

Autosomal recessive congenital ichthyoses (ARCI) form a group of rare, severe disorders of keratinization with a prevalence of 1 in 100.000 to 200.000 persons in the European population. Phenotypes and genetic etiology are both extremely heterogeneous. Up to date six different loci and the genes at these loci were described. Scales affect the entire body and vary in size, color, adherence and shape from patient to patient depending on patient age, the climate, and state of therapy. Erythema and palmoplantar hyperkeratosis are also often seen.

In 2002, when this work started, only 3 disease causing genes, *TGM1*, *ALOXE3*, and *ALOX12B* were known. *ALOXE3* and *ALOX12B* on chromosome 17p13, with 15 exons each, code for two epidermal lipoxygenases, 12R-LOX and eLOX-3. Epidermis-type lipoxygenases (LOX) are preferentially synthesized in skin.

This work describes the molecular and clinical findings in 208 families with ARCI originating from Middle Europe, Turkey, and India. In summary 20 novel point mutations of *ALOXE3* and *ALOX12B*, including 15 missense mutations, in 26 families have been identified. To analyse the activity of proteins carrying missense mutations, recombinant mutated genes were expressed in HEK-293 cells, total protein was isolated and incubated with the corresponding genuine substrate, and enzymatic activity was measured.

Analysis of reaction products demonstrated that all but one recombinant mutants showed no enzymatic activity. The active mutant (c.434G>A) was shown to represent a splice-site mutation. The destroyed splice-site was analysed in a cell-based mini-gene assay. This work showed, that missense mutations in *ALOX12B* or *ALOXE3* lead to inactive enzymes and can be associated with the ARCI phenotype.

Genotype/phenotype correlation studies showed that mutations in *ALOX12B* or *ALOXE3* result in a mild form of ARCI.

The gene coding for *Ichthyin* on chromosome 5q33 was recently found to be mutated in patients with ARCI.

In this work a total of 182 ARCI patient samples from non related families were analysed for mutations in *Ichthyin*. Additionally 144 non related healthy control samples were analyzed. The gene for *Ichthyin* consists of 6 exons coding for a 404 aa protein. In result five different mutations on 40 chromosomes of 31 families were identified. However, two mutations previously found in patient samples were identified on 26 chromosomes of 144 control samples. In silico characterisation of the so far unknown ichthyin-protein was part of this work. This made it possible to discuss the mutations found. The cDNA of *Ichthyin* was then cloned for further functional studies and a polyclonal antibody against the protein was generated.