

showed the greatest increase in risk (odds ratio (OR) 52.9 (95% CI 6.6–∞) and OR 8.0 (95% CI 1.6–37.2), respectively) for a subsequent diagnosis of SCLE. No increased risks were found when other systemic antimycotics were investigated. Exposure to anti-epileptic and proton pump inhibitors (PPIs) 0–6 months before SCLE diagnosis showed approximately three-fold elevated risk estimates and two-fold elevated risks were seen for thrombocyte inhibitors, angiotensin-converting-enzyme (ACE)-inhibitors and non-specific anti-inflammatory drugs (NSAIDs). The analysis was repeated after excluding SCLE cases previously diagnosed with SLE. However, no significant

changes in the estimates were found. Approximately one-third of all SCLE cases can be attributed to previous drug exposure.

This thesis adds to previous knowledge about epidemiology, disease progression to SLE, comorbidity and the association with certain drugs in CLE. Swedish population-based epidemiological data on CLE will potentially be useful in the planning of healthcare as well as clinical trials. For prospective studies, especially of the intermediate group between CLE and SLE, population-based quality registers will be needed to further improve healthcare for patients with CLE.

Genetic studies of skin barrier defects

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Mårten C.G. Winge defended his thesis entitled “genetic studies of skin barrier defects with focus on atopic dermatitis” at Karolinska Institutet, Stockholm on February 10th 2012. His main supervisor was Associate Professor Maria Bradley and co-supervisors were Professor Magnus Nordenskjöld, Professor Carl-Fredrik Wahlgren and Med Dr Agne Liedén. The opponent was Associate Professor Charlotta Enerbäck from Linköping University. The thesis is available at <http://hdl.handle.net/10616/40880>.

The thesis comprised five papers focusing on the skin barrier dysfunction underlying common disorders of keratinization such as atopic dermatitis, ichthyosis vulgaris and x-linked recessive ichthyosis.

Atopic dermatitis (AD) is a common, complex inflammatory skin disorder where a defect skin barrier is central in the pathogenesis. Mutations in the filaggrin gene cause ichthyosis vulgaris (IV). IV is one of several keratinization disorders named ichthyoses where mutations in skin barrier genes are a common underlying genetic factor. Furthermore, filaggrin mutations are a major risk factor for moderate to severe AD. The aim of the work reported in the thesis is to improve the understanding of the genetic mechanisms of skin barrier defects associated with AD, and to identify whether AD and other common disorders of keratinisation may share genetic susceptibility factors related to skin barrier dysfunction.

The thesis presents data suggesting that filaggrin mutations may be rare in AD and IV patients from Ethiopia (1). This is the first study investigating an association in a native African population and highlights the population-specificity flag-



Mårten Winge defended his thesis in Stockholm, Sweden on February 10th 2012. From left: Mårten Winge, Associate Professor Maria Bradley, Professor Carl-Fredrik Wahlgren, Professor Magnus Nordenskjöld, Med Dr. Agne Liedén, Opponent Associate Professor Charlotta Enerbäck.

grin mutations display. A lack of association with filaggrin indicates that other mechanisms should be more important in the pathogenesis of IV and AD in this ethnic group and further studies are warranted to elucidate the pathogenesis among these patients.

Both psoriasis and AD are considered to exhibit disturbed epidermal barrier function. As filaggrin mutations are associated with an early onset of AD, and is a modifying factor in χ -linked recessive ichthyosis, filaggrin association to childhood onset of psoriasis was tested. No association to any prevalent filaggrin mutations was found, and no novel mutations. This indicates that filaggrin loss-of-function variants is not associated with age of onset of psoriasis (2).

A patient was encountered with clinical signs of common ichthyosis type. Our analysis did not reveal any filaggrin mutations or any steroid sulfatase gene deletions (which is the common causative genetic factor underlying χ -linked recessive ichthyosis). Instead, a novel point mutation in the steroid sulfatase gene was detected in this patient, which emphasizes the value of genotyping the entire gene (3).

The molecular pathways and functional parameters *in vivo* is also further outlined in patients with AD and IV in relation to filaggrin mutations. Functional parameters and gene expression in molecular pathways *in vivo* is altered in patients suffering from AD and IV and depend on filaggrin genotype. Patients with filaggrin mutations displayed a severe phenotype with impaired barrier function measured as increased trans-epidermal water loss, and significantly altered pH levels. Furthermore, the numbers of genes with altered expression were significantly higher in patients with low or absent filaggrin expression. These pathways include many genes involved in

inflammation, epidermal differentiation, lipid metabolism, cell signalling and adhesion (4).

Finally, a candidate gene study is presented, where expression analysis links the epidermal transglutaminases 1 and 3 to the manifestation of AD and genetic analysis suggests that genetic variation at the transglutaminase 1 locus could be involved in the development of the disease (5).

The results of the work reported in the thesis provide additional descriptive information and further elucidates the pathogenesis underlying AD and other disorders of keratinization, in particular in relation to filaggrin deficiency. Better understanding of the genetic factors and molecular and functional consequences should hopefully enable future individually designed barrier restoring therapy.

List of publications

1. Winge MCG, Bilcha KD, Liedén A, Shibeshi D, Sandilands A, Wahlgren CF, et al. Novel filaggrin mutation but no other loss-of-function variants found in Ethiopian atopic dermatitis patients. *Br J Dermatol* 2011; 165: 1074–1080.
2. Winge MCG, Suneson J, Lysell J, Nikamo P, Liedén A, Nordenskjöld M, et al. Lack of association between filaggrin gene mutations and onset of psoriasis in childhood. *J Eur Acad Dermatol Venereol* 2011 Dec 20. doi: 10.1111/j.1468-3083.2011.04403.x. [Epub ahead of print].
3. Winge MCG, Hoppe T, Liedén A, Nordenskjöld M, Vahlquist A, Wahlgren CF, et al. Novel point mutation in the STS gene in a patient with X-linked recessive ichthyosis. *J Dermatol Sci* 2011; 63: 62–64.
4. Winge MCG, Hoppe T, Berne B, Vahlquist A, Nordenskjöld M, Bradley M, et al. Filaggrin genotype determines functional and molecular alterations in skin of patients with atopic dermatitis and ichthyosis vulgaris. *PLoS One* 2011; 6: e28254.
5. Liedén A, Säaf A, Winge MCG, Kockum I, Ekelund E, Wahlgren CF, Nordenskjöld M, Bradley M. Genetic association and expression analysis of the epidermal transglutaminases in atopic dermatitis. Submitted for publication.