500 | Haplosufficiency for alpha- and gamma-adaptin binding protein (AAGAB) p.14 causes clinical features of a spectrum of palmoplantar keratoderma on.

E Pohler,1 O Mami,1 J Hirn,1 M Zarnier,3 H Hsu,3 AD Irving,1 T Nomura,1 JA McGrath,1 CA Murrell1 and W McMahan2 1 Dermatology and Genetic Medicine, University of Dundee, Dundee, United Kingdom, 2 Fararl Furchted University Hospital, Stourao, Tokyo, Japan, 3 Cambroide Insitute for Medical Research, Cambroide, United Kingdom, 4 Southern Central Hospital, Glaaswe, United Kingdom, 5 Royal Intital of Edinburgh, Edinburgh, United Kingdom, 6 Our Lady’s Children’s Hospital, Dalin, Ireland, 7 University of Hokkaido, Sapporo, Japan, and 8 King’s College London, London, United Kingdom.

Palmoplantar keratoderma (PPK) is characterized by circumscribed hyperkeratotic lesions on palms and soles. These genodermatoses exhibit both clinical and genetic heterogeneity. By applying whole exome sequencing to a Scotti kindred with autosomal dominant PPK (OMIM #148600), we identified a heterozygous nonsense mutation in AAGAB, encoding alpha- and gamma-adaptin binding protein p.14. This gene is located within a previously reported PPK locus on chromosome 15p22. Conventional sequencing identified a further 7 heterozygous loci in patients with p.14-associated PPK. Interpreted in the context of severe or mild forms of PPK, the p.14 polypeptide has a GTPase domain related to the Rab superfamily of vesicle transport proteins and was shown biochemically to bind both alpha- and gamma-adaptins, indicative of a role in vesicle trafficking. Consistent with this notion, a number of individuals with p.14 mutations have leukoderma and photosensitivity. Immunohistochemistry showed marker enrichment at cell membranes within the keratinocyte layer. The observed molecular and phenotypic heterogeneity in p.14 mutations paves the way for future therapy of PPK.

501 | Integrin α3 Mutations cause a new disease affecting kidney, lung and skin.

R Shalom-Feuerstein,1 I Petit,2 L Serror,2 E Aberdam,1 H Zhou,3 H van Bokhoven,3 KW im a n4 and GF Laube 2 and L Bruckner-Tuderman 1

In a mouse model, loss of integrin α3 caused skin fragility associated with abnormal keratinization. Here, we identified three patients with homozygous mutations in the integrin α3 gene, which were associated with disrupted basal membrane structures and compromised barrier functions in kidney, lung and skin. The patients had a multi-systemic phenotype that included congenital nephropathic syndrome, interstitial lung disease and epidermolysis bullosa. The renal and respiratory features predominated, and the lung involvement determined the lethal course of the disease. Although skin fragility was mild, it provided clues to the diagnosis. Integrin α3-negative human skin was atrophic, and exhibited detachment of basal keratinocytes from the basement membrane. Transmission electron microscopy and immunofluorescence staining revealed abnormalities of the dermo-epidermal junction, with a thin and discontinuous lamina densa. Electron dense lamina densa deposits were detected by immunohistochemistry. Apoptosis in the skin and basement membrane were increased in integrin α3-null keratinocytes. TGF1 was down-regulated in integrin α3-null keratinocytes, and the inhibitory effect of integrin α3 on TGF1 signaling was enhanced. In integrin α3-null, TGF1-driven matrix remodeling and cell apoptosis were increased. These findings suggest an important role for integrin α3 in the regulation of basement membrane stability and keratinocyte apoptosis. These results demonstrate that integrin α3 plays an important role in the development and maintenance of the basement membrane and its potential therapeutic applications.

502 | Impaired epithelial differentiation of induced pluripotent stem cells from EEC ectodermal dysplasia patients is rescued by a small compound AP4-24/PRIMA-1MET.

R Kishimoto1,2, I Petri1, L Serror2, E Aberdam1, H Zhou3, H van Bokhoven3, W Cha4, H van Bohemen4, W Kwan5 and D Aberdam1 1 INSERM U1063, Evry, France, 2 INSINERCH, Haifa, Israel, 3 Rudolph University, Niemegen Medical Centrum, Niemegen, Netherlands, and 4 Karolinska Institutet, Stockholm, Sweden.

Ectodermal dysplasia is a group of congenital syndromes affecting a variety of ectodermal derivatives. Among them, ectodermal ectodermal dysplasia and cleft lip/palate (EEC) syndrome is caused by single point mutations in the p63 gene, which controls epidermal development and homeostasis. Phenotypic defects of the EEC syndrome include skin defects and limbal stem cell deficiency. In this study, we developed a novel cellular model that recapitulated major embryonic defects related to EEC. Fibroblasts from healthy donors and EEC patients carrying two different point mutations in the DNA-binding domain of p63 were reprogrammed into induced pluripotent stem cell (iPSC) lines. EEC iPSCs showed delayed epithelialization, as evident from K18+ progenitor cells in vitro. K18 expression was shown biochemically to bind both alpha- and gamma-adaptins, indicative of a role in vesicle trafficking. Consistent with this notion, a number of individuals with p.14 mutations have leukoderma and photosensitivity. Immunohistochemistry showed marker enrichment at cell membranes within the keratinocyte layer. The observed molecular and phenotypic heterogeneity in p.14 mutations paves the way for future therapy of EEC.

503 | Topical enzyme replacement therapy restores transglutaminase 1 activity and corrects architecture of transglutaminase 1 deficient skin.

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Transglutaminase 1 deficient lamellar ichthyosis (II) is a severe genetic skin disease, caused by mutations in TGM1. TGM1 encodes transglutaminase 1 (TGI), an intracellular key enzyme for formation of the cornified envelope. TGI deficiency is characterized by collodion baby at birth, dramatically increased transepidermal water loss and lifelong pronounced scaling of the skin. In addition to clinical investigations and sequencing of TGM1, we set up a skin-humanized mouse model for TGI activity and ultrastructural analysis showing cholesterol clefts as important markers further confirm the diagnosis. Currently no causative therapy is available. A variety of methods only provide symptomatic relief. In this study, we had the goal to develop a therapy, which overcomes the problem of keratinocyte migration and intercellular adhesion, and was able to replace the functions of TGI. We therefore tested the effects of a topical TGI on the skin of NOD-SCID mice as a humanized murine model. The topical administration of a TGI liposome containing a synthetic TGI protein had no effect on the skin of NOD-SCID mice. Only when we used a topical TGI liposome containing a synthetic TGI protein and a novel cholesterol cleft mimetic, did we observe a marked improvement of the skin. This finding shows that the previously described TGI enzyme activity is not restricted to the cornified envelope but also present in keratinocytes and keratin in the intercellular space.

504 | p63 transcription factor controls expression of the nuclear envelope components and organization of the nuclear architecture during development of the epidermis.

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During development, multipotent progenitor cells establish tissue-specific programmes of gene expression. p63 is a transcription factor that plays a crucial role in the specification of the ectodermal lineage and has been shown to control gene expression in various epidermal processes such as cell proliferation, differentiation and apoptosis. However, the role of p63 in epidermal development and differentiation is not yet completely understood. We analyzed the expression of the nuclear envelope components lamin A/C, B1, nS1, nS2, lamins A/C and B1 in mouse skin. By measuring the expression of the nuclear envelope components in the epidermis, we show that p63 controls the expression of these proteins in the epidermis. The expression of lamin A/C and B1 is significantly increased in p63-null skin and keratinocytes to demonstrate that the molecular disease mechanisms relate to perturbed epithelial-mesenchymal interactions.

505 | Revertant mosaicism in Kindler syndrome results from slipped mispairing and mitotic recombination.

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Spontaneous gene repair, also referred to as revertant mosaicism, has been documented in several genetic disorders including mitotic recombination, including in the skin. Here, we describe a disseminated pattern of revertant mosaicism observed in six patients with Kindler syndrome, a genodermatosis caused by loss of kindlin-1 and clinically characterized by skin blistering and progressive photosensitivity. All patients exhibited numerous normal-appearing skin patches on the back ground marked by atrophy and dyspigmentation, and presented germline duplication mutations (c.456dupA and c.676dupC) in the kindlin-1 gene. Using laser dissection microscopy to isolate these different skin patches, we identified slipped mispairing in direct nucleotide repeats as the repair mechanism in all investigated revertant skin spots. The sequence around the mutations demonstrated high propensity to mutations, favoring both microinsertions and -deletions. Additionally, in a nucleus in which mitotic recombination generated areas with homologous normal keratinocytes. Restoration of kindlin-1 expression led, not only to clinically, but also structurally (i.e. epidermal thickness, proliferation, dermo-epidermal junction) normal skin. Since loss of kindlin-1 severely impairs keratinocyte proliferation, we predict that revertant cells have a selective advantage that allows their clonal expansion and, consequently, the improvement of the skin condition.
Role of dermal microenvironment in basal cell carcinoma susceptibility of Nevoid Basal Cell Carcinoma Syndrome

E Burty, Y Gache, G Gendronneau, F Brellier, A Valin, M Avril1 and T Claessens

A Genetic and Functional Link Between iRhom2 and ADAM17 in Tylosis with Oesophageal Cancer

MA Brook, SL Etheridge, DC Blaydon and DP Kelkell Centre for Cutaneous Research, Blazeard Institute, GIMLS, London, United Kingdom

Porokeratotic eccrine nevus may be caused by somatic connexin26 mutations

J Euston, P Martin and M van Steensel

Porokeratotic eccrine nevus is caused by somatic connexin26 mutations

A Genetic and Functional Link Between iRhom2 and ADAM17 in Tylosis with Oesophageal Cancer

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A Genetic and Functional Link Between iRhom2 and ADAM17 in Tylosis with Oesophageal Cancer

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Porokeratotic eccrine nevus may be caused by somatic connexin26 mutations

J Euston, P Martin and M van Steensel

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Role of dermal microenvironment in basal cell carcinoma susceptibility of Nevoid Basal Cell Carcinoma / Gorlin’s syndrome

EClinicalDermatology,Paris,France

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Skin fragility is associated with reduced desmosome formation in AEC syndrome

G Ferrone, HAThomson, LD Rea, HOUZHOU, VHvanBlokken, DJ Dixon and CMoreno

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A Fracturing Genomine Mutation In The Gene Encoding Follucin-Interacting Protein FNPI Is Associated With Familial Multiple Discoid Fibromas, A Look-Alike Of Birt-Hogg-Dubé Syndrome

T Claessens, MYvanSteenel, S Sturink, QWalisza and FMerko

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Activators of the ectodysplasin pathway are redefining the timing and opportunities for modulating ectodermal development

K Huhtinen, M Casal, O Gaide, C Kowalczyk, D Heaton and P Schneider

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HDAC inhibition prevents loss of subcutaneous fat in CSB-deficient mice

Gene Can Cause Generalized Arterial Calcification of Infancy in Addition to Pseudoxanthoma Elasticum

Mutations in the ARCC5 Gene Can Cause Generalized Arterial Calcification of Infancy in Addition to Pseudoxanthoma Elasticum

Identification of MCP-1 as a key effector of IL-31 signaling in Primary Cutaneous Amyloidosis

Identification of gain-of-function STAT1 mutations in patients with chronic mucocutaneous candidiasis

Intradermal injection of recombinant human type VII collagen restores collagen function in a canine model of dystrophic epidermolysis bullosa

Diverse TGF-beta signaling activation in fibroblasts from phenotypically discordant monozygotic twin pair affected by recessive dystrophic epidermolysis bullosa

ABCC6 ablation of the ENPP1 gene sequences. To discover the disease-causing gene, we identified genomic regions with sequence homology shared between the two affected siblings but nonsignificant differences in DNA methylation patterns. The more affected twin showed increased DNA methylation at 14 loci with 92 differentially methylated regions within those loci. Interestingly, we found that the more affected twin also had increased expression of TGF-beta receptors 1 and 2, as well as increased expression of TGF-beta signaling molecules, including SMAD3, SMAD7, and SMAD2. These findings suggest that the increased methylation of TGF-beta signaling genes in the more affected twin may be a key contributor to the disease phenotype.

In conclusion, our study highlights the potential role of TGF-beta signaling in the pathogenesis of RDEB and suggests that targeting TGF-beta signaling may be a promising therapeutic strategy for this disease.
518 Comparative genome-wide transcriptome analysis reveals novel human skin-associated genes encoding membrane and secreted proteins

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Using a genome-wide database of gene expression representing 105 different adult human tissues, we were able to conduct the most comprehensive genetic profiling of the normal human skin to date. We identified 689 skin-associated genes (SAGs) that are highly expressed in skin compared to all other tissues. Of the top 100 SAGs, 66 encode known skin markers, 25 are known proteins not previously associated with skin, and most significantly, 9 encode uncharacterized proteins. High levels of skin-associated expression of eight selected uncharacterized SAGs, that encode either secreted or plasma membrane-associated proteins, was confirmed using qPCR and a panel of normal and skin-derived primary cell RNA samples. Two membrane protein SAGs, GRPLB7 and GRPLR115, and two secreted protein SAGs, WFDC5 and SERPINB8, were expressed exclusively by keratinocytes. Finally, WFDC5, GRPLR115 and TIMM45A protein expression was confirmed by immunohistochemistry on skin sections. Our study provides a comprehensive molecular profile of human skin and identifies candidate novel genes for further investigation in skin diseases.

519 Biodegradable and Cationic Polymer Coupled with Minicircle COL7A1 DNA for the Correction Gene Therapy of Recessive Dystrophic Epidermolysis Bullosa

A Akied,1 E Mauer,1 X Hu,1 I Callar,1 Y Zheng,1 A Pandit1 and W Wang
1 National University of Ireland, Galway, Galway, Ireland
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PXE patients are transduced with specific 5' RTMs and are then transplanted back to

Mayr1,1 P Hevezi,1 BA Buhren,1 C Martinez Reyes,1 H Schrumpf,1 BH o home1 and A Zlotnik2
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524 Rare Subtypes of Epidermolysis Bullosa Simplex: Molecular Criteria for Diagnosis

M. Piatkowski, D. Kirisits, C. Cobzaru, A. Schwerdel-Holz,1 I. Suárez, F. Falater,1 T. Hencz-Peet,1 C. Weiss,1 L. Buczkowski-Tuderman, C. Has1 Dermatology, University of Freiburg Medical Center, Freiburg, Germany; 2 Dermatology, University Hospital Nihsafo Seidai in Kanazawa, Kanazawa, Japan; 3 Institute for Maternal and Child Health IRCCS “Burlo Garofolo”, Trieste, Italy; 4 Dermatology, University of Cologne, Cologne, Germany; and 5 Dermatology, University of Hamburg, Hamburg, Germany.

Epidermolysis bullosa simplex (EBS) is a heterogeneous group of genetic malformation bullous disorders characterized by intra-epidermal cleavage. The vast majority of EBS cases is caused by dominantly inherited mutations in the genes keratin 5 or 14, but in approximately 25% of patients no mutations can be disclosed in these genes. The aim of this study was to elucidate the genetic background in a cohort of 60 patients with suspected EBS without keratin defects by screening mutations in EBS-associated genes, including plakoglobin (PLG), exon 31, and BP230 (DESG). Since mutations in the gene for transglutaminase 5 (TGM5) cause acral peeling skin syndrome (APSS), a rare genetic entity that resembles EBS particularly in young individuals, this gene was included in the screening. Eight affected members of five families were diagnosed with the dominantly inherited EBS-Ogna subtype caused by the unique PLE mutation, p.R200W. Characteristic for EBS-Ogna skin was reduction of the plectin immunofluorescence signal with nod-dominant specific anti-plexin antibodies. Thirteen patients with APSS carrying recurrent and previously unreported TGM5 mutations were identified. Immunofluorescence and blotting analysis showed that TGM5 mutations significantly altered the expression of suprabasal keratin expression and therefore may contribute to hyperkeratosis. We propose that the screening unravelled the genetic defects in 30% of the suspected EBS cases, and demonstrated that the specific findings in APSS and EBS-Ogna represent useful molecular criteria that facilitate the diagnosis of these commonly unrecognized skin fragility disorders.

525 Double RNA trans-splicing induced gene correction in epidermolysis bullosa

M. Kirn1, A. Haidl1, A. Klausegger1, V. Wally1, EM Murauer1, EM ayr1, C. Gruber1, J. Harper2 and R O’Shaughnessy1.1 Immunobiology and Dermatology, UCL, 105 – intron 105 flanked by the 5’ and 3’ coding ends of GFP and the most efficient randomly double RNA trans-splicing is the gene COL7A1 with a transcript size of over 9kb. A double RNA binding domains, specific for the surrounding introns 51 and 53. The best RTMs lead to the expression of significant higher levels of GFP in up to 61% assayed cells. Another promising target for double RNA trans-splicing is the gene COL7A1 with a transcript size of over 9kb. A double RNA trans-splicing strategy enables the correction of internal COL7A1 exons and minimizes the size of the RTM significantly, avoiding many size-associated hurdles. Co-transfection of the target molecule, including the gene region intron 103 – exon 103 – intron 103 – exon 104 – intron 104 – exon 105, intron 105 was carried out in the 5’3’ coding ends of the molecule. Co-transfection with the plasmid designed RTM harboring the missing internal GFP sequence, into HEK293 cells, induced the restoration of full-length GFP by trans-splicing in over 25% of analysed cells. We assume that RNA trans-splicing is a promising tool to correct but new steps may come to the hypothesizes, for which we propose that MAD2 is not only a potential diagnostic marker, but also, due to the availability of MAD2 inhibitors such as the naltins, an attractive target for therapy.

528 Cell-Based Therapeutics for Pseudoxanthoma Elasticum

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Aberrant mineralization of peripheral connective tissues is a characteristic feature of pseudoxanthoma elasticum (PXE), a hereditary-metabolic disorder caused by mutations in the ABCC6 gene. This gene, which encodes an ABC membrane efflux transporter, is expressed primarily in the liver. There is currently no effective treatment for PXE. In this study, we have investigated the potential of induced pluripotent stem cells (iPSCs), the whole bone marrow (BM), and bone marrow derived mesenchymal stem cells (MSCs) for liver regeneration, with the aim to rescue PEX phenotype in Abcc6 mice, a model system that recapitulates the genetic, histopathological, and ultrastructural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE. First, we characterized mouse fibroblast-derived iPSCs, BM and purified MSCs, which were derived from GFP+ transgenic mice, and we demonstrated that iPSCs and MSCs structural features of PXE.

529 A phoshotyking-like phenotype in dermal equivalent: evidence for proteasomal dysregulation in KSF fibroblasts

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Mutations of mitochondrial (mt) DNA are frequently detected in aged tissues. It has therefore been suggested that mtDNA mutations are causally related to the aging process, but mechanistic details still remain largely unknown. We have previously shown that human dermal equivalents (DEs) containing fibroblasts from Kears-Sayre syndrome (KSS) patients harboring high levels of reactive oxygen species (ROS), increased expression of the collagenase MMP-1, and progressive loss of intact collagen fibers. Moreover, increased expression of VEGF, lysyl oxidase (LOX) and IL-8 was also noted in KSS DEs. We now provide evidence that the photoaging-like phenotype in KSF DEs is caused by dysregulation of the proteasome and postulate a functional link between mtDNA deletions, elevated ROS production, and photoaging. To verify our hypothesis, KSS and NIH DEs were treated with salubrline, a substance which is known to improve proteasomal activity. Salubrline treatment not only reduced in reduced the elevated mtROS levels in KSS DEs but also the interactions between C-linked, a chaperonin receptor, and its ligand and SDF-1, a stem cell derived factor, could be critical for recruitment and homing of transplanted cells for liver targeting. These therapeutic models provide a platform for translational application of cell based liver reconstitution as a means of regenerative therapy for PEX.

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Recessive epidermolysis bullosa simplex due to plectin 1a deficiency causes only skin blisters

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Plectin is a major crosslinking element of the cytokeratinlen, and plays an essential role in epithelial tissues, mucosae, and stratified muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardio-myopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardiomyopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardiomyopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardiomyopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardiomyopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bullosa simplex associated with cardiomyopathy, muscular dystrophy, or pyloric atresia. It is the only gene in epithelial tissues, myocardium, and striated muscle. Its deficiency may result in epidermolysis bulbos...
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Mosaic STS-D1 downregulation alters ECM remodelling enzymes in Linear morphea fibroblasts
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Linear morphea is a fibrotic, disorder affecting children, where excessive collagen deposition causes a localized hardening of the skin. The cause is currently unknown, but the disorder notably incides along the lines of Blaschko, suggesting an early mosaic fibroblast defect leading to disease in the child. This study characterised the effects of the downregulation of STS-D1, a consistent feature of fibroblasts from affected regions of linear morphea patients. The altered release of extra-cellular remodelling proteins and ECM components was studied in 1) the desmos of a linear morphea patient; 2) the supernatant of primary fibroblast cultures derived from affected and unaffected, site matched areas and 3) fibroblasts expressing shRNA causing a downregulation of STS-D1. As well as direct visualisation, expression levels were surveyed by western, and activity of released factors were assessed using a zymography. In site-matched morphea fibroblasts, expression of MMP2 was upregulated compared to controls, with a concomitantly increase in activity. The migration of LM fibroblasts, as measured by scratch assay, was also increased relative to site matched controls. This phenomenon was also observed in altered piliation pattern of collagen fibrils, cell-cell and cell-fibronectin interactions in in vitro and in vivo conditions. STS-D1 downregulation alone is sufficient to alter the expression and activity of ECM remodelling molecules seen in Linear morphea fibroblasts. We propose that STS-D1 downregulation is an important controlling factor in early fibroblast activation, could be a contributing factor in the Linear morphea phenotype, and presents a novel avenue of treatment for this disease.

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The identification of fifteen novel psoriasis susceptibility loci highlights the skin's role in innate immune defence
RC Trembath1, G Abecasis2, JT Elder1, Q Qi2, O of Psoriasis1, AT Association Genetics Extension2, T Psoriasis Consortium1 and A Consortium2 1Queens Mary University of London, Barts and the London School of Medicine and Dentistry, London, UK; 2University of Michigan, Ann Arbor, Michigan, MI and 3Division of Genetics and Molecular Medicine, King's College London, London, UK

The existence of a genetic component underlying the pathogenesis of psoriasis has long been recognised and genome-wide association studies (GWAS) of Caucasian populations have successfully identified 19 susceptibility loci. To gain further insights into the genetic architecture of the disease, we conducted a meta-analysis across three case-control resources examined in previous GWAS and two independent datasets genotyped on the Immunochip (a custom genotyping platform including the immune-related SNPs). The analysis of 11,586 cases and 22,806 controls identified 15 novel psoriasis susceptibility regions and 5 independent signals mapping within previously known loci. Shared disease intervals overlapped most often with CRTH2 in disease loci and encompassed a number of E-cell related genes (e.g. RUNX3, TACAP and ST3GAL5). Conversely, psoriasis-specific susceptibility regions were notable for candidates involved in innate host defense. These included genes contributing to interferon-mediated antiviral responses (DDX58), macrophage activation (ZC3H12C), and NF-kB signaling (CARD14, CARMA1). These findings underline the importance of unique genetic determinants of immune-mediated disorders and emphasize the importance of innate defense in the pathogenesis of psoriasis.

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Revertant mosaicism in children with non-Herlitz junctional epidermolysis bullosa
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Revertant mosaicism refers to the coexistence of cells carrying inherited genetic mutations with cells in which the inherited disease-causing mutation is corrected by a spontaneous genetic event, thereby giving rise to a clinically healthy phenotype. This phenomenon of ‘natural gene therapy’ occurs in all Dutch patients with the genetic blistering disease non-Herlitz junctional epidermolysis bullosa (JEB-NH) all patients with one or more clinically healthy (= revertant) patches of skin where no blisters developed. The revertant patches did not significantly vary in size or age. One patient, however, indicated that new patches had arisen in childhood, though supportive photo-material was lacking. To learn more about possible expansion of revertant patches, we investigated two children with JEB-NH. Both the 11-year-old male (COL7A1 c.2576dupC/p.859Serdup) and the 9-year-old male (COL7A1 c.1266delC/p.422Lysdel) displayed several revertant patches. From each one new biopsy was taken of a revertant patch to investigate the molecular reversion mechanism. Gene conversion corrected the c.2576dupC mutation in the girl, whereas in the boy an additional one biopsy was taken of a revertant patch to investigate the molecular reversion mechanism. A gene conversion is highly unlikely in the boy, but reverse myoblast formation. The increase in MMP2 activity was mirrored in fibroblasts engineered with reduced STS-D1 expression. In conclusion, LM fibroblasts show altered proliferation and viability of cells in affected skin. In the boy, cells in affected skin that were thought to be affected showed that 6 years of age different revertant patches could already be identified. In contrast to what was noted in adulthood, these patches changed in size between the age of 6 to 9 years. Some of the patches increased, while other patches decreased. As revertant mosaicism has possible therapeutic options by using autologous keratinocytes, knowledge about the development of revertant patches is essential. This phenomenon is likely to be more frequent than previously anticipated, and hence a source of natural gene therapy leading to disease regression.

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Gene profiling of drugs induced herpesvirus reactivation in B lymphoblastoid cell lines from DRESS patients
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Drug-induced cutaneous reactions (DRESS) are severe drug-induced cutaneous reactions involving the skin and visceral organs. We analysed the effects of EBV reactivation, in vitro model based on EBV transformed B lymphoblastoid cells from DRESS patients and healthy donors were used to study the effects of drugs on reactivation. Expression profiles were obtained for cell lines treated or not by allopurinol, amoxicilline, sulfamethoxazole, valproic acid or carbamazepine. Significant differences in expression of genes involved in immune-mediated disorders and emphasise the importance of innate defense in the pathogenesis of DRESS.

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Epidermolysis bullosa simplex: new phenotypes and PLEC genetic mutations
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Patients presented hallmarks of inherited EBS: congenital cutaneous and mucous blistering with healing without scarring, atrophy or milia. Two children with EBS-PA were thoroughly investigated. Both the 11-year-old female (COL7A1 c.2576dupC/p.859Serdup) and the 9-year-old male (COL7A1 c.1266delC/p.422Lysdel) displayed several revertant patches. From each one new biopsy was taken of a revertant patch to investigate the molecular reversion mechanism. Gene conversion corrected the c.2576dupC mutation in the girl, whereas in the boy an additional one biopsy was taken of a revertant patch to investigate the molecular reversion mechanism. A gene conversion is highly unlikely in the boy, but reverse myoblast formation. The increase in MMP2 activity was mirrored in fibroblasts engineered with reduced STS-D1 expression. In conclusion, LM fibroblasts show altered proliferation and viability of cells in affected skin. In the boy, cells in affected skin that were thought to be affected showed that 6 years of age different revertant patches could already be identified. In contrast to what was noted in adulthood, these patches changed in size between the age of 6 to 9 years. Some of the patches increased, while other patches decreased. As revertant mosaicism has possible therapeutic options by using autologous keratinocytes, knowledge about the development of revertant patches is essential. This phenomenon is likely to be more frequent than previously anticipated, and hence a source of natural gene therapy leading to disease regression.

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Screening for highly efficient RTMs to improve 3 trans-splicing for COL7A1 gene
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Mutations in the COL7A1 gene cause functional defects of type VII collagen, the major component of anchoring fibrils within the basal membrane zone of the skin. Loss of function of the protein leads to the inherited skin fragility disorder dystrophic epidermolysis bullosa (DEB). Gene therapy efforts for DEB are still accompanied by a number of technical challenges due to the size of the COL7A1 transcript (> 9 kb). Spleenosecreted Mediated RNA trans-splicing (SMART) may serve as an repair strategy overcoming this obstacle. Using a fluorescent-based screening system we are able to identify most efficient RNA trans-splicing molecules (RTMs) with improved binding properties for the target intron 46 of the COL7A1 gene. Most efficient RTMs binding to Intron46-Exeuc47 of COL7A1 were able to induce specific trans-splicing in up to 95% of RET and target expressing cells. The identified RTMs with high efficiency differ in length and localization of the specific binding site within the Intron 46 of the COL7A1 pre-mRNA. The identification of the most functional RTM will improve trans-splicing in the COL7A1 gene in order to lay the basis for gene therapy of DEB patients.
ABSTRACTS | Genetic Disease, Gene Expression and Gene Therapy

542 | Conditional Analysis Identifies Three Novel Major Histocompatibility Complex Loci Associated With Psoriasis

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Many genetic loci have now been shown to influence psoriasis and these implicate a number of genes providing evidence for an integrated model for the pathogenesis of psoriasis that combines skin barrier function, innate immune pattern sensing, adaptive immunity and TH17 cell responses. There is a major disease susceptibility locus located within the major histocompatibility complex (MHC), in which the signal is thought to be driven by HLA-C. Other independent association loci have been identified within the MHC, but determining the number and location of these has been hampered by extensive linkage disequilibrium across the region. We leveraged the power of large discovery and replication datasets of European ancestry to look for association signals specific within the MHC region. In addition to the major loci at HLA-C (p=1.7 x 10^-20), we found and replicated eight additional loci, three novel and five previously reported; CNRIR2 (rs3809195 p=1.5 x 10^-10), HLA-DRB1 (rs3809597 p=4.4 x 10^-10), HLA-DQB1 (rs3809194 p=1.8 x 10^-10) and HLA-DQA1 (rs3809196 p=2.5 x 10^-10). A final locus was identified at C6orf21 (p=0.0008). In other non-HLA regions we did not find any significant association.

543 | Archichromes as new therapy delivery vehicles for skin cells

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Archichromes are a type of lipid bilayer vesicles (liposomes) that are made from extracted arachid lipids. These have unique structural characteristics that increase the lipid bilayer's stability even under high pH, high osmotic pressures and bile salts. Consequently this has led to the development of new potential drug, gene and vaccine delivery systems. Here we present the data obtained on large unilamellar archichromes (400 nm size) extracted from Arachypnum perinus K1, as a potential new method for drugtherapy delivery to skin cells. The core lipid of A. perinus consists solely of C25:5-archichrome 2,13-dis-epoxy-lyso-cerol C25:3-archichrome lyso-cerol (both with glycosylcerol and glycosylinositol polar head group) accounts for 9 mol%. The potential cytotoxic effect of archichromes on skin cells was measured using an in vitro cell metabolic activity assay. HaCaT keratinocytes grown in culture proved unaffected by archichromes, even when higher concentrations were used (500 µg/ml). Subsequently, large (400 nm in size) unilamellar archichromes were prepared, which were packed with calcine as reporter dye: Calcine is a fluorescent dye that binds calcium and is brightly emitted in response to changes in the calcium concentration. In addition, archichromes containing calcine were also used to test the calcium release effect of archichromes in keratinocytes. Functional restoration of COL7A1 assessed by wound simulation assay was carried out and results showed migration rates decrease to normal levels will be confirmed shortly. Furthermore, functional restoration of COL7A1 assessed by wound simulation assay was carried out and results showed migration rates decrease to normal levels will be confirmed shortly. Furthermore, functional restoration of COL7A1 assessed by wound simulation assay was carried out and results showed migration rates decrease to normal levels will be confirmed shortly. Furthermore, functional restoration of COL7A1 assessed by wound simulation assay was carried out and results showed migration rates decrease to normal levels will be confirmed shortly.
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Seven novel families with ADCL confirm clinical and molecular homogeneity
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Introduction and objectives: Elastin gene aberrations have been associated with a variety of phe-
notypes. Grossly, loss-of-function mutations result in arterial stenoses, while mutant protein expres-
sion induces cutis laxa. Autosomal dominant cutis laxa is a rare disorder that further presents with
typical facial characteristics, inguinal hernia, aortic root dilatation and pulmonary emphysema.
In most patients, frameshift mutations are found in the 3’ region of the elastin gene (exons 30-34) and
result in a truncation of the protein. In contrast, exon 32 frameshift mutations in the elastin gene in all
probands. Our data favor homogeneity both on the clinical and molecular level. All mutations reside in
exons 30, 31, 32 and 34. One mutational hotspot in exon 32 (c.4057_4059delAA) is documented. We confirm the previously reported findings comprising
generalized skin involvement, inguinal hernia, aortic root dilatation and emphysema, necessitating
regular cardiovascular and pulmonary evaluations. We further evidence intra- and inter-familial
variability and amelioration of the skin phenotype in ageing patients. The two first and the two last
authors contributed equally to this work

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Only Four Genes (EDA1, EDAR, EDARADD, and WNT10A) Account for 90% of Hypo-
Hidrosis/Athodermic Ectodermal Dysplasia Cases
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Introduction: Hypohidrotic and athodermic ectodermal dysplasia (HED/EDA) is a rare genodermatosis
characterized by abnormal development of sweat glands, teeth, and hair. Three disease-causing
mutations have been identified, namely, (1) EDA1 accounting for 5%-linked forms, (2) EDAR, and (3)
EDARADD, causing both autosomal dominant and recessive forms. Recently, WNT10A gene
was identified as responsible for various autosomal recessive forms of ectodermal dysplasias, includ-
ging hypohidrotic-athodermic dysplasia (ODD) and Schötot Schüll-Passarge syndrome. Methods: We
systematically studied EDA1, EDAR, EDARADD, and WNT10A genes in a large cohort of 65
unrelated patients, of which 61 presented with HED/EDA. Results and conclusions: A total of 50
mutations (including 32 novel mutations) accounted for 60%-cases in our series. These four genes
accounted for 92% (56/61) of HED/EDA cases: (1) the EDA1 gene was the most common
disease-causing gene (58% of cases), (2) WNT10A and EDAR were each responsible for 16% of
cases. Although no clinical differences between patients carrying EDA1, EDAR, or EDARADD
mutations could be identified, patients harboring WNT10A mutations displayed distinctive clinical
features compatible with our clinical observations: no diaphanous metamorphosis, no facial dysmorphism, helping to decide which gene should be first
investigated in HES/EDA.

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Long-term follow-up of patients with Herlitz type junctional epidermolysis bullosa
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In the Dutch Epidermolysis Bullosa Registry between 1988 and 2011 and they were followed lon-
gitudinally by our EB team. All patients deceased before they reached the age of three years, at
an average age of 2.6 years (range, 3 months to 3.5 years). The causes of death were, in order of fre-
quency, failure to thrive, respiratory failure, pneumonia, dehydratation, anemia, sepsis, and euthana-
sia. The pattern of initial weight gain was the only predictor of lifespan that we could identify. Inva-
sive treatments, such as endoscopy did not promote survival in our patients. It is important to diagnose
EB/HJB as soon as possible after birth, so that the management can be shifted from life saving to
comfort care. The palliative end-of-life care can take place in hospital, but is also safe in the home setting.
Suffering in HJB patients can become so unbearable, that in some patients, who do not respond to
adequate analgesic and sedative treatment, newborn euthanasia, performed according to the Groningen
protocol, is legally permitted in the Netherlands.

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A “Late-but-Fitter Revertant Cell” Explains the High Frequency of Revertant Mosaicism in Epi-
dermolysis Bullosa
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Revertant mosaicism is the phenomenon in which germline mutations are corrected by postzygotic
events. Revertant mosaicism was first reported in the heritable blistering disorder epidermolysis bul-
osa (EB) in 1997 by us. Although considered rare at first, revertant skin patches have been observed
in a reassuring number of EB patients since, including all Dutch patients with generalized non-
Herlitz junctional EB. Revertant mosaic mosaicism might therefore be present in all EB patients with strongly
reduced protein expression in mutant skin. To gain further support for this hypothesis, we have used a
mathematical approach to estimate the probability that revertant skin patches were formed in adult
age. As the probability for reverse mutations to occur during early embryogenesis is low, a
clinically recognizable revertant patch could be expected only once in ~10,000 patients. This dis-
crepancy with our clinical observations cannot be explained by the various limitations to our
developmental model, like ignorance of cell loss and hierarchy among basal keratinocytes. We there-
fore hypothesize that reverse mutations provide revertant cells with a selective growth advantage in
such settings, allowing them to result in clinically recognizable patches even if they occur during later
stages of development. Our “late-but-fitter revertant cell” hypothesis is supported by observations
in other genetic diseases and the continual expansion of revertant patches into adjacent Blaschko-
segments.

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Effects of an extract of Arctium lappa on gene expression of macrophages and dermal fibro-
blasts under oxidative stress
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Although the biological activities of Arctium lappa (burdock) have been already investigated in
human and other species, no data evaluating the molecular mechanisms in skin have been reported.
We analysed the cytotoxicity of the extract of burdock on murine macrophages (RAW 264.7) and
canine dermal fibroblasts (DFs) at 24h. Then, we studied the activity of the extract (1ug/ml/1) on
mRNA expression of specific inflammatory genes like Nuclear factor NFκB1 (Nfkb1), Nuclear factor NFκB2 (Nfkb2), Interferon γ (Ifnγ), Interferon α (Ifnα), Interferon β (Ifnβ), Transforming growth factor β (Tgfβ), Interleukin 1α (Il1α) and Interleukin 1β (Il1β) in DFs with or w/o a H2O2 (200 μM for 1h) pretreated RAW 264.7 with qRT-PCR at 3 and 24h, and 2) on molecular response to adequate analgesic and sedative treatment, newborn euthanasia, performed according to the Groningen protocol, is legally permitted in the Netherlands.

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ABCC6 mutations in the Japanese patients with pseudoxanthoma elasticum
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Pseudoxanthoma elasticum (PXE, OMIM; #264800) is an autosomal recessive disorder character-
ized by the aggregation, fragmentation, and calcium deposition of elastic fibers. It primarily affects
organs and tissues that are rich in elastic fibers, such as the skin and mucous, eye and blood ves-
sels. Patients with PXE are at an increased risk of visual loss or cardiovascular disease. The respon-
sible gene for PXE is ABCC6, which encodes MRP8, a transmembrane transporter protein. Although
hundreds of Caucasian PXE patients had been analyzed, there was no mutation correlation between the
clinical phenotype and the genetic polymorphism of PXE. We have started mutation analysis of ABCC6 gene in the Japanese PXE patients. Here, we present the result of the ABCC6 gene mutations. Data was collected from 141 PXE patients (mean age 58 ± 11, 42 males, 99 females) from all over the coun-
try. In the 124 patients with skin symptoms, there are 88 cases with, 6 cases without angioid streaks, and 35 cases have not been examined. In the 108 patients with angioid streaks, there are 88 cases with, 9 cases without skin symptoms, and 3 cases have not been examined. Pathological examinations revealed that calcification and degeneration of elastic fibers in 120 cases out of 141 patients. We have completed DNA sequence of ABCC6 in 48 alleles of the 24 cases until now. We identi-
fied germline mutations in 9 cases, and compound heterozygous mutations in 8 cases, and no mutations in 2 cases. We identified nonsense mutations in 10 alleles, missense mutations in 20 alleles, deletion in 4 alleles, and insertion in 6 alleles. The most common mutation was nonsense mutation G378X found in 9 allele. The other mutations were observed as a frequent mutation of ABCC6 in previous studies. The mutations were found in exon 2, 3, 8, 9, 10, 11, 12, 13, 14, 15, 16, and 18. So far, there seems to be no correlation between mutations and severity in Japanese PXE patients.

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Establishment and characterization of keratinocyte cell lines derived from RDEB patients to
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produce pluripotent stem and organ cells from skin biopsies of a patient with type II
mutation analysis.
putative not detected second mutation appeared clearly in the sequence of PCR. Therefore in spe-
alternative binding sites within the introns to exclude TLOH. Using the alternative primer set the
3 suggesting a partial isodisomy. Analysis of this exon with a new primer set showed a heterozy-
was missing. This had a dramatically impact on prenatal diagnosis for the family as it was impossi-
The paternal deletion of 1644delG in exon14 was detected in the first cycle of screening, while the
exon was found in the Spanish population. Recently, several experimental therapeutic strate-
ner studies showed that both cell lines faithfully recapitulated the EB blistering phenotype in vivo.
clonogenic human keratinocytes. Thus, cell lines with enhanced proliferative and clonogenic capac-
models of genodermatoses including EB appear as robust systems to test enduring cell/gene thera-
to address the molecular cell processes of the generated iPS cells, we analysed among others the
parental somatic cells and their corresponding iPS cells with regard to chromosomal integrity and
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Production of pluripotent stem and organ cells from skin biopsies of a patient with type II
disease and examination of the cellular and molecular processes in comparison to the corresponding parental cells
A Klausegger, 1 A Prigione, 2 B Lichtner, 2 E Makrantonaki, 1 JA d j a y e2 and CC Zouboulis 1

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Cutaneous Genes Therapy Approach For The Correction Of Congenital Generalized Lipodys-
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Congenital generalized lipodystrophy is a rare autosomal recessive disorder characterized by marked
sensitivity, acanthosis nigricans, polycystic ovarian disease and hypertension. These compli-
low from two low serum levels of leptin and adiponectin, chemokines produced and secreted by

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Expression of miRNAs in cutaneous squamous cell cancer
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Establishment and characterization of keratinocyte cell lines derived from RDEB patients to

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Technical loss of heterozygosity (TLOH) in mutation analysis by a SNP located in the primer
binding site in two cases of epidermolysis bullosa (eb)
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Late onset pretilial recessive dystrophic epidermolysis bullosa
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Production of pluripotent stem and organ cells from skin biopsies of a patient with type II
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Cutaneous Genes Therapy Approach For The Correction Of Congenital Generalized Lipodys-

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Establishment and characterization of keratinocyte cell lines derived from RDEB patients to

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Expression of miRNAs in cutaneous squamous cell cancer

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Technical loss of heterozygosity (TLOH) in mutation analysis by a SNP located in the primer
binding site in two cases of epidermolysis bullosa (eb)

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Late onset pretilial recessive dystrophic epidermolysis bullosa
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Methyleneetahydrofolate reductase C677T and A1298C mutations and chronic idiopathic acrocyanosis

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The purpose of the study was to investigate the presence of two methylenetetrahydrofolate reductase (MTHFR) polymorphisms, C677T and A1298C, in patients with chronic idiopathic acrocyanosis, and to compare their prevalence to a control group. The case-control study was conducted on 43 consecutive patients with acrocyanosis and on 100 controls. Genomic DNA was isolated and amplified using the polymerase chain reaction. Odds ratios (OR) and 95% confidence intervals (95% CI) were used to estimate the risk of developing chronic idiopathic acrocyanosis according to the genotypes. The risk of acrocyanosis was significantly higher in patients homozygous for the mutation C677T compared to those with no mutation, with an OR of 4.8 (95%CI 1.5-14.9). In cases, the presence of the C mutation of the A1298C polymorphism was lower than in the control group. The homozygosity for the C677T polymorphism was associated with an increased homocysteine level. On the basis of our findings, acrocyanosis could be considered as a cutaneous sign of a "latent" cleft palate. This article is protected by copyright. For personal use only. Reprints and permissions: https://www.copyright.com.  

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A case report on the combination of Neurofibromatosis type 1 and Klippel-Trenaunay Syndrome

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Neurofibromatosis type 1 (NFI; OMIM 162200), an autosomal dominant condition characterized by the development of cafe-au-lait spots, axillary freckling, Loesch nodule, cutaneous fibromatoses, tumors, scoliosis and increased susceptibility to malignant tumors, is the consequence of mutations in the neurofibromin gene (NFI). Klippel-Trenaunay Syndrome (KTS; OMIM 143600) is characterized by angio-oedematous localization typically unilaterally on lower extremity. The genetic background of KTS has not yet been fully elucidated. Recently we identified a 32-year-old Hungarian woman presenting the clinical phenotypes of both NFI and KTS. We aimed to identify the underlying genetic abnormalities of this interesting case. Direct sequencing of the coding regions and the flanking introns of the NFI gene revealed a novel frameshift mutation (c.5727insT, p.V1909fsX1912) in exon 39. The patient carried the mutation in a heterozygous form, while the unrelated controls carried only the wild type sequence. Further studies are needed to unravel whether the newly identified mutation is responsible for the development of both the phenotypes of NFI and KTS or there is a second yet unidentified mutation responsible for the angio-oedematous localization of the right leg of the patient.

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Regulating the expression of genes associated with the protection and maintenance of skin structure via topical treatment

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One of the most noticeable signs of skin aging is the loss of skin structure resulting in a sagging, wrinkled appearance. Within the skin there are hundreds of studies done on ingredients that address this attribute of skin aging. This study investigates the in-vitro effect of a blend of Narcissus Tazetta Bulb Extract and Schizandra Chinensis Fruit Extract on genes related to skin structure integrity. Narcissus Tazetta Bulb Extract and Schizandra Chinensis Fruit Extract are well-known for their health benefits when taken orally. However, limited research has been done on the benefits of topical applications of these extracts. Recent unpublished in-house studies of a combination of these two extracts have led to the hypothesis that when combined Narcissus Tazetta Bulb Extract and Schizandra Chinensis Fruit may be able to protect and maintain the structure of the skin, helping to prevent the appearance of aging. This article is protected by copyright. For personal use only. Reprints and permissions: https://www.copyright.com.  

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Genetic investigations on a Hungarian family with Brooke-Spiegler Syndrome

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Brooke-Spiegler syndrome (BSS; OMIM 605041) is an autosomal dominant condition characterized by the development of skin appendage tumors, such as cylindromas, trichoepitheliomas and spiradenomas. BSS develops due to mutations in the tumour suppressor gene, CYLD. We investigated a Hungarian BSS pedigree with Bukovinian (Romanian) origin containing 21 affected family members spanning 7 generations. Direct sequencing of the coding region of the CYLD gene revealed a nonsense mutation (c.2860C>T, p.Arg936X) in exon 20 of the CYLD gene. Since this nonsense mutation is present in an Anglo-Saxon pedigree from the north of England, we are planning to perform the haplotype analysis of the two geographically distant pedigrees to reveal whether the mutation they carry is the result of two independent mutational events or they are carrying the same founding mutation.

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R Equol and/or Racemic Equol Demonstrate Better Expression of Skin-Related Genes Compared to S-Equol: In Vitro Evidence with Clinical Implications

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Nu Skin Enterprises, Provo, UT  
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Equal is a polyphenolic molecule similar in chemical structure to other plant-derived compounds like resveratrol. Equal is an isoflavonoid derived from intestinal metabolism and dietary plant and animal sources. Equal has the unique characteristics to bind specifically Sulpha-dihydriotriestenone (to decrease this negative impact in skin), has affinity for estrogen receptor beta (to increase positive influences on skin) and can be found as R-equol and S-equol. The purpose of this study was to show the differential expression of skin-related genes when the positive effects of equal is due to R-equol and/or Racemic equal and not S-equol. The methods utilized were EpiDermal Thickness Measurements of these extracts. Recent unpublished in-house studies of a combination of these two extracts have led to the hypothesis that when combined Narcissus Tazetta Bulb Extract and Schizandra Chinensis Fruit may be able to protect and maintain the integrity and structure of skin resulting in younger skin appearance.

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Absence of filaggrin mutation in Pachyonychia Congenita-6a and atopic dermatitis

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Pachyonychia Congenita (PC) is a rare autosomal-dominant inherited keratin disorders characterized by onychodystrophy and other associated ectodermal features. Since in PC there can be differences in phenotype severity between mutation in the same genes and between patients carrying the same mutation, environmental or genetic modifiers were suggested. In particular, PC shares some genetic, immunologic and clinical features in a 3-month-old girl of Moroccan origin, our proband, affected by the same severe form of PC and mild atopic dermatitis. Genomic DNA was extracted from peripheral blood of our proband, her parents and her brother, using standard procedures to detect keratin and filaggrin gene mutations. At clinical examination, we observed thickening of fingernails and toenails with progressive distal extension associated to subungual hyperkeratosis, leukoderma of the tongue and left plantar blister, pathognomonic features of PC but also follicular hyperkeratosis associated to cutaneous senesce and repeated cases of perioral impetigo, minor signs of atopic dermatitis. Since mutation analysis, revealed the presence of a deletion in exon 1 of K6a gene only in our proband, which removed a splice site, we performed the diagnosis of sporadic case of PC-6a. Sequencing of FLG gene on our patient blood sample did not reveal any mutations. The absence of FLG mutation in our patient suggest that other environmental and genetic modifier should be investigated to explain the different clinical phenotypes of PC.