ANNALS OF MEDICAL AND SURGICAL DERMATOLOGY
2023, VOL. 1, ISSUE 1, pp. 16-19
https://doi.org/10.61577/amsd.2023.100004

RESEAPRO JOURNALS

REVIEW

OPEN ACCESS

Molecular genetics and pathogenesis of ichthyosis

Suman Panda

Department of Biotechnology, MITS School of Biotechnology, Utkal University, Odisha, India

ABSTRACT

Ichthyosis encompasses a group of rare and heterogeneous genetic skin disorders characterized by defective epidermal barrier function, resulting in various clinical presentations of hyperkeratosis and scaling. In recent years, significant advances have been made in understanding the molecular genetics and pathogenesis of ichthyosis. The pathogenesis of ichthyosis is complex and varies depending on the underlying genetic defect. Over 20 genes have been identified as causing ichthyosis, and many more are likely to be discovered in the future. Recent research has unveiled the complex pathogenic mechanisms contributing to ichthyosis, from defects in epidermal barrier function to immune system involvement. This increased understanding is driving the pursuit of innovative treatment modalities, including biologics, small molecular inhibitors, and gene therapy, potentially revolutionizing ichthyosis management. This review provides a comprehensive understanding of the molecular genetics and pathogenesis of ichthyosis, a group of rare skin diseases characterized by abnormal skin barrier function and a range of clinical manifestations. It underscores the importance of recent genetic discoveries in shedding light on the underlying causes of various forms of ichthyosis and the potential for nanotechnology-based formulations to enhance therapeutic efficacy in managing these challenging conditions.

KEYWORDS

Mutation; Keratosis; Genetic therapy; Phenotype; Dermatitis

ARTICLE HISTORY

Received 20 August 2023;
Revised 13 October 2023;
Accepted 19 October 2023

Introduction

The study of the molecular genetics and pathogenesis of ichthyosis has significantly advanced, identifying various causative genes and underlying mechanisms responsible for this group of inherited skin disorders. The First Ichthyosis Consensus Conference 2009 played a pivotal role in achieving international consensus on the nomenclature and classification of inherited ichthyoses. This consensus led to a revised classification and terminology for these conditions. Skin barrier defects are a central component of the pathogenesis in several types of ichthyosis. The genetic mutations associated with ichthyosis encompass a range of molecules, including ABCA12, lipoxygenase-3, 12R-lipoxygenase, CYP4F22, ichthyin, and steroid sulfatase, which are all linked to intercellular lipid layers [1]. ABCA12, for instance, is responsible for transporting lipids in keratinocytes, and mutations in this gene can result in severe phenotypes, such as harlequin ichthyosis. Other causative molecules include transglutaminase 1, keratins (specifically, keratins 1, 10, and 2), and filaggrin. Transglutaminase 1 forms the cornified cell envelope, while keratins and filaggrin are essential for various aspects of skin structure. Understanding these genetic defects and ichthyotic disease pathomechanisms is critical for developing effective treatments and providing valuable genetic counseling, including prenatal diagnosis for affected families [2].

Ichthyosis is a hereditary skin disorder characterized by distinctive features, including skin abnormalities resembling fish scales and a skin integrity disruption. It is classified into two main categories: congenital and acquired ichthyosis. Congenital ichthyosis is further divided into various subtypes based on the presentation of skin changes, the disease's course, and any associated pathologies. Notable subtypes within this category include ichthyosis vulgaris, lamellar ichthyosis, and X-linked ichthyosis. Each subtype has its distinct mode of inheritance, prevalence in the population, and clinical features, and can be confirmed through histological examination of skin biopsies and electron microscopic assessment [3,4]. Acquired ichthyosis, conversely, can result from a wide range of underlying causes, including neoplastic conditions, infectious diseases, drug reactions, endocrine disorders, metabolic abnormalities, autoimmune conditions, and malabsorptive states. Managing ichthyosis involves topical treatments and, in severe cases, systemic therapies tailored to the specific subtype and its underlying etiology. These findings underscore the importance of understanding the diverse manifestations of ichthyosis for accurate diagnosis and effective management.

Congenital ichthyosis constitutes a group of rare genetic skin diseases caused by pathogenic mutations in more than 50 genes. These disorders are clinically characterized by dry skin, peeling, hyperkeratosis, and, in some cases, erythroderma. While they predominantly affect the skin, syndromic forms of congenital ichthyosis can also lead to severe complications in other organs and systems. Patients with congenital ichthyosis often experience reduced quality of life due to their physical appearance, uncomfortable symptoms, and treatment limitations. Management of these conditions involves daily skin care and, in some cases, systemic medications [5]. However, no definitive cure exists for ichthyosis, requiring a multidisciplinary approach to alleviate the symptoms and improve the patient's quality of life. The heterogeneity and similarity in clinical manifestations pose diagnostic challenges, particularly in the syndrome.

***Correspondence:** Suman Panda, Department of Biotechnology, MITS School of Biotechnology, Utkal University, Odisha, India, e-mail: sumanpanda1397@gmail.com

Pathogenesis of Ichthyosis

The study investigates the molecular genetics and pathogenesis of ichthyosis, a group of rare skin disorders primarily characterized by impaired skin barrier function. These conditions often result from genetic mutations affecting lipid metabolism in the epidermis. The research focuses on X-linked recessive ichthyosis (XLRI) as a representative case, where mutations in the steroid sulfatase (STS) gene lead to cholesterol sulfate accumulation, disrupting the skin's permeability barrier. The study identifies specific gene expression changes in XLRI patients, highlighting the absence of inflammation or repair pathways activation. Additionally, the research explores the effects of moisturizers on the skin barrier, revealing improvements in skin dryness without significant impact on transepidermal water loss, skin pH, or gene expression [6]. The findings underscore the need for a deeper understanding of the molecular mechanisms underlying ichthyosis to develop more targeted therapeutic strategies, such as utilizing pathway-specific interventions, as demonstrated in other lipid metabolic disorders like CHILD syndrome and X-linked ichthyosis. This pathogenesis-driven approach offers a promising and cost-effective avenue for potential treatments in the field of ichthyosis.

The review explores the molecular genetics and pathogenesis of ichthyosis, a diverse group of rare skin diseases characterized by localized or generalized scaling, palmoplantar keratoderma, erythroderma, recurrent infections, and hypohidrosis. A fundamental feature of ichthyoses is the abnormal barrier function of the skin, which triggers compensatory hyperproliferation and transepidermal water loss [7]. The stratum corneum is the primary contributor to maintaining barrier function, comprised of cornified cells enclosed by a corneocyte lipid envelope and intercellular lipid layers, primarily composed of ceramides. Human genetics research has played a pivotal role in unraveling the significance of the epidermal lipid barrier in ichthyoses. In addition, discoveries in animals and humans have identified mutations in novel genes responsible for disorders of keratinization. Recent advances in next-generation sequencing have expanded our knowledge, revealing novel mutations disrupting the ceramide pathway and resulting in disorders of keratinization.

Ichthyosis comprises a rare and clinically diverse group of 36 skin diseases with Mendelian inheritance, collectively called Mendelian Disorders of Cornification (MeDOC) [8]. These diseases result from mutations in 35 known genes, impacting various processes such as keratinocyte differentiation, lipid synthesis, metabolism, and DNA repair. Despite the high molecular heterogeneity that arises from these mutations, they lead to a common effect: the disruption of the epidermal barrier and an elevation in transepidermal water loss. This disturbance in the fundamental function of the epidermal barrier activates repair mechanisms within the epidermis, resulting in hallmark symptoms of MeDOC, including hyperkeratosis, skin scaling, erythema, fissures, and inflammation. Notably, the secondary effect of mutations in different genes is consistent –the disruption of the epidermal barrier and elevated transepidermal water loss [9]. Consequently, hyperkeratosis is driven by the compromised epidermal barrier. The diagnosis of ichthyosis is critical not only for genetic counseling but also for providing patients with adequate information about prognosis and available therapeutic options, and recent advancements in genetic knowledge and DNA sequencing methods have made accurate diagnosis increasingly feasible.

The etiology of ichthyosis can vary, with some cases attributed to genetic factors and others appearing in an acquired or paraneoplastic context. The genetic forms of ichthyosis, known as inherited ichthyoses, are particularly well-documented [10]. They stem from gene mutations, mainly expressed in the upper epidermal layers. They are classified into syndromic and non-syndromic entities based on the presence or absence of additional symptoms beyond skin abnormalities. Irrespective of the specific genetic mutation, these conditions typically share a common pathological feature—a defective epidermal barrier. The disturbance in the epidermal barrier function is at the core of ichthyosis pathogenesis. The skin barrier's primary function is to prevent water loss and protect the body from external threats. In ichthyosis, abnormal scaling and hyperkeratosis are associated with disruptions in this crucial function [11]. The stratum corneum, a critical component of the skin barrier, comprises cornified cells surrounded by a corneocyte lipid envelope and intercellular lipid layers, predominantly consisting of ceramides. Mutations in various genes affect the synthesis and metabolism of these lipids, leading to a compromised skin barrier and clinical features such as hyperkeratosis, skin scaling, erythema, fissures, pruritus, inflammation, and skin pain.

Ichthyosis can take on various forms, with different genetic mutations resulting in unique clinical presentations. For example, autosomal recessive exfoliative ichthyosis, characterized by dry, scaly skin exacerbated by moisture and minor trauma, has been linked to mutations in the protease inhibitor cystatin A (CSTA) gene [12]. The absence of CSTA protein leads to cell-cell adhesion defects in keratinocytes, particularly under mechanical stress. In other cases, ichthyosis may be associated with mutations in the filaggrin gene (FLG) or the CASP14 gene, which plays a role in filaggrin processing. These genetic mutations disrupt epidermal differentiation processes and compromise the epidermal barrier.

The epidermal barrier impairment in ichthyosis triggers compensatory responses within the skin, ultimately leading to the observed hyperkeratosis and skin abnormalities. Consequently, a deeper understanding of the pathogenesis of ichthyosis has led to the development of therapeutic approaches, such as emollients, humectants, and keratolytic agents, to alleviate the skin's distressing symptoms [13]. Recent advances in genetic knowledge and DNA sequencing techniques have contributed to more accurate diagnosis and the identification of novel mutations associated with ichthyosis, thus facilitating genetic counseling and improved patient information about prognosis and treatment options. Another dimension of the pathogenesis of ichthyosis concerns the skin microbiome. The skin of individuals with ichthyosis exhibits significant alterations in bacterial and fungal abundances, varying across different subtypes of ichthyosis. Notable shifts in microbial populations, such as reductions in Cutibacterium acnes and Malassezia, indicate skin barrier disruption and lipid depletion. Such changes may play a role in the pathogenesis of ichthyosis [14].

Moreover, epidermal SM synthase (SMS)2, which

https://doi.org/10.61577/amsd.2023.100004

RESEAPRO JOURNALS

modulates sphingomyelin (SM) and ceramide (Cer) levels on plasma membranes, has been investigated. Knockout of SMS2 in mice led to an ichthyotic phenotype characterized by epidermal hyperplasia and hyperkeratosis. These observations highlight the significance of SM and Cer in maintaining epidermal permeability, and the study suggests that exposure to a dry terrestrial environment can trigger compensatory responses that normalize ichthyotic abnormalities over time. While significant progress has been made in understanding the molecular genetics and pathogenesis of ichthyosis, the impact of these disorders extends beyond the skin. Patients with ichthyosis may experience nutrition-related challenges, growth abnormalities, and, in some cases, tissue compromise around the eyes and ears [15]. The rarity of some forms of ichthyosis underscores the need for ongoing research and improved diagnostic and therapeutic approaches.

Quality of life in individuals with ichthyosis can be significantly affected, especially in childhood. Nutritional needs, growth, and the compromise of tissues around the eyes and ears are among the considerations that healthcare practitioners must consider when managing ichthyosis patients. While systemic retinoid therapy has shown some success in treating ichthyosis, challenges in nosology and classification persist, and further research is necessary to advance our understanding of these conditions and to develop more targeted therapies.

Genetics of Ichthyosis

The molecular genetics and pathogenesis of ichthyosis represent an intricate field of study within dermatology and genetics. Ichthyosis is a diverse group of hereditary cornification disorders affecting the skin, characterized by thickened, scaly, and often dry skin. The study of ichthyosis has made remarkable progress in recent years, offering deeper insights into its molecular underpinnings, classification, and pathogenesis. This understanding has paved the way for improved disease classification, prenatal diagnosis, genetic counseling, and clinical management, benefiting patients and healthcare providers [16].

Molecular genetics plays a pivotal role in elucidating the genetic causes of ichthyosis. The genetic basis of these disorders is multifaceted and has been linked to mutations in more than 50 genes. Understanding these genetic abnormalities is crucial for effectively diagnosing and managing patients with ichthyosis. One of the most common types of ichthyosis is ichthyosis vulgaris, which is often inherited in an autosomal dominant manner. This form of ichthyosis is associated with mutations in the gene encoding filaggrin (FLG), a key protein in skin barrier function. While the clinical manifestations of ichthyosis vulgaris can vary, its genetic underpinnings demonstrate the complexity of these disorders [17]. Another noteworthy form of ichthyosis is X-linked ichthyosis, caused by steroid sulfatase (STS) gene mutations. In this condition, males are predominantly affected due to the X-linked inheritance pattern. However, female carriers can exhibit some clinical manifestations, highlighting the importance of understanding ichthyosis's genetics and inheritance patterns.

The genetic basis of autosomal recessive congenital ichthyosis (ARCI) is multifaceted, with mutations in different genes responsible for various phenotypes. For instance, transglutaminase 1 (TGM1) gene mutations can lead to lamellar ichthyosis. In contrast, mutations in the ABCA12 gene can cause harlequin ichthyosis, a severe and often life-threatening form of the disease [18]. Additionally, advances in molecular genetics have also revealed rare forms of ichthyosis associated with specific genes, such as Netherton syndrome, which results from abnormalities in a serum protease inhibitor, and Refsum's disease, linked to the accumulation of phytanic acid. These discoveries have expanded our knowledge of the genetic landscape of ichthyosis [19]. The genetic discoveries in ichthyosis have led to the emergence of genotype-phenotype correlations, providing clinicians with valuable information for diagnosis and prognosis. These correlations offer insights into the clinical presentation of ichthyosis based on specific genetic mutations, which can aid in tailoring treatment approaches and genetic counseling.

Furthermore, advancements in genetic sequencing techniques, such as whole exome sequencing (WES), have facilitated the identification of novel mutations in these genes, broadening the understanding of the genetic underpinnings of ichthyosis. Functional studies and 3D protein modeling have demonstrated how specific mutations, like the p.Arg81His variant in CLDN1, impact protein expression, and structure, leading to the manifestation of ARCI [20]. Moreover, studies have identified genetic variants unique to certain populations, like the c.232C>T variant in the TGM1 gene, which appears as a possible founder mutation among the Pakistani population.
Clinically, ichthyosis is diverse, and the presentation of these conditions can vary significantly. From the severe manifestations of lamellar ichthyosis to the milder forms, such as ichthyosis vulgaris and X-linked ichthyosis, the clinical spectrum has been examined in a review of 127 cases in Sweden [21]. Patients were categorized into three main groups using a combination of phenotypic and genotypic criteria: bullous ichthyosis, non-bullous ichthyosiform erythroderma, and syndromic ichthyosis. Within these groups, further stratifications revealed distinct entities based on mutation analysis, electron microscopy of the epidermis, and various diagnostic techniques. This classification aids in the accurate diagnosis and management of ichthyosis.

In summary, the field of molecular genetics and pathogenesis of ichthyosis has made significant strides in recent years. Identifying causative genes, understanding inheritance patterns, and recognizing genotype-phenotype correlations have enriched our knowledge of these complex skin disorders [22]. This progress enhances our ability to diagnose and manage ichthyosis and opens doors to potential therapeutic interventions that can relieve affected individuals. We must continue exploring the genetic foundations of ichthyosis to advance our understanding of these conditions further and improve patient outcomes.

Discussion

The field of molecular genetics and the pathogenesis of ichthyosis, a group of rare genodermatoses characterized by skin scaling, has witnessed significant progress in recent years [23]. Sequencing technology has played a pivotal role in elucidating the genetic basis of these disorders and shedding light on their pathomechanisms. Despite this remarkable advancement, therapeutic developments have remained limited. Patients with ichthyosis have primarily relied on symptomatic relief treatments, including keratolytics, topical anti-inflammatory agents, emollients, and systemic retinoids. These therapies are often non-specific and accompanied by

https://doi.org/10.61577/amsd.2023.100004

RESEAPRO JOURNALS

side effects, leaving much room for improvement.

The future, however, holds promise for ichthyosis patients. A growing number of researchers are dedicated to developing new, targeted therapies that address the underlying molecular causes of the disease. Recent breakthroughs in the genodermatoses field have fueled this endeavor [23]. The approach to therapeutic intervention is becoming increasingly diverse and multifaceted as different strategies are explored. It remains uncertain whether a single, universal approach will prevail, but the current consensus suggests that a competitive "best athlete approach" will likely offer the most significant benefits for patients.

One noteworthy development in the quest for targeted therapies is the emergence of mechanism-targeted treatments. These therapies are specifically designed to address the root causes of ichthyosis at the molecular level. Several examples of such treatments are in various stages of development, and their potential benefits are eagerly anticipated.

Clinical practice has also evolved in response to these advancements [24]. Pediatric dermatologists who encounter ichthyosis patients now face a transformed landscape. Following recent consensus conferences, the traditional classification system of only six major types of ichthyosis has given way to a more nuanced categorization that distinguishes 36 different types of ichthyosis and 10 related clinical entities. This reclassification has categorized ichthyosis into two main types: non-syndromic, where the genetic defects phenotypic expression is limited to the skin, and syndromic, where the genetic defect manifests in the skin and other organs [25].

Conclusions

The field of ichthyosis research has made significant strides in elucidating the molecular genetics and pathogenesis of these rare and challenging skin disorders. The transition from a simplistic classification to a more detailed and comprehensive system, which recognizes various types of ichthyosis and related clinical entities, reflects the growing understanding of the heterogeneity within this group of conditions. These advancements have improved diagnostic accuracy and enabled better genetic counseling for affected individuals and their families. Recent findings have shed light on the genetic mutations and pathogenic mechanisms responsible for ichthyosis, from disrupted epidermal barrier function to immune system involvement. The prospect of personalized, molecular-based therapies offers hope to those affected by these rare and often debilitating genetic skin disorders. These combined efforts will undoubtedly continue to shed light on the molecular genetics and pathogenesis of ichthyosis and enhance the quality of life for those living with these conditions. The journey toward effective, targeted therapies for ichthyosis is well underway, and it is a journey fueled by determination, innovation, and the shared goal of improving patients' lives.

Disclosure statement

No potential conflict of interest was reported by the authors.

References

1. DiGiovanna JJ, Robinson-Bostom L. Ichthyosis: etiology, diagnosis, and management. Am J Clin Dermatol. 2023;4(2):81-95.
2. Wells RS, Kerr CB. Genetic classification of ichthyosis. Arch Dermatol. 1965;92(1):1-6.
3. Williams ML. Ichthyosis: mechanisms of disease. Pediatr. Dermatol. 1992;9(4):365-368.
4. Goldsmith LA, Baden HP. Management and treatment of ichthyosis. NEJM. 1972;286(15):821-823.
5. Metze D, Süßmuth K, Traupe H. Ichthyoses: a dermatopathological spectrum from heterogeneous cornification disorders to psoriasiform dermatitis. Pathologe. 2020;41(4):326-333.
6. Traupe H, Fischer J, Oji V. Nonsyndromic types of ichthyoses–an update. JDDG. 2014;12(2):109-121.
7. Richard G. Molecular genetics of the ichthyoses. In American Journal of Medical Genetics Part C: Seminars in Medical Genetics. Hoboken: Wiley Subscription Services, Inc., A Wiley Company; 2004. p. 32-44.
8. Malinovská Z, Čonková E. Ichthyosis in Dogs—Congenital Dermatologic Disorder. Folia Vet. 2021;65(3):22-29.
9. Mohamad J, Samuelov L, Assaf S, Malki L, Malovitski K, Meijers O, et al. Autosomal recessive congenital ichthyosis caused by a pathogenic missense variant in CLDN1. Am J Med Genet. Part A. 2022;188(10):2879-2887.
10. Ullah R, Ansar M, Durrani ZU, Lee K, Santos-Cortez RL, Muhammad D, et al. Novel mutations in the genes TGM 1 and ALOXE 3 underlying autosomal recessive congenital ichthyosis. Int J Dermatol. 2016;55(5):524-530.
11. Khan N, Shah K, Fozia F, Khan SA, Muhammad N, Nasir A, et al. Biallelic mutations in FLG, TGM1, and STS genes segregated with different types of ichthyoses in eight families of Pakistani origin. Int J Dermatol. 2023;62(5):672-680.
12. Tao J, Koster MI, Harrison W, Moran JL, Beier DR, Roop DR, et al. A spontaneous Fatp4/Scl27a4 splice site mutation in a new murine model for congenital ichthyosis. PLOS One. 2012;7(11):e50634.
13. Francis JS. Genetic skin diseases. Curr Opin Pediatr. 1994;6(4):447-453.
14. Wohlrab J. Update on ichthyosis with Special Emphasis on Dryness and the impact of Moisturizers. InTreatment of Dry Skin Syndrome: The Art and Science of Moisturizers. Berlin: Springer Publ;ishers; 2012. p. 279-284.
15. Deddy D, Devi M. Epidermal Proliferation and Differentiation in Ichthyosis Vulgaris. JBTR. 2021;5(2):235-247.
16. Oji V, Traupe H. Ichthyosis: clinical manifestations and practical treatment options. Am J Clin Dermatol. 2009;10(6):351-364.
17. Takhtarova TG, Khismatullina ZR, Panova LD, Panova AN. Ichthyosis (concept, pathohistology, clinical picture, treatment). Vestn Dermatol Venerol. 2021;97(3):6-13.
18. Metze D, Traupe H, Süßmuth K. Ichthyoses—a clinical and pathological spectrum from heterogeneous cornification disorders to inflammation. Dermatopathology. 2021;8(2):107-123.
19. Dsane M, Mamta T, Puplampu P, Brefo D, Newman-Nartey M. Case report: The oral health status of siblings with suspected ichthyosis in a peri-urban community of the Central Region of Ghana. Ghana Dent J. 2022;19:65-69.
20. Jaffar H, Shakir Z, Kumar G, Ali IF. Ichthyosis vulgaris: An updated review. Skin health dis. 2023;3(1):e187.
21. Fozia F, Nazli R, Alam Khan S, Bari A, Nasir A, Ullah R, et al. Novel homozygous mutations in the genes TGM1, SULT2B1, SPINK5 and FLG in four families underlying congenital ichthyosis. Genes. 2021;12(3):373.
22. Lefèvre C, Bouadjar B, Karaduman A, Jobard F, Saker S, Özguc M, et al. Mutations in ichthyin a new gene on chromosome 5q33 in a new form of autosomal recessive congenital ichthyosis. Hum Mol Genet. 2004;13(20):2473-2482.
23. Getling ZN, Kuklin VT. Ultrastructural changes in the epidermis in ichthyosis vulgaris. Vestn Dermatol Venerol. 1989;1(6):17-20.
24. Moll I, Traupe H, Voigtländer V, Moll R. The cytoskeleton in hereditary ichthyoses. Hautarzt. 1988;39(2):82-90.
25. Sakai S, Makino A, Nishi A, Ichikawa T, Yamashita T, Taniguchi M, et al. Pathogenic and compensatory mechanisms in epidermis of sphingomyelin synthase 2-deficient mice. Skin Pharmacol Physiol. 2021;34(5):246-252.

https://doi.org/10.61577/amsd.2023.100004