Dermatology

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Genodermatoses as a clue to cancer development

Genodermatoses are inherited skin diseases, some of them with a high impact on life quality. We are doing research on genodermatoses with an increased risk to or a remarkable frequency of non-melanoma skin cancer (NMSC), the most common skin cancer in the human general population. Most frequent NMSC are basal cell carcinomas (BCC) and cutaneous squamous cell carcinoma (cSCC). We focus our studies on epidermodysplasia verruciformis (EV) and ichthyosis with confetti (IWC), and aim to improve the knowledge on correlation of mutation and development of NMSC.

EV

Epidermodysplasia verruciformis (EV) is a rare autosomal recessively inherited genodermatosis with about 500 patients described in literature. EV patients develop plane wart-like lesions mainly on neck and extremities during childhood and have a high risk for early development of NMSC (Fig. 1). Patients have an increased susceptibility to specific human papilloma virus (HPV), usually beta-HPV. These HPV are harmless for the general population because they miss a specific gene named E5. E5 is supposed to be necessary for HPV to overcom the human immune system. About 60 % of EV patients present bi-allelic mutations in the genes *TMC6*/*EVER1* or *TMC8*/*EVER2*. Function of both proteins and pathomechanism in EV are unknown. Since EV patients are prone to infections by E5-missing HPV it is assumed that TMC6 and TMC8 are part of innate immune system. Immunocompromised patients after organ transplatation have a 60-fold increased risk for development of NMSC compared to the immunocompetent population. We hypothesized that rare SNPs in one of both *TMC* genes are correlated to their risk, but our investigations of renal transplant cohort from Basel could not confirm such a correlation. Our team was able to expand the phenotypical spectrum of EV by careful examination of patients. Investigations of both *TMC* genes revealed new mutations and we characterized the stability of correlated mRNA. Identification and analysis of an undescribed gene in EV by the group from J-L Casanova (Rockefeller University, NY; INSERM and Imagine Institute Paris, France) in collaboration with our group will help to characterize pathomechanisms beyond EV.

IWC

IWC is an ultra-rare autosomal dominant inherited genodermatosis with less than 50 patients described in literature. IWC patients are born with an erythematous scaling skin (Fig. 2A). During childhood patients develop thousands of white spots on their skin which look like normal skin (Fig. 2B). By conscientious clinical examination of largest patient group we defined additional clinical features such as malformation of ears (Fig. 2C) and hypoplastic mammillae (Fig. 2D). Those specific

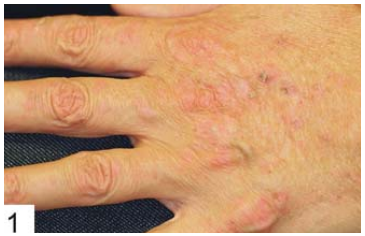

Fig. 1: Plane wart-like lesions typical in EV are present on the left hand of a patient.

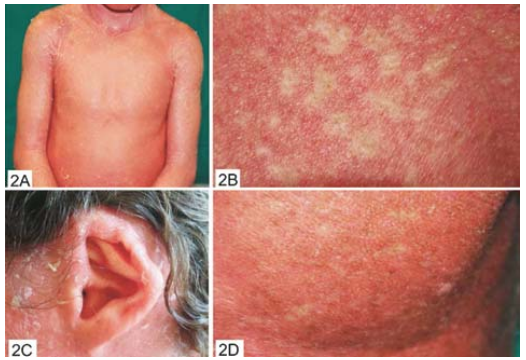

Fig. 2A: IWC patients are born with an erythematous and scaly skin covering the whole body. **B.** Later on life, usually during early childhood, white spots arise which are typical for IWC. **C.** Clinical features which may help to differentiate IWC from other ichthyoses are malformation of ears and **D.** hypoplastic mamillae.

characteristics may help to distinguish IWC patients from other erythematous ichthyoses before development of typical white spots. Patients with IWC carry a heterozygous mutation in the 3'-end of *keratin 10 (KRT10)* which leads to an arginine-rich C-terminus in the resulting protein instead of glycin-richness. Presumably that switch in charge induces a nuclear signal of the aberrant keratin 10 (K10) resulting in a nuclear accumulation instead of cytoplasmic localisation. In epidermal keratinocytes of IWC patients, but not in the underlying dermis as we could show, lots of mitotic recombinations or gene conversions occur on the chromosome with the *KRT10* gene. That leads to a loss of heterozygosity (LOH) of the mutation without loss of copy number and results in keratinocytes which express only wildtype KRT10. Those cells present as white spots on patients' skin. Even though examined IWC patients carried various mutations and the detected number of arginine differed relevant, no genotype-phenotype correlation could be defined. In contrast to EV, patients with IWC are not excessively reported to develop cSCC, but single reports of early NMSC development exists. Since the disease is ultra-rare estimation of NMSC risk is very difficult. Future research of our group aims for identification of the mechanism underlying the disease and leading to a prognosis for the patients regarding their tumour risk, especially on the skin.

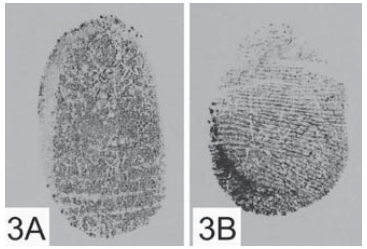

Fig. 3A: Adermatoglyphia is a rare phenotype which can be sign of a syndrome or occur as an isolated feature. In that case it is caused by specific mutations in *SMARCAD1*. **B.** Healthy control.

Connection to Clinical Practice

Molecular investigation of genetically determined skin diseases

Our research focuses on rare genetic skin diseases which could function as a model for general mechanisms. Most impact is applied to skin carcinoma development with the aim to understand basic mechanisms and identify new targets for tumour therapy. Patients who suffer from the related disease are under medical treatment in the Clinic of Dermatology. Since all of our research activities is close-by the needs of the patients we also examine single families outside of carcinoma topics. For instance, we could analyse the germline mutation in a family without fingerprints. In cooperation with an Israeli dermatological research group we identified a specific splice variant of *SMARCAD1* as a transcript responsible for development of fingerprints on human palms and soles (Fig. 3).
The knowledge of the underlying cause of their skin disease is important for the patients, not only for estimation of cancer risk but also for the interpersonal relationships as skin is an important mediator between human individuals.

Selected Publications

Spoerri I, Brena M, De Mesmaeker J, Schlipf N, Fischer J, Tadini G, Itin PH, Burger B. (2015) The phenotypic and genotypic spectra of ichthyosis with confetti plus novel genetic variation in the 3' end of KRT10. From disease to a syndrome. JAMA Dermatol, 151: 64–69

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Burger B, Itin PH. (2014) Epidermodysplasia Verruciformis. Curr Probl Dermatol. 45: 123–131

Nousbeck J, Sarig O, Magal L, Warshauer E, Burger B, Itin P, Sprecher E. (2014) Mutations in SMARCAD1 cause autosomal dominant adermatoglyphia and perturb the expression of epidermal differentiation-associated genes. Br J Dermatol. 171(6): 1521–1524

Eytan O, Qiaoli L, Nousbeck J, van Steensel MAM, Burger B, Hohl D, Taieb A, Prey S, Bachmann D, Avitan-Hersh E, Chung HJ, Shemer A, Trau H, Bergman R, Fuchs-Telem D, Warshauer E, Israeli S, Itin PH, Sarig O, Uitto J, Sprecher E. (2014) Increased epidermal expression and absence of mutations in CARD14 in a series of sporadic PRP patients. Br J Dermatol. 170(5):1196–8

Bruegger C, Spoerri I, Arnold AW, Itin PH, Burger B. (2013) MicroRNA expression differs in cutaneous squamous cell carcinomas and healthy skin of immunocompetent individuals. Exp Dermatol. 22: 426–428