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MINI-REVIEW

The *ABCA12* gene in Harlequin ichthyosis: Insights from bioinformatics and clinical research

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Abstract

Harlequin ichthyosis (HI) is a rare, severe, and congenital disorder that is often life-threatening, characterized by thick, rigid skin and large, diamond-shaped plates. These skin changes are not only aesthetically distressing but also pose significant functional challenges for affected individuals, such as impaired thermoregulation, restricted mobility, and heightened susceptibility to infections. The condition arises due to mutations in the *ABCA12* gene, which encodes a critical lipid transporter protein essential for skin barrier function. Historically, HI was nearly fatal in the neonatal period due to complications such as sepsis, respiratory distress, and electrolyte imbalances from excessive transepidermal water loss. However, advances in intensive neonatal care–including humidified incubators, prophylactic antibiotics, and early nutritional support–have improved survival rates to over 50% in recent decades. Despite these gains, lifelong morbidity persists, with survivors often facing chronic skin inflammation, recurrent infections, and psychosocial challenges stemming from disease visibility. This review paper explores the genetic underpinnings of HI, focusing on *ABCA12* mutations and their effects on epidermal differentiation and the formation of the skin's stratum corneum. By utilizing advanced bioinformatics tools, including whole-exome sequencing, researchers are now able to identify mutations with high precision and investigate the genotype–phenotype correlations in HI. The review also examines the clinical challenges posed by HI, therapeutic strategies currently available, and the potential for innovative treatments such as gene therapy and skin-engineering. The paper aims to highlight the vital role bioinformatics plays in understanding the molecular mechanisms of HI, facilitating earlier diagnosis and personalized management for affected individuals. Advances in genetic research have provided new hope for improved outcomes and better quality of life for those affected by this debilitating condition.

Keywords: Harlequin ichthyosis; *ABCA12* gene; Genetic mutations; Lipid transport; Whole-exome sequencing; Gene therapy

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1. Introduction

Harlequin ichthyosis (HI) is a rare, autosomal recessive disorder that manifests at birth with distinctive, severe skin abnormalities. The hallmark features of HI include hyperkeratotic plaques, a rigid and thickened skin surface, and deep fissures.[1] These skin changes are not only aesthetically distressing but also pose significant functional challenges for affected individuals. The disease is caused by mutations in the *ABCA12* gene, which encodes a lipid transporter protein integral to maintaining the skin's barrier function. Defective lipid transport, a result of these mutations, disrupts the epidermal differentiation process and impairs the formation of the stratum corneum, leading to the characteristic features of HI.[2]

Conventionally, HI was associated with a high neonatal mortality rate due to complications such as dehydration, infections, and respiratory distress.[3] However, thanks to advances in neonatal care and early interventions, survival rates have markedly improved in recent years. Understanding the genetic basis of HI and the role of ABCA12 has opened the door to innovative treatment options, which this paper will explore in detail.

In this review, we delve into the genetic mechanisms underlying HI, focusing on *ABCA12* mutations and their effects on the skin's structure and function. Moreover, we examine how bioinformatics techniques, especially whole-exome sequencing (WES), contribute to the identification of mutations and help establish genotype-phenotype correlations. We also explore current therapeutic approaches, including topical treatments, systemic therapies, and the emerging possibilities offered by gene therapy and skin-engineering technologies.

2. Genetic mechanisms and the role of ABCA12 in HI

Mutations in the *ABCA12* gene, located on chromosome 2q34, are the primary causal factor of HI.[4] This gene encodes the ABCA12 protein, a member of the ATP-binding cassette family of transporters. The protein plays a crucial role in lipid transport, particularly in the synthesis and transfer of lipids to the outermost layer of the epidermis, known as the stratum corneum.[2] The stratum corneum forms a critical barrier against environmental insults, preventing dehydration and infection.

The pathophysiology of HI can be understood through the lens of epidermal differentiation and lipid metabolism. The skin is composed of several layers, with the outermost layer (the stratum corneum) acting as the first-line defense against dehydration, pathogen invasion, and other environmental threats. The stratum corneum consists of dead keratinocytes (corneocytes) that are surrounded by a lipid-rich extracellular matrix, which provides a barrier function.[5]

In individuals with HI, *ABCA12* mutations lead to defective lipid transport, disrupting the synthesis of essential lipids such as ceramides, cholesterol, and fatty acids.[6] These lipids are crucial for the formation of the lipid bilayer in the stratum corneum. When lipid transport is impaired, the corneocytes do not properly mature or form a stable barrier, resulting in the characteristic thick, scaly plaques, and fissures seen in HI. The severity of the disease is influenced by the nature of the *ABCA12* mutations. Loss-of-function mutations, such as deletions or nonsense mutations, typically lead to more severe forms of the disease, while missense mutations may cause milder presentations.[4]

However, it must be noted that not all mutations are created equal. Over 60% of HI-associated *ABCA12* mutations are nonsense or frameshift variants (*e.g.*, p.Arg130*), leading to truncated, non-functional proteins and severe phenotypes.[7] In contrast, missense mutations (*e.g.*, p.Gly1501Val) may retain partial lipid transport activity, correlating with milder disease.[4] Structural modeling predicts that mutations in nucleotide-binding domains disrupt ATP hydrolysis, essential for lipid translocation.

3. The role of bioinformatics in the study of genetic diseases

Bioinformatics has become an indispensable tool in the study of genetic diseases, enabling researchers and clinicians to identify mutations and explore genotype–phenotype correlations with unprecedented precision. With advancements in sequencing technologies and computational tools (Table 1), the field of bioinformatics has transformed our understanding of rare genetic disorders such as HI.

3.1. WES and mutation identification

WES has revolutionized the identification of genetic mutations in rare disorders such as HI. This technique focuses on sequencing the protein-coding regions of the genome, which contain the majority of disease-causing mutations. This approach is both cost-effective and efficient, allowing researchers to pinpoint pathogenic mutations that would be challenging to identify using traditional genetic testing methods.[8]

Through WES, researchers can efficiently identify mutations in the *ABCA12* gene, which is responsible for HI. Identifying the specific mutation(s) in a patient not only facilitates accurate diagnosis but also offers insights

Table 1. Summary of the contributions of bioinformatics and sequencing technologies to the study and management of HI

Approach/ Technology	Function	Benefits	Challenges/ Limitations
WES	Focuses on protein-coding regions	Efficiently identifies disease-causing mutations	Limited to exons, may miss non-coding mutations
Genotype-phenotype analysis	Correlates mutations with clinical outcomes	Predicts disease severity, guides treatments	Requires comprehensive datasets
Functional prediction tools	Assesses impact of mutations on proteins	Enhances understanding of molecular mechanisms	May have limited accuracy for novel mutations
NGS	Comprehensive genomic analysis	Rapid, accurate, and applicable to neonates	High cost, data interpretation complexity

Abbreviations: HI: Harlequin ichthyosis; NGS: Next-generation sequencing; WES: Whole-exome sequencing.

into the potential severity of the disease. For instance, certain mutations in the *ABCA12* gene are associated with more severe clinical manifestations, enabling clinicians to predict disease outcomes and tailor treatment strategies accordingly.[4] Beyond variant calling, however, WES pipelines must handle large-scale genomic datasets, requiring tools like GATK for variant filtering and ANNOVAR for annotation, ensuring robust data quality control.[8-10]

3.2. Genotype-phenotype correlations and functional predictions

One of the key strengths of bioinformatics lies in its ability to establish genotype–phenotype correlations. By analyzing genetic data, researchers can determine how specific mutations influence disease severity and clinical presentation.[9] In the case of HI, bioinformatics tools can predict the functional consequences of *ABCA12* mutations, providing insights into how these alterations disrupt lipid transport and epidermal differentiation. These tools include PolyPhen-2 and SIFT, which typically analyze missense variants and predict pathogenicity based on evolutionary conservation and structural disruption.[8,9] For novel variants, AlphaFold-generated ABCA12 structures model atomic-level impacts, such as ATP-binding domain destabilization, while MD simulations (molecular dynamics) assess lipid-binding affinity changes.[10] In addition, tools such as KEGG and Reactome map *ABCA12* variants to disrupted lipid metabolism pathways, clarifying how mutations alter ceramide biosynthesis and epidermal barrier formation.[6,9] These tools collectively refine genotype–phenotype maps, guiding prognostic stratification.[4,9]

3.3. Next-generation sequencing (NGS) technologies

The advent of NGS technologies has significantly improved the speed, accuracy, and accessibility of genetic diagnoses. This technology allows for comprehensive analysis of the *ABCA12* gene and other relevant genomic regions, even in neonates.[10] Early detection of pathogenic mutations through NGS facilitates timely interventions and the development of personalized treatment plans, improving patient outcomes. Moreover, the scalability of NGS enables large-scale studies, contributing to a broader understanding of HI and similar genetic disorders.[11]

By integrating bioinformatics, WES, and NGS, researchers and clinicians are better equipped to tackle the challenges of diagnosing and managing genetic diseases like HI. These tools not only enhance diagnostic accuracy but also pave the way for personalized medicine and targeted therapies.

4. Current therapeutic approaches in HI

The management of HI has evolved significantly over the past few decades, largely due to advancements in neonatal care and a deeper understanding of the disease's genetic basis.[12] While there is no definitive cure for HI, several treatment strategies have been developed to manage symptoms and improve the quality of life for affected individuals.[13] In the following sections, we expand on the primary therapeutic approaches and explore additional emerging strategies. These comparisons are summarized in Table 2.

4.1. Neonatal care in HI

Effective neonatal management is critical for HI survival. Immediate placement in humidified incubators (60 – 80% humidity) reduces life-threatening fluid loss and electrolyte imbalances.[3,12] Prophylactic antibiotics (*e.g.*, ampicillin/ gentamicin) and ceramide-based emollients mitigate infection risk and partial barrier restoration.[12-15] Nutritional support via nasogastric tubes addresses hypermetabolic demands, while non-adhesive dressings minimize skin trauma.[16-18] Despite improved survival (>50%), challenges persist due to the lack of standardized protocols and long-term sequelae.[12,18] Rapid WES in neonatal intensive care units may enable mutation-specific care, such as tailored lipid formulations.[4,10]

4.2. Topical treatments

Topical treatments remain the cornerstone therapies for managing the characteristic skin abnormalities

Table 2. Comparative summary of the different therapeutic approaches

Therapeutic approach	Mechanism of action	Benefits	Challenges/ Limitations
Topical emollients	Hydrate and soften skin, reduce water loss	Improves skin integrity, prevents cracking	Requires frequent application
Keratolytic agents	Break down excessive keratin buildup	Enhance skin texture, prevent fissures	Risk of irritation or systemic absorption
Oral retinoids	Regulate epidermal differentiation	Reduce hyperkeratosis, improve appearance	Side effects like teratogenicity, toxicity
Gene therapy	Deliver functional *ABCA12* gene	Potentially addresses root cause	Still in preclinical stages
Skin- engineering techniques	Create bioengineered skin replacements	Long-term solution for skin defects	Experimental, require further research
Therapeutic bathing	Softens scales, maintains hygiene	Improves hydration and comfort	Time-consuming, requires special setups
Multidisciplinary support	Comprehensive care across specialties	Addresses holistic needs	Requires coordination and resources

in HI.[12] Emollients, such as petroleum-based ointments or specialized moisturizers, help to hydrate the skin and maintain its elasticity. They soften the thickened, scaly skin and provide a protective barrier to reduce water loss and prevent cracking.[3] Keratolytic agents, including salicylic acid, urea, and topical retinoids, are used to reduce the buildup of keratin.[14] These treatments improve skin texture and prevent the formation of fissures, which are prone to infection. Careful application is necessary to avoid irritation or systemic absorption. In addition, the use of topical antiseptics or antibiotics may be warranted in cases where the skin barrier is compromised, as this can help to prevent bacterial colonization and secondary infections.[15]

4.3. Systemic therapies

Systemic therapies aim to address the underlying skin abnormalities by targeting the excessive keratinization seen in HI. Oral retinoids, such as acitretin or isotretinoin, are used to regulate epidermal differentiation and reduce hyperkeratosis.[16] These medications can lead to dramatic improvements in skin thickness and scaling. However, due to potential adverse effects–including teratogenicity, liver dysfunction, and hyperlipidemia–their use requires careful monitoring and individualized dosing.[17] Supportive care, including systemic hydration, nutritional support, and electrolyte management, is often necessary for neonates and infants with HI, given their compromised skin barrier and increased risk of fluid loss.[18]

4.4. Gene therapy

Emerging therapeutic strategies are focusing on addressing the genetic root of HI, encompassing both gene replacement therapy and gene editing technologies, and offering hope for more definitive treatments. Since HI is caused by mutations in the *ABCA12* gene, gene therapy represents a promising approach. The goal is to deliver a functional copy of the gene to skin cells, potentially restoring normal lipid transport and improving the skin barrier. Although still in preclinical stages, advances in gene-editing technologies such as CRISPR-Cas9 have shown potential in correcting genetic mutations *in vitro*.[19]

4.5. Skin-engineering techniques

In addition, bioengineered skin substitutes and cultivated skin grafts are being explored as treatments for HI. These approaches involve the creation of skin replacements that can mimic the structure and function of normal skin. Early studies in animal models suggest that such techniques could provide a sustainable solution for replacing damaged skin.[20,21]

4.6. Adjunctive and supportive therapies

Adjunctive and supportive therapies also play a crucial role in managing HI. Regular therapeutic bathing with water or saline, often combined with antiseptic agents, can help to soften scales and maintain hygiene.[16,22] Adding emollients to bathwater can also improve hydration. Pain and discomfort from skin cracking or infections may require the use of analgesics or anti-inflammatory medications. Living with HI can have a significant emotional and social impact, so counseling and support groups are essential for improving the mental health and quality of life of patients and their families.[17,23] The management of HI often involves a team of specialists, including dermatologists, neonatologists, geneticists, and nutritionists, to address the complex needs of affected individuals.

5. Novel hypothesis: The inflammatory-lipidome axis in HI

While *ABCA12* mutations are well-established as the primary drivers of HI through their disruption of lipid transport and epidermal barrier formation, emerging evidence suggests a broader, systems-level mechanism involving the interplay between lipid metabolism and cutaneous inflammation.[18] We propose a novel hypothesis–the inflammatory-lipidome axis–which conceptualizes HI

pathogenesis as a self-sustaining cycle in which lipidomic disruption, innate immune activation, and secondary barrier dysfunction reinforce one another.

From a systems biology perspective, multi-omics studies in related keratinization disorders such as lamellar ichthyosis and atopic dermatitis have revealed that lipid deficiency in the stratum corneum does not merely compromise the structural barrier but also initiates inflammatory signaling cascades.[18,19] These pathways, often mediated by Toll-like receptors and inflammasomes, lead to the release of pro-inflammatory cytokines and recruitment of immune cells. Although such mechanisms have not been comprehensively characterized in HI, the clinical presentation–marked by fissured, hyperkeratotic skin and recurrent infections–suggests a similar pattern of immune activation. In particular, the profound deficiency of ω-hydroxyacyl sphingosines in HI, essential for acylceramide-mediated barrier formation, may alter keratinocyte stress signaling pathways. This alteration could result in the upregulation of key cytokines, including interleukin (IL)-1β, IL-36γ, and tumor necrosis factor alpha (TNF-α), which further compromise barrier integrity and drive chronic inflammation.

Supporting this hypothesis, bioinformatic pathway enrichment analyses using KEGG and Reactome databases have identified significant intersections between lipid metabolic pathways and inflammatory signaling cascades in gene networks associated with *ABCA12*. Genes such as *ALOX12B*, *ELOVL4*, and *SMPD1*, which are co-expressed with *ABCA12* during epidermal differentiation, contribute not only to the biosynthesis of structural lipids but also to the production of lipid-derived inflammatory mediators, including prostaglandins and leukotrienes.[20] These mediators are potent activators of NF-κB and MAPK signaling pathways. This convergence suggests a feedback loop in which defective lipid biosynthesis amplifies inflammatory signaling, which in turn further disrupts lipid homeostasis and epidermal function.

Clinically, patients with HI frequently display signs of persistent erythema and inflammatory skin changes that are only partially responsive to systemic retinoids and topical corticosteroids.[21] While these treatments are typically employed for their effects on differentiation and keratinization, their anti-inflammatory properties may also play a significant role. Importantly, targeted anti-inflammatory therapies–such as IL-1 inhibitors or phospholipase A2 blockers–have not been systematically studied in HI, despite their success in treating other inflammatory skin conditions.[21] Under the proposed inflammatory-lipidome axis framework, such agents may have therapeutic potential, particularly in individuals with residual ABCA12 activity, where inflammation rather than complete lipid absence may predominate.

Testing this hypothesis will require integrative research approaches that combine advanced lipidomic profiling of HI skin to distinguish structural from inflammatory lipid species, and single-cell RNA sequencing to delineate the composition and activation status of immune cell populations in lesional versus unaffected epidermis. In addition, keratinocyte models generated via CRISPR-Cas9 editing of *ABCA12* could be employed to examine the cellular response to lipid perturbation and its link to inflammatory signaling *in vitro*.[22] Together, these strategies may uncover new therapeutic targets and support the repositioning of existing anti-inflammatory drugs within a precision medicine framework for HI. If validated, the inflammatory-lipidome axis could represent a paradigm shift in our understanding of HI, expanding the focus beyond structural lipid restoration to include active immunomodulation as a core component of treatment.[23]

6. Challenges and future directions

Despite the advances in genetic research and treatment options, several challenges remain in the management of HI. The disease's rarity, combined with the complexity of *ABCA12* mutations, makes it difficult to develop standardized treatment protocols. The limited number of affected individuals globally creates challenges for conducting large-scale clinical trials, which are necessary to validate emerging therapies. In addition, the high variability in disease severity based on genotype–phenotype correlations necessitates highly personalized treatment plans for each patient, requiring substantial resources and multidisciplinary care teams.[4]

This is where identification of mutations may play a key role in the treatment of HI. Advances in mutation identification (*e.g.*, WES, NGS) now enable tailored HI management. For loss-of-function mutations (*e.g.*, p.Arg130), early aggressive barrier repair with ceramide-dominant emollients (discussed above) may compensate for absent ABCA12 activity.[6,12] In contrast, missense variants (*e.g.*, p.Gly1501Val) with residual function may respond to lower-dose oral retinoids, minimizing toxicity.[16,17] Emerging therapies such as *ABCA12*-targeted CRISPR (also discussed above) are being prioritized for severe truncating mutations in preclinical models.[19] This mutation-centered paradigm underscores the need for rapid genetic diagnosis to stratify treatment intensity.

However, access to advanced diagnostic tools, such as whole-exome and NGS, can also be limited in resource-poor settings, further complicating timely and accurate diagnoses. The long-term safety and efficacy of emerging

treatments, such as gene therapy and bioengineered skin substitutes, remain largely unknown, underscoring the need for rigorous preclinical and clinical evaluation.

Future research is needed to further elucidate the full spectrum of mutations in the *ABCA12* gene and their relationship to clinical outcomes. Collaborative international efforts can help to establish comprehensive genetic databases, facilitating better genotype-phenotype mapping and improving our understanding of the disease's molecular mechanisms. The integration of bioinformatics tools with advanced genomic techniques will play a pivotal role in these endeavors, enabling the discovery of novel therapeutic targets and strategies. In addition, advancements in patient-derived organoid models and CRISPR-Cas9 gene-editing technologies hold promise for developing personalized treatments that directly address the underlying genetic defects in HI.

7. Conclusion

HI represents one of the most severe forms of congenital ichthyosis, characterized by profound abnormalities in skin barrier function due to mutations in the *ABCA12* gene. These mutations disrupt lipid transport mechanisms critical for normal epidermal differentiation and stratum corneum formation, leading to the characteristic hyperkeratotic and fissured skin phenotype seen in affected neonates.

Over the past decade, advances in bioinformatics and high-throughput genomic technologies–most notably WES–have revolutionized our understanding of HI. These tools have not only facilitated early and accurate diagnosis, often within days of birth, but have also uncovered novel *ABCA12* variants, elucidated genotype–phenotype correlations, and illuminated broader molecular pathways that are disrupted in the disease. Functional annotation tools and network-based pathway analyses are beginning to reveal the downstream inflammatory and metabolic consequences of ABCA12 dysfunction, offering new avenues for therapeutic targeting beyond symptomatic skin care.

While there remains no definitive cure for HI, the therapeutic landscape is slowly expanding. Current treatment strategies, which include systemic retinoids, emollients, keratolytics, and infection control, have improved survival rates and patient outcomes. Meanwhile, emerging approaches–such as gene therapy, lipid replacement therapy, and bioengineered skin grafts–are being explored as next-generation interventions aimed at correcting the underlying molecular defect or restoring barrier integrity. These approaches, though experimental, underscore the translational potential of integrating genomic data with regenerative medicine.

Importantly, the integration of bioinformatics into neonatal care protocols presents a promising future for precision medicine in HI. The prospect of implementing WES in newborn screening, followed by rapid *in silico* analysis of pathogenic variants and affected signaling pathways, could enable mutation-tailored interventions during the critical neonatal period–potentially altering disease trajectory before irreversible damage occurs.

In summary, HI serves as a paradigm for how rare genetic disorders can benefit from interdisciplinary synergy among genomics, informatics, and clinical medicine. Continued investment in these areas will not only enhance our understanding of HI's pathophysiology but also pave the way for highly personalized, effective, and potentially curative therapies. As our molecular toolkit expands, so too does the hope for transforming HI from a devastating neonatal disorder into a manageable chronic condition.

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Conflict of interest

The authors declare they have no competing interests.

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References

1. *Harlequin Ichthyosis: Medline Plus Genetics*. Available from: https://medlineplus.gov/genetics/condition/harlequin-ichthyosis [Last accessed on 2025 Jan 26].
2. *ABCA12 Gene: Medline Plus Genetics*. Available from: https://medlineplus.gov/genetics/gene/abca12 [Last accessed on 2025 Jan 26].
3. Elkhatib AM, Omar M. Ichthyosis Fetalis. In: *StatPearls*.

StatPearls Publishing; 2025. Available from: https://www.ncbi.nlm.nih.gov/books/nbk560492 [Last accessed on 2025 Jan 26].

4. Kelsell DP, Norgett EE, Unsworth H, *et al*. Mutations in ABCA12 underlie the severe congenital skin disease harlequin ichthyosis. *Am J Hum Genet*. 2005;76(5):794-803.

   doi: 10.1086/429844

5. Craiglow BG. Ichthyosis in the newborn. *Semin Perinatol*. 2013;37(1):26-31.

   doi: 10.1053/j.semperi.2012.11.001

6. Bouwstra JA, Nădăban A, Bras W, MCabe C, Bunge A, Gooris GS. The skin barrier: An extraordinary interface with an exceptional lipid organization. *Prog Lipid Res*. 2023;92:101252.

   doi: 10.1016/j.plipres.2023.101252

7. Haller JF, Cavallaro P, Hernandez NJ, *et al*. Endogenous β-glucocerebrosidase activity in Abca12−/−epidermis elevates ceramide levels after topical lipid application but does not restore barrier function. *J Lipid Res*. 2014;55(3):493-503.

   doi: 10.1194/jlr.M044941

8. Meyts I, Bosch B, Bolze A, *et al*. Exome and genome sequencing for inborn errors of immunity. *J Allergy Clin Immunol*. 2016;138(4):957-969.

   doi: 10.1016/j.jaci.2016.08.003

9. Baumgartner C, Mátyás G, Steinmann B, Eberle M, Stein JI, Baumgartner D. A bioinformatics framework for genotype-phenotype correlation in humans with Marfan syndrome caused by FBN1 gene mutations. *J Biomed Inform*. 2006;39(2):171-183.

   doi: 10.1016/j.jbi.2005.06.001

10. King AD, Deirawan H, Klein PA, Dasgeb B, Dumur CI, Mehregan DR. Next-generation sequencing in dermatology. *Front Med (Lausanne)*. 2023;10:1218404.

    doi: 10.3389/fmed.2023.1218404

11. Buermans HP, Den Dunnen JT. Next generation sequencing technology: Advances and applications. *Biochim Biophys Acta*. 2014;1842(10):1932-1941.

    doi: 10.1016/j.bbadis.2014.06.015

12. Tsivilika M, Kavvadas D, Karachrysafi S, Sioga A, Papamitsou T. Management of harlequin ichthyosis: A brief review of the recent literature. *Children (Basel)*. 2022;9(6):893.

    doi: 10.3390/children9060893

13. *What Is Harlequin Ichthyosis? Cleveland Clinic*. Available from: https://my.clevelandclinic.org/health/diseases/harlequin-ichthyosis [Last accessed on 2025 Jan 26].

14. Jacobi A, Mayer A, Augustin M. Keratolytics and emollients and their role in the therapy of psoriasis: A systematic review. *Dermatol Ther (Heidelb)*. 2015;5(1):1-18.

    doi: 10.1007/s13555-015-0068-3

15. Lainingwala AC, Gajula S, Fatima U, *et al*. A unique case of harlequin ichthyosis in the tertiary health care system in a rural Area. *Cureus*. 2023;15(8):e43342.

    doi: 10.7759/cureus.43342

16. DiGiovanna JJ, Mauro T, Milstone LM, Schmuth M, Toro JR. Systemic retinoids in the management of ichthyoses and related skin types. *Dermatol Ther*. 2013;26(1):26-38.

    doi: 10.1111/j.1529-8019.2012.01527.x

17. *Retinol Intoxication - an Overview. Science Direct Topics*. Available from: https://www.sciencedirect.com/topics/medicine-and-dentistry/retinol-intoxication [Last accessed on 2025 Jan 26].

18. Parikh K, Brar K, Glick JB, Flamm A, Glick SA. A case report of fatal harlequin ichthyosis: Insights into infectious and respiratory complications. *JAAD Case Rep*. 2016;2(4):301-303.

    doi: 10.1016/j.jdcr.2016.06.011

19. Sharma G, Sharma AR, Bhattacharya M, Lee SS, Chakraborty C. CRISPR-Cas9: A preclinical and clinical perspective for the treatment of human diseases. *Mol Ther*. 2021;29(2):571-586.

    doi: 10.1016/j.ymthe.2020.09.028

20. Foley E, Robinson A, Maloney M. Skin substitutes and dermatology: A review. *Curr Derm Rep*. 2013;2(2):101-112.

    doi: 10.1007/s13671-013-0044-z

21. Anish S. Skin substitutes in dermatology. *Indian J Dermatol Venereol Leprol*. 2015;81:175.

    doi: 10.4103/0378-6323.152288

22. Chakraborty A. Bathing practices in dermatology: Uses and implications for patient management. *Indian Dermatol Online J*. 2023;14(5):686-691.

    doi: 10.4103/idoj.idoj_40_23

23. Cortés H, Cariño-Calvo L, Reyes-Hernández OD, *et al*. High levels of anxiety, depression, risk of suicide, and implications for treatment in patients with lamellar ichthyosis. *Healthcare (Basel)*. 2023;11(14):2071.

    doi: 10.3390/healthcare11142071