Identification of Mutations in SDR9C7 in 6 Families with Autosomal Recessive Congenital Ichthyosis

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Autosomal recessive congenital ichthyosis (ARCI) is a heterogeneous group of disorders of keratinization. To date, ARCI has been associated with following genes: ABCA12, ALOX12B, ALOXE3, CERS3, CYP4F22, NIPAL4, TGM1, PNPLA1 and recently SDR9C7 and SULT2B1.\(^1\)\(^-\)\(^6\) Furthermore, seven patients from a large consanguineous family were described as ARCI due to a homozygous mutation in LIPN.\(^7\) However, the first symptoms appeared only from the age of 5 years and the criterion of a congenital form of ichthyosis is not fulfilled. In this study we report the clinical and molecular findings of seven ARCI patients

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who carried five previously unreported mutations in *SDR9C7*. We could identify homozygous mutations in *SDR9C7* using whole exome sequencing in three patients belonging to two families (P1-1, P1-2, P2). A subsequent screening of genetically unsolved ARCI cases revealed four additional patients (P3-P6) with mutations in *SDR9C7* (reference sequence NM_148897.2).

All seven patients showed a relatively mild ichthyosis phenotype with generalized dry and scaly skin and a mild or local erythema (Fig. 1). With one exception (P2), the patients were not born as collodion babies (CB). In one case (P3), the ichthyosis phenotype firstly appeared at the age of 6 months. In three patients (P2, P3, P4) keratoderma of feet and/or hands was observed, P3 showed only a mild palmar hyperkeratosis. Three further patients (P1-1, P1-2 and P6) presented hyperlinearity of palms and soles. Erythema was present in most of our patients, but only at birth or in mild and local forms. Fungal infections were frequent in three patients (P1-1, P1-2, P3). Anhidrosis was observed in four patients (P2, P3, P4, P6), while two patients (P1-1, P1-2) had no problems with sweating. Two patients (P3, P6) had swollen hands, feet or legs.

The mutation c.112G>A (p.Gly38Arg, rs764593071), that we found in three families (homozygous in P1-1/P1-2, heterozygous in P4, P6), is located in the motif Thr-Gly-X-X-X-Gly-X-Gly in SDR9C7 and corresponds to the last glycine. This highly conserved region is important for the maintenance of the central β-sheet, which is essential for cofactor binding, suggesting a strong functional impairment of SDR9C7 in these patients. In P4 and P6, we identified the heterozygous mutation c.551A>G (p.Asp184Gly, rs138435128). The amino acid Asp at position 184 is highly conserved in mammals and birds and is located in the neighbouring region of the motif Tyr-X-X-X-Lys, which responds amino acids 172-176 in
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contrast, the patients of Mohammad et al.\textsuperscript{3} present a relatively mild phenotype with mild fine whitish scales. Furthermore it is noteworthy that many cases had complicating dermatophytic infections, which appears to be a frequent finding in patients with \textit{SDR9C7} mutations.

In summary, we identified five previously unreported pathogenic \textit{SDR9C7} mutations. The mutation c.112G>A seems to be a recurrent mutation that is predicted to impair a highly conserved region. Our results strongly support the findings of previous studies,\textsuperscript{2-5} and thus underlines that \textit{SDR9C7} is a novel causative gene for ARCI. Further analyses are necessary to understand the function of the SDR9C7 protein in the skin, the interaction with other proteins and the pathological pathway to develop the phenotype.

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**References**


**figure legend:**

Figure 1: Clinical and histological features in patients with $SDR9C7$ mutations. (a-c) (P1-2, 35 years old man): Peculiar reticular scaly pattern on the trunk (a), plate-like scales with redness are observed on extremities (b), palmar hyperlinearity on the hand (c). (d-f) (P3, 72 years old woman): Left arm and upper back showing coarse scaling (d), lower arms with lamellar scaling (e), palms with mild hyperkeratosis (f). (g-i) (P6, 28 years old woman): coarse scaling on the back (g), hyperkeratosis on dorsal feet with mild pitting oedema (h), moderate palmoplantar keratoderma and palmar erythema (i). (j-k): HE staining revealed acanthosis with thickening of the stratum spinosum and stratum granulosum in the skin of P1-2 (k) compared to control (j). In P1-2, the number of horny lamellae is increased with absence of parakeratosis. Scale bar (j-k): 25µm. (l-m): Ultrastructure in P3 revealed no consistent aberrations of components involved in terminal differentiation and keratinization. Granular cells display normal morphology with keratin bundles (K), keratohyaline granules (KH), desmosomes (D) and lamellated lamellar bodies (LB). Scale bars 500nm (l) and 200nm (m). (n-o): IF staining of $SDR9C7$ (green) revealed an expression of $SDR9C7$ in the stratum granulosum and lower stratum corneum. There is no significant difference in the expression of $SDR9C7$ in P6 (o) compared to control (n). (p-q): IF staining of $SDR9C7$ (green) and TGM1 (red). The TGM1 expression is increased in P6 (q) compared to control (p). Scale bar (n-q): 20µm. We used the primary antibodies Goat polyclonal anti-$SDR9C7$ ($SDR$-O) (E-14, sc-169269, Santa Cruz) and Mouse monoclonal anti-TGM1 (TGase1) (E-6, sc-166467, Santa Cruz) and the Donkey anti-Goat IgG (H+L) Secondary Antibody, Alexa Fluor 488 (Thermo Fisher Scientific).