further be classified into syndromic and nonsyndromic ichthyosis. Ichthyosis is a rare disorder with only five to 10 cases per 100 000 people [2].

It is estimated that there are more than 50 different genetic variants that cause this disease. These genetic variants are inherited in various inheritance patterns, including autosomal dominant, autosomal recessive, and X-linked [3]. Ichthyosis can be distinguished from its subtypes by the pattern of hyperkeratosis/scales, the pattern of descent, onset, skin changes over time, other organ manifestations, and family history.

Classification of lamellar ichthyosis

Although lamellar ichthyosis (LI) is a rare genetic disease present at birth, LI is one of three rare skin diseases classified as autosomal recessive congenital ichthyosis (ARCI). LI is a significant type of inherited ichthyosis in nonsyndromic form [4]. Harlequin ichthyosis and congenital ichthyosiform erythroderma are two other conditions in this spectrum [5]. The clinical classification for ichthyosis is described later (Table 1).

Global epidemiology and prevalence

LI affects approximately one in every 200 000 people. This condition is not limited to a specific sex, race, or ethnicity but can affect people of all races [5]. According to data obtained in the United States, the incidence rate ranges from five to 10 cases per 100 000 people. However, for individuals with this condition, it depends on the pattern of decline and demographic location. Studies conducted worldwide have found that 45 patients have this condition; of those, ~19 patients are from Pakistan. Higher cases in Pakistan could be owing to a lack of awareness, genetic counseling, or marriages between close relatives (such as cousins) [3]. Patients with LI are also susceptible to depression and impairment of quality of life owing to the patient's appearance. Most patients are concerned about the prevalence of scale, whereas others are worried about alopecia and erythema [7].

Genetic alterations

TGM1 is the primary gene involved in LI. *NIPAL4*, *ALOX12B*, and *CYP4F22* are additional genes that determine the presence of LI. Involvement of the *TGM1* gene in protein and enzyme synthesis is well documented. *TGM1* and other genes encode enzymes and proteins responsible for skin cell shedding. LI can be passed down recessively, meaning a person can

Table 1 Classification of ichthyosis [6]

Vulgar ichthyosis, isolated	Ichthyosis vulgaris
	X-linked recessive ichthyosis
Vulgar ichthyosis, syndromic	Refsum syndrome
	Multiple sulfatase deficiency
Congenital ichthyosis, isolated	Keratinopathic ichthyosis
	Autosomal recessive congenital ichthyosis (ARCI)
	Harlequin ichthyosis (subtype of ARCI)
	Autosomal dominant lamellar ichthyosis
	Congenital reticular ichthyosiform erythroderma
	Ichthyosis hystrix type Curth-Macklin
	Peeling skin disease
	Erythrokeratodermia
	And others
Congenital ichthyosis, syndromic	HID/KID syndrome
	Netherton syndrome
	CHILD syndrome
	SAM syndrome
	Conradi-Hunermann-Happle syndrome
	Sjogren-Larsson syndrome
	Chanarin-Dorfman syndrome
	Trichothiodystrophy
	IFAP syndrome
	And others

receive it from the faulty gene from each parent. If both parents have the gene, there is a one in four (25%) chance that they will have a child with LI [5].

Pathophysiology

LI is part of the spectrum of ARCI. A lack of transglutaminase-1 mainly causes LI. The clinical manifestation of LI in infants is shiny stratum corneum. This condition then could exacerbate and cause fluid loss, heat intolerances, dehydration, ectropion, and eclabium. Some states could be severe and life-threatening [6]. In some cases, a severe form of LI is associated with mutations of p.Leu207pro and p.Tyr544Cys in the *TGM1* gene [8]. Another case report stated that mutations in p.ARG396leu and p.Gln203 are also associated with a severe form of LI [9].

Skin's primary functions are to prevent transepidermal water loss and exposure to toxins and other dangerous substances. The stratum corneum is the main structure of the skin barrier and consists of corneocytes and keratinocyte-derived lipids. *TGM1* is an essential enzyme in cross-linking of keratinocyte-derived involucrin and loricrin. This process happens during the change of granular cells to corneocytes [10].

TGM1 is central to the pathophysiology of LI. Recent studies suggest that L362R and L388P mutations were the two most destabilizing mutations in *TGM1* protein [11]. *TGM1* phenotypic variability varies from patient to patient. *TGM1* encodes transglutaminase-1 and catalyzes the formation of isopeptides from glutamyl lysine in catalyzing calcium-dependent proteins. Transglutaminase catalyzes the cross-linking of cellular proteins such as involucrin, loricrin, proline-rich proteins, keratin, filaggrin, and others during stratum corneum formation. This process results in protein complexes, which are then stored inside the plasma membrane, forming a cornified sheath. Transglutaminase also binds to ceramides secreted in the intracellular space by cornified envelope proteins with lamellar bodies, such as involucrin, which are essential in forming proteins and lipids in the stratum corneum [12]. The diagram of ARCI Pathophysiology is described in Fig. 1.

Clinical presentation

At birth, neonates with LI still have the collodion membrane covering their skin, which causes their skin to have a redder appearance than the skin of normal neonates. However, as reported in some case reports, a collodion membrane could not be found [13]. Then, with more time passing, large scales will start to appear. The scales are usually quite large, with the majority of them located on the lower extremities. Large scales that closely mimic plates can be found separated from one another by superficial fissures that appear like a dry trough [12].

In newborns, collodion membranes could transform into a condition called classic LI. This condition is associated with plate-like scales, dark brown color, and adherent scale. White or red color could also be observed with varying degrees. The patient could also have nail dystrophies, alopecia, and hypohidrosis [6].

Erythema of the skin can present itself in varying degrees from childhood into adulthood; the condition can be mild or severe, depending on how severe it is. In most cases, the erythema of the skin will also affect the lips and the mucous membranes. The presence of thick scales characterizes Aknesa's structure. In certain instances, the condition may be accompanied by alopecia, typically observed on the edges of the scalp. There is also the possibility that LI will be accompanied by hyperkeratosis of the sweat

Figure 1

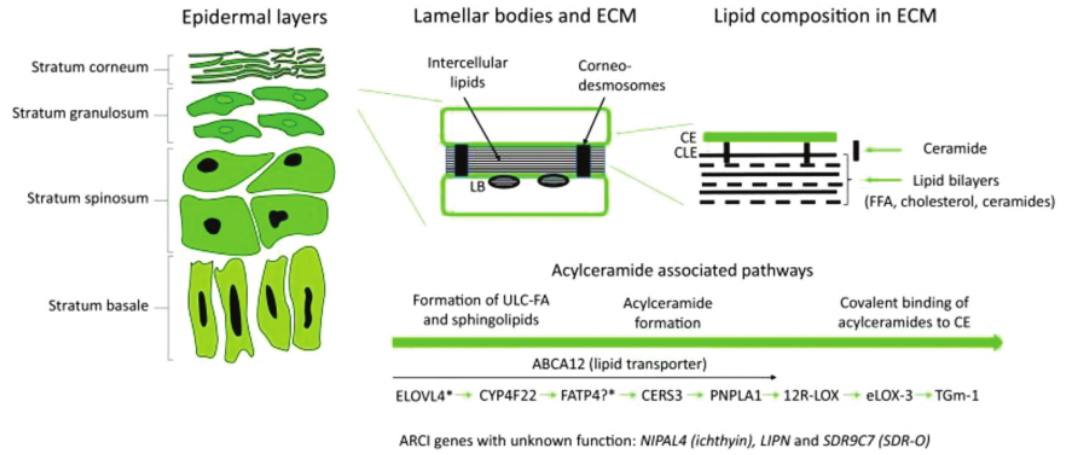

Diagram of ARCI pathophysiology [10]. ARCI, autosomal recessive congenital ichthyosis.

glands, resulting in hyperhidrosis [12]. Evaporative dry eye disease is also usually found in patients with LI [14].

Novel diagnostic modalities

Diagnosis for LI is usually made clinically. However, gene testing could be done for ambiguous cases to establish the diagnosis. Genes associated with LI are *ABCA12*, *ALOX12B*, *ALOXE3*, *CASP14*, *CERS3*, *CYP4F22*, *LIPN*, *NIPAL4*, *PNPLA1*, *SDR9C7*, *SLC27A4*, and *TGM1*. Ideally, multiple gene testing should be carried out, but a single gene setting of *ABCA12* could also be a choice in a limited resource setting [15].

Recently, a new noninvasive diagnostic method was investigated to evaluate patients with ichthyosis using a device to quantify several biomechanical parameters such as skin distensibility, skin hydration, and melanin index. The author concluded that this new device could be used for monitoring the skin progression in patients with ichthyosis quantitatively. However, this technology still needs further study to be applied in clinical settings [16].

Management of lamellar ichthyosis

Treatment for ichthyosis typically involves topical and oral pharmacological treatments, such as hydration aids, keratolytic, and keratinocyte differentiation regulators. Oral retinoids can be used as a treatment option for people with LI to improve their condition or prevent sequelae. Although some unpleasant adverse effects are associated with retinoid treatment, such as blepharitis and conjunctivitis, the treatment is generally well tolerated by patients with LI. Both systemic and topical retinoids can reduce the thickness of particular scales and, as a result, the likelihood of developing ectropion [12].

Topical agents consist of skin moisturizers in form of creams and ointments, and a low concentration of salts, urea, or glycerol are also used to provide good hydration for the skin. Moisturizers act as a barrier and aid in scale removal. Microfiber washcloths and urea are also used to remove the scales. Keratolytic agents such as alpha-hydroxy acids (lactic acid, glycolic acid), salicylic acid, N-acetylcysteine, propylene glycol, and high-dose urea are also important topical agents for desquamation. Retinoids (tretinoin, adapalene, and tazarotene) and calcipotriol are also effective at controlling epidermal proliferation. However, these topical agents could also cause adverse effects such as skin irritation [17].

Recently, topical tazarotene was evaluated for children with LI. This agent showed improvement for ectropion, with two patients experiencing full resolution (out of five patients) [18]. Another report also stated the effectiveness of dupilumab for patients with LI and atopic dermatitis, but this result needs further studies to be recommended for LI [19].

Aside from oral retinoids as first-line treatment, LI should be treated holistically with multiple approaches.

For severe ectropion, surgical management may be required, with skin grafts being the standard therapy. As the child grows, inverting sutures may help to stabilize the ectropion, and it is remarkably well tolerated. Treatments with multiple approaches, staff, and discipline provide better patient outcomes [20].

Genetic counseling for lamellar ichthyosis

In general, LI can be passed to offspring in an autosomal recessive pattern. Every sibling of a patients with LI has ¼ chance of having LI. Sibling of a patient with LI also have 50% chance to be a carrier without any symptoms. Genetic counseling is also recommended for people with LI. Siblings of patients and parents of patients could be asymptomatic carriers. Genetic testing and counseling are recommended to prevent new cases [15].

Conclusion

LI is a rare genetic disease affecting 5–10 per 100 000 people. Patients with LI could be susceptible to depression and low quality of life. Diagnosis of LI is usually established clinically, but in difficult cases, genetic testing of *TGM1* gene can be useful. Treatment of LI consists of oral retinoid, topical agents, supportive therapy, avoidance of certain agents, and genetic counseling.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Majmundar VD, Baxi K. Hereditary and acquired ichthyosis vulgaris. [Updated 2022 Aug 8]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK562318/.

2 Tabri F. Lamellar ichthyosis: one case report. Int J Med Rev Case Rep 2019; 1:270.

3 Karim N, Iqbal J, Naeem M. Co-occurrence of autosomal recessive lamellar ichthyosis and x-linked recessive ichthyosis in a consanguineous Pakistani family. Ann Dermatol 2019; 31:581.

4 Arias-Pérez RD, Gallego-Quintero S, Taborda NA, Restrepo JE, Zambrano-Cruz R, Tamayo-Agudelo W, *et al.* Ichthyosis: case report in a Colombian man with genetic alterations in ABCA12 and HRNR genes. BMC Med Genomics 2021; 14:140.

5 Cavusgil PL. Lamellar Ichthyosis [Internet]. National Organisation for Rare Disease. 2020 [cited 2021 Aug 16]. Available at: https://rarediseases.org/rare-diseases/ichthyosis-lamellar/

6 Metze D, Traupe H, Süßmuth K. Ichthyosis—a clinical and pathological spectrum from heterogeneous cornification disorders to inflammation. Dermatopathology 2021; 8:107–123.

7 Cortés H, Rojas-Márquez M, Reyes-Hernández OD, Morales-Morfín JC, Guapillo-Vargas MRB, Varela-Cardoso M, *et al.* Increased risk of depression and impairment in quality of life in patients with lamellar ichthyosis. Dermatol Ther 2021; 34:1.

8 Takeda M, Nomura T, Sugiyama T, Miyauchi T, Suzuki S, Fujita Y, *et al.* Compound heterozygous missense mutations p.Leu207Pro and p.Tyr544Cys in TGM1 cause a severe form of lamellar ichthyosis. J Dermatol 2018; 45:1463–1467.

9 Zeng J, Shan B, Guo L, Lv S, Li F. Compound heterozygous mutations in TGM1 causing a severe form of lamellar ichthyosis: a case report. Pharmgenomics Pers Med 2022; 15:583–588.

10 Vahlquist A, Fischer J, Törmä H. Inherited nonsyndromic ichthyosis: an update on pathophysiology, diagnosis, and treatment. Am J Clin Dermatol 2018; 19:51–66.

11 Nasser KK, Banaganapalli B, Shinawi T, Elango R, Shaik NA. Molecular profiling of lamellar ichthyosis pathogenic missense mutations on the structural and stability aspects of TGM1 protein. J Biomol Struct Dynamics 2021; 39:4962–4972.

12 Kang S, Amagai M, Bruckner A, Enk A, Margolis D, McMichael A, *et al.* Fitzpatrick's dermatology in general medicine. 9th ed. New York: McGraw-Hill Education; 2019.

13 Chao K, Aleshin M, Goldstein Z, Worswick S, Hogeling M. Lamellar ichthyosis in a female neonate without a collodion membrane. Dermatol Online J 2018; 24:2.

14 Palamar M, Karaca I, Onay H, Ertam I, Yagci A. Dry eye and Meibomian gland dysfunction with meibography in patients with lamellar ichthyosis. Contact Lens Anterior Eye 2018; 41:154–156.

15 Richard G. Autosomal recessive congenital ichthyosis. GeneReviews®. StatPearls [Internet]; 2017.

16 Cortés H, Magaña JJ, Reyes-Hernández OD, Zacaula-Juárez N, González-Torres M, Diaz-Beltrán W, *et al.* Non-invasive analysis of skin mechanical properties in patients with lamellar ichthyosis. Skin Res Technol 2019; 25:375–381.

17 Mazereeuw-Hautier J, Hernández-Martín A, O'Toole EA, Bygum A, Amaro C, Aldwin M, *et al.* Management of congenital ichthyosis: European guidelines of care, part two. Br J Dermatol 2019; 180:484–495.

18 Hanson B, Becker L, Hook K, Polcari I, Areaux RG, Maguiness S. Ectropion improvement with topical tazarotene in children with lamellar ichthyosis. Pediatr Dermatol 2017; 34:584–589.

19 Binkhonain FK, Aldokhayel S, BinJadeed H, Madani A. Successful treatment of an adult with atopic dermatitis and lamellar ichthyosis using dupilumab. Biol Targets Ther 2022; 16:85–88.

20 Moraes ELL de, Freire MH, de S, Rocha F, Secco IL, Costa T, Afonso RQ. Nursing care for a newborn with lamellar ichthyosis. Rev Escola Enfermagem USP 2019; 53:e03519.

Genetics of Lamellar Ichthyosis

ORIGINALITY REPORT

19%	14%	15%	9%
SIMILARITY INDEX	INTERNET SOURCES	PUBLICATIONS	STUDENT PAPERS

PRIMARY SOURCES

1	Submitted to National postgraduate Medical College of Nigeria Student Paper	4%
2	mdpi-res.com Internet Source	3%
3	Submitted to University of Iowa Student Paper	3%
4	www.dovepress.com Internet Source	2%
5	"Harper's Textbook of Pediatric Dermatology", Wiley, 2019 Publication	2%
6	www.mdpi.com Internet Source	1%
7	pediatricneurosciences.com Internet Source	1%
8	www.ncbi.nlm.nih.gov Internet Source	1%
9	staffsites.sohag-univ.edu.eg	

	Internet Source	1%
10	www.dermaamin.com Internet Source	1%
11	Submitted to So. Orange County Community College District Student Paper	1%
12	www.coursehero.com Internet Source	1%
13	www.researchgate.net Internet Source	1%

Exclude quotes	On	Exclude matches	< 1%
Exclude bibliography	On		