Skin Barrier Function and mRNA Expression Profiles in Patients with Atopic Dermatitis, Ichthyosis Vulgaris, and X-linked Recessive Ichthyosis: Aetiopathogenic Differences and the Impact of Moisturizing Treatment

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Torborg Sturesdotter Hoppe defended her PhD thesis on March 8th 2013 in Uppsala, Sweden. The thesis was supervised by Professor Berit Berne, Associate Professor Hans Törmä and Professor Anders Vahlquist, Department of Medical Sciences, Dermatology and Venereology, Uppsala University Hospital, Uppsala, Sweden. The opponent was Prof Charlotta Enerbäck, Faculty of Health Sciences at Linköping University, Linköping, Sweden.

Atopic dermatitis (AD), ichthyosis vulgaris (IV), and X-linked recessive ichthyosis (XLRI) are characterized by dry skin and impaired skin barrier. AD and IV are related to loss-of-function mutations in *FLG* (encoding filaggrin), whereas XLRI is caused by deletions or inactivating mutations in the *steroid sulphatase* gene (*STS*). Patients regularly use moisturizing creams, but little is known about the creams' effects on the skin barrier.

The present work combines objective scorings, non-invasive techniques, and molecular analyses of skin biopsies to characterize the skin in 57 patients with AD, IV, or XLRI, and in 14 healthy controls. Patients were classified according to their FLG and STS mutation status: AD with *FLG*+/+ ($n=14$), AD with *FLG*+/– ($n=14$), AD/IV with *FLG*–/– ($n=15$), and XLRI with *STS*– ($n=14$), including one man with a novel point mutation. Assessments were conducted at baseline and after 4 weeks of treatment with 3 different moisturizers applied to volar forearm skin.

At baseline, dryness scoring and non-invasive assessments verified impaired skin barrier function in all patients. The microarray analysis identified several up- or down-regulated mRNA transcripts involved in signalling pathways important for inflammation and barrier repair in patients with AD and/or IV. The skin phenotype and number of altered transcripts were correlated with the *FLG* mutation status; *FLG*–/– patients displayed the highest transepidermal water loss (TEWL) and the most altered transcript levels. In contrast, despite an equally dysfunctional skin barrier, only 27 altered mRNA transcripts were found in XLRI patients (Fig. 1.).

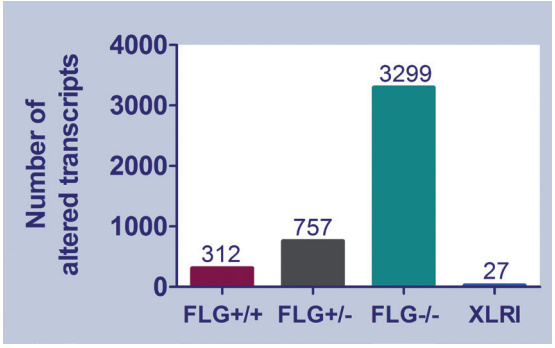

Fig. 1. Number of transcripts with altered expression, identified using oligonucleotide array analysis, in the 4 patient groups versus healthy controls.

From left: Professor Jan Faergemann, Associate Professor Hans Törmä, Professor Berit Berne, Torborg Sturesdotter Hoppe, Professors Anders Vahlquist, Charlotta Enerbäck, Tove Agner, and Lennart Emtestam.

Treatment with moisturizers improved skin dryness similarly in all groups, but TEWL behaved differently in the two types of ichthyosis: it decreased slightly in the AD/IV group and increased in the XLRI group, especially after urea treatment. Despite increased TEWL and massive up- or down-regulation of epidermal genes at baseline, especially in *FLG*–/– patients, qPCR analysis performed before and after treatment with moisturizer

detected virtually no change in the genes selected as biomarkers of epidermal inflammation, lipid metabolism, and barrier repair.

In conclusion, FLG mutations elicit pro-inflammatory mechanisms probably aimed at restoring barrier competence. This does not occur in patients with XLRI, presumably because accumulation of cholesterol sulphate in association with STS deficiency automatically increases the barrier thickness without need of a compensatory up-regulation of epidermal genes. Moisturizing treatment improves skin dryness in patients with AD, IV, or XLRI, but does not seem to normalize the altered epidermal gene expression profile in AD/IV patients.