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Genetic studies of skin barrier defects with focus on atopic dermatitis

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ABSTRACT

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 this 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. **Paper I** presents data suggesting that filaggrin mutations may be rare in Ethiopian AD and IV patients, implying other mechanisms should be more important in the pathogenesis of IV and AD in this ethnic group. **Paper II** presents a novel mutation in the steroid sulfatase gene in a patient with clinical signs of common ichthyosis type. In **paper III** association between filaggrin mutations and 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 do not have a strong effect on the onset of psoriasis in childhood. In **paper IV** it is demonstrated that 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. **Paper V** represents a candidate gene study 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. The results of the work reported in this thesis provides 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. **ISBN 978-91-7457-631-3**