Causative genes of ichthyoses
Ichthyoses are heterogeneous genetic skin diseases that are characterized by thickened and desquamating skin. Causative genes are associated with stratum corneum (SC) formation. The two most common ichthyoses are ichthyosis vulgaris and recessive X-linked ichthyosis. Ichthyosis vulgaris is caused by gene variants in FLG encoding FLG (Oji et al., 2010), and it is known to increase the risk of developing atopic dermatitis (AD). Recessive X-linked ichthyosis results from variants in STS. STS encodes steroid sulfatase, and STS abnormalities lead to the accumulation of cholesterol sulfate and result in corneocyte retention (Oji et al., 2010). In addition to the most common two ichthyoses, there are nonmajor forms. Representatives of these rare ichthyoses include lamellar ichthyosis (LI), congenital ichthyosiform erythroderma (CIE), Netherton syndrome (NS), and epidermolytic ichthyosis (EI). LI, CIE, and NS are autosomal recessive, and EI is autosomal dominant. There are several causative genes for CIE and EI, some of which are shared, whereas most cases of LI are due to biallelic variants of TGM1 that encodes transglutaminase 1, a gene involved in the formation of the cornified envelope (Oji et al., 2010). Variants in genes involved in lipid metabolisms such as ALOX12B, ALOXE3, CYP4F22, and NIPAL4 more commonly lead to CIE (Paller, 2019). NS results from variants in SPINK5, in which deficiency of the proteinase inhibitor LEKTI causes excessive corneocyte exfoliation (Oji et al., 2010). EI most commonly results from heterozygous variants in keratin genes K1 or K10, showing severe blister and erosion formation as well as hyperkeratosis (Oji et al., 2010).

Skin inflammation and treatment resistance in nonmajor ichthyoses
Ichthyosis vulgaris and recessive X-linked ichthyosis usually respond to topical emollients and keratolytic agents. The current treatments for rare subtypes of ichthyoses are challenging, despite the discovery of causative gene variants and their functions. The nonmajor ichthyoses usually show resistance to topical therapies, and the efficacy of oral retinoids is also often inadequate. In addition, anti-inflammatory ointments such as topical calcineurin inhibitors are difficult to use because of systemic absorption (Allen et al., 2001). Differences in treatment responsiveness may reflect the presence or absence of skin inflammation. Ichthyosis vulgaris and X-linked ichthyosis usually do not show skin inflammation. Erythema is absent unless complicated by other inflammatory conditions such as AD. In contrast, nonmajor ichthyoses often feature skin inflammation as well as hyperkeratosis (Oji et al., 2010), which might cause low treatment responses. Therefore, further understanding of the inflammatory aspects of each ichthyosis, based on molecular mechanisms, is needed.

Although several studies using RT-qPCR and microarray have previously suggested that the four orphan-form ichthyoses (i.e., LI, CIE, NS, and EI) shared T helper (Th) 17/Th22-type inflammation similar to psoriasis, these were not conclusive because of small sample sizes (Malik et al., 2019; Paller et al., 2017). In their article in the Journal of Investigative Dermatology, Kim et al. (2022) performed skin transcriptomic analysis on more samples (Total: n = 54, NS: n = 7, LI: n = 16, CIE: n = 18, and EI: n = 13), showing that the Th17/Th22 pathway was upregulated and that genes related to tight junctions were downregulated in these rare ichthyosis subtypes.

Barrier dysfunction in nonmajor ichthyoses
Using global transcriptomic analysis, Kim et al. (2022) showed that the downregulation of several lipid metabolism markers was observed, except in the case of EI. These markers included genes related to the synthesis of intercorneocyte
lipids such as sphingolipids and ceramides (e.g., ELOVL3 and FA2H), which could be involved in SC barrier dysfunction through impairment of moisture retention and increased transepidermal water loss. Furthermore, downregulation of the genes encoding cadherins and claudins (CDH10/12/19/20 and CLDN5/8/11/23), components of adherence junctions and tight junctions in stratum granulosum, is shared among the orphan-form ichthyoses examined (i.e., LI, CIE, NS, and EI). Because the genes responsible for ichthyoses are involved in SC formation and are not directly related to the formation of the tight junction barrier, the downregulation of the tight junction–related genes may be due to skin inflammation consequent to disruption of the SC barrier rather than due to a primary phenomenon in orphan-form ichthyoses. Barrier function abnormalities in the stratum granulosum may lead to further inflammation by triggering immune responses to external pathogens and antigens (Figure 1).

In contrast, many genes that are related to epidermal differentiation were upregulated. These included genes that play a role in cornified envelope formation such as those encoding some small proline-rich proteins (SPRP1A/1B/2C/2G), involucrin (IVL), late cornified envelope 3D (LCE3D), and cornifelin (CNFN). Cornified envelope lines the cornified lipid envelope, the outermost layer of corneocytes, from the inside, acting as a strong barrier against mechanical stress and external substances such as chemicals and pathogens. Upregulation of these cornified envelope–associated genes may be a compensatory response to barrier dysfunction due to the downregulation of tight junction and lipid metabolism genes, resulting in desquamative and hyperkeratotic skin that is apparent clinically (Figure 1).

These variances of gene expression involved in barrier function are not being proposed for the first time. Previous skin microarray data, albeit from fewer samples (n = 21), had already shown downregulation of genes related to tight junctions (CLDN1/8/23) and lipid metabolism (ELOVL3) and upregulation of cornified envelope-related genes such as LCE3D (Malik et al., 2019).

**Inflammatory profiles in nonmajor ichthyoses**
Unlike the two major ichthyoses, ichthyosis vulgaris and recessive X-linked ichthyosis, nonmajor ichthyoses often feature marked skin inflammation. Several studies have suggested that upregulation of the Th17/Th22 pathway is shared among nonmajor ichthyoses. Induction of IL17A/C/F and several other IL-17–related genes such as CXCL1 and CCL20 in the lesional skin of several orphan-form ichthyoses was shown by RT-qPCR in 21 patients (Paller et al., 2017) and 29 patients (Malik et al., 2019), respectively. Skin microarray data (n = 21) also showed upregulation of IL-17, although statistical significance was not observed (Malik et al., 2019).
Kim et al. (2022) performed a comprehensive transcriptomic analysis on 54 patients with one of the four orphan-form ichthyoses (i.e., LI, CIE, NS, and EI) that showed a significant upregulation of various Th17- and Th22-related genes, including IL17A/C/F, CXCL1, elafin gene PI3, LCN2, and S100A7/8/9/12 in all of the subtypes. IL23R was upregulated in CIE, EI, and LI, and IL22 was upregulated in NS and CIE. Gene Set Variation Analysis also indicated a skewing of the Th17/Th22 pathway with robust upregulation in its markers. The authors additionally performed RT-qPCR on these samples and confirmed that Th17/Th22-related genes were upregulated. Integrating these transcriptomic results with previously published flow cytometry data (Czarnowicki et al., 2018), the authors showed significant positive correlations between several Th17/Th22 markers and IL-22.

The Downregulation of the epidermal barrier–related genes, Th17/Th22 inflammation is a principal player in the pathogenesis of nonmajor ichthyoses and may contribute to SC and stratum granulosum barrier dysfunction that could lead to further inflammation, which extends beyond the skin (Figure 1).

Although robust activation of the Th17/Th22 pathway was shared by all of the four orphan-form ichthyoses examined, Kim et al. (2022) also showed that other inflammatory pathways such as Th1 and Th2 showed somewhat different trends in each subtype, although these were generally modest. IL12RB2 was upregulated in NS, CIE, and EI, but other Th1-related genes such as IFNγ, IL12B, and CXCL9/11 were upregulated in CIE alone. Changes in the Th2 pathway were minimal among LI, CIE, and EI. Even in NS, where clinical similarities to AD are known, several Th2-related genes such as CCL18 and IL4R were elevated, whereas many other important genes involved in the Th2 pathway (e.g., IL31, IL13, CCL13, and CCL17) did not show a statistically significant increase in expression.

**Therapeutic prospects for nonmajor ichthyoses**

Uregulation of the Th17/Th22 inflammatory pathway and epidermal differentiation genes indicates shared inflammatory reactions between nonmajor ichthyoses and psoriasis. Several case reports have already shown favorable efficacy of several molecular-targeted drugs for psoriasis in patients with rare subtypes of ichthyoses, including mAbs against IL-17A (Luchsinger et al., 2020) and IL-12/IL-23 (Volc et al., 2020). This study has validated these empirical cases on the basis of the molecular characteristics of the inflammatory reactions, and this will facilitate future clinical research.

Psoriasis causes systemic as well as skin inflammation, and it is associated with an increased risk of cardiovascular events (Liu et al., 2022). Although much remains unknown about extracutaneous manifestations of nonmajor ichthyoses, blocking inflammatory pathways may benefit patients with these rare ichthyoses beyond the improvement of skin symptoms, as may also be the case in psoriasis.

**Challenges and opportunities**

The pathophysiology of nonmajor ichthyoses involves impairment of SC formation as well as tight junction barriers, downregulation of lipid metabolism, and significant Th17/Th22 inflammation. It is still unknown how abnormalities in SC formation lead to secondary Th17/Th22 type inflammation and why Th17/Th22 is predominant rather than other types of inflammation. AD is another disease that is characterized by epidermal barrier dysfunction and chronic skin inflammation, in this case, in association with impaired SC formation due to FLG deficiency. However, the predominant inflammation in AD is Th2 driven and not Th17/Th22 driven. Why nonmajor ichthyoses and AD induce different immune responses, despite both of them having SC barrier dysfunction due to genetic variants, is a challenging unsolved mystery. In addition, it is intriguing that each subtype of ichthyosis shows a characteristic phenotype (enhanced Th1 in CIE, enhanced Th2 in NS, and preserved lipid metabolism in EI). Solving these difficult issues in these rare genetic diseases should clarify the fundamental mechanisms of immune responses in the skin.

**CONFLICT OF INTEREST**

The authors state no conflict of interest.

**REFERENCES**


