MICRO LABS LIMITED

DERMA TODAY

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Dear Doctor,

Greetings from Micro Labs. We are happy to bring you "Derma Today" which contains latest and interesting news in the field of Dermatology.

This issue contains:

1. **Investigation of factors associated with comorbidities in adults with atopic dermatitis**
2. **Association between somatic mutations in healthy, sun-exposed skin and increased skin cancer risk**
3. **Clinical and genetic spectrum of patients with palmoplantar keratoderma**
4. **Case report on vitiligo universalis repigmentation after hemodialysis**

Should you require any article or, medical information, please feel free to contact us medicalservices@microlabs.in

Looking forward to your valuable feedback.

Best Regards,

Medical Team, Micro Labs Limited.

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Investigation of factors associated with comorbidities in adults with Atopic Dermatitis

Introduction:

Atopic Dermatitis

Atopic dermatitis (AD) is a common chronic inflammatory systemic disease characterized by pruritus and polymorphic eczematous lesions. The prevalence of AD ranges from 13.5% to 41.9% in children and adolescents, and 3.4% to 33.7% in adults.[1] The treatment of AD includes moisturizers, emollients, and both systemic and topical medications, though these therapies are often ineffective in managing comorbidities associated with AD, which are frequently underestimated. While studies have focused on specific comorbidities, evidence regarding multiple concurrent diseases is limited. There is a lack of scoring systems and insufficient clinical evidence on how factors like family atopy, initial onset site, and elevated immunoglobulin E levels relate to AD comorbidities. Both dermatologists and patients often overlook the impact of these associations on treatment and prevention.[2] This study aimed to identify key factors influencing comorbidity development in adults with AD and to create binomial logistic regression models to predict these associations.

Methods:

A univariate and multivariate regression analysis was conducted on cross-sectional data from the Clinical Research and Homogenization Diagnosis and Treatment Project for Type 2 Inflammatory Dermatosis, which included 439 adult AD cases. Clinical variables collected included demographic information, onset sites, rash distribution, comorbidities, IgE levels, pruritus severity (assessed by NRS), and various disease severity indices such as Eczema area and severity index (EASI), investigator's global assessment (IGA), patient-oriented eczema measure (POEM), dermatology life quality index (DLQI), AD control tool (ADCT), hospital anxiety and depression scale (HADS). Three outcome groups were defined: 1) all comorbidities (e.g., asthma, diabetes), 2) allergic disorders (e.g., asthma, allergic rhinitis), and 3) atopic diseases (e.g., asthma, allergic rhinitis and allergic conjunctivitis). The family history of atopy was also assessed, and an atopic family history score was calculated. Disease severity was categorized based on EASI, IGA, POEM, and DLQI scores.

Results:

A total of 439 AD patients were analyzed, with 50.57% of them were male. Pruritus was reported by 429 patients, with common onset sites being the trunk, lower, and upper extremities. Elevated IgE levels were found in 292 patients, and 89.98% had active disease. Seasonal birth in Spring/Autumn was observed in 52.62% of patients. Severity scores revealed: 37.81% mild, 38.27% moderate, and 23.92% severe EASI; 12.30% mild, 52.62% moderate, and 35.08% severe POEM; 22.55% mild, 51.48% moderate. Over half (52.62%) had at least one comorbidity, with the most common being allergic rhinitis (34.40%), food allergy (13.44%), and asthma (5.01%). Logistic regression identified elevated IgE, familial atopy, and family history of allergic rhinitis as significant predictors of comorbidities. Nomograms were developed to predict comorbidities based on these factors (Figure 1).

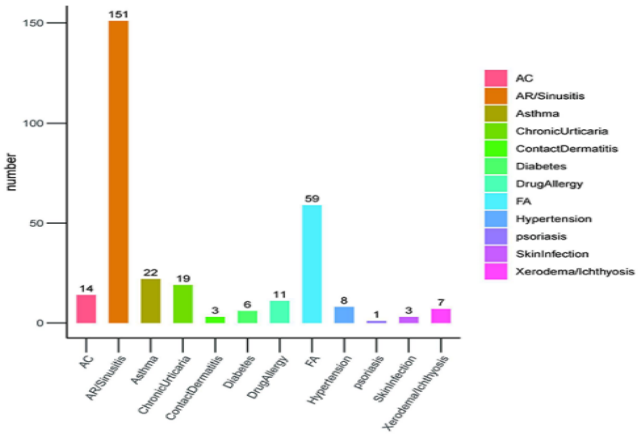

Figure 1: Prevalence of comorbidities in AD patients, with no cases of alopecia areata, inflammatory bowel disease, coronary heart disease, depression/anxiety, or ADHD.

Discussion:

This study found a positive association between familial atopy and comorbidities in individuals with AD, with higher familial atopy scores and a family history of allergic rhinitis (AR) or sinusitis being linked to increased comorbidity risk. This finding aligns with a prior study that suggested a genetic predisposition to atopic diseases, where family history is a significant factor in the development of comorbid conditions in AD.[3] In contrast to current evidence on the link between IgE levels, AD severity, and comorbidities has been inconsistent. Unlike previous studies, no significant associations have been found between AD severity, as measured by various clinical indicators, and the presence of comorbidities.[4]

Conclusion:

Comorbidities in AD patients are associated with a family history of atopic rhinitis or sinusitis, elevated IgE levels, and higher familial atopy scores, which can aid in early identification and intervention.

Family history of allergies, elevated IgE, and high atopy scores predict comorbidities in adult atopic dermatitis, aiding early intervention.

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Association Between Somatic Mutations in Healthy, Sun-Exposed Skin and Increased Skin Cancer Risk

Introduction:

Skin cancer is an increasing global public health issue with significant economic and workforce implications. The skin comprises the epidermis and dermis, with the epidermis containing melanocytes, keratinocytes, Merkel cells, and Langerhans cells. Mutations in the epidermis can lead to skin cancer.[1] Recent studies have shown that even clinically normal skin contains clonal cell populations with mutations in cancer-associated genes, although their role in cancer development is not fully understood. Ultraviolet radiation (UVR) is the primary cause of skin cancer, inducing somatic mutations and clonal expansion of mutated cells, potentially leading to precancerous lesions. Despite the interest in somatic mutations and their potential association with skin cancer, these mutations have not been used in the quantitative assessment of skin cancer risk.[2] To address this, a non-invasive test has been developed to sample DNA from clinically normal (non-lesional) skin and measure the frequency of somatic mutations at cancer-associated hotspots within the TP53 and NOTCH1 genes.

Methods:

This single-arm, population-based study investigated somatic mutations in healthy sun-exposed skin and their role in skin cancer risk. Skin specimens were collected from four facial locations using DermTech Smart Stickers, ensuring lesion-free areas. DNA was extracted by pooling the eight adhesive patches into a single vial with lysis buffer. Genomic regions were amplified and sequenced using Illumina's iSeq100 platform (2x150 bp chemistry). Somatic variants were identified using the DRAGEN Somatic app, targeting 232 mutations in TP53 and NOTCH1, selected based on pathogenicity (FATHMM score ≥0.8) and association with skin cancer. The mutation panel was curated from the COSMIC database. To model skin cancer

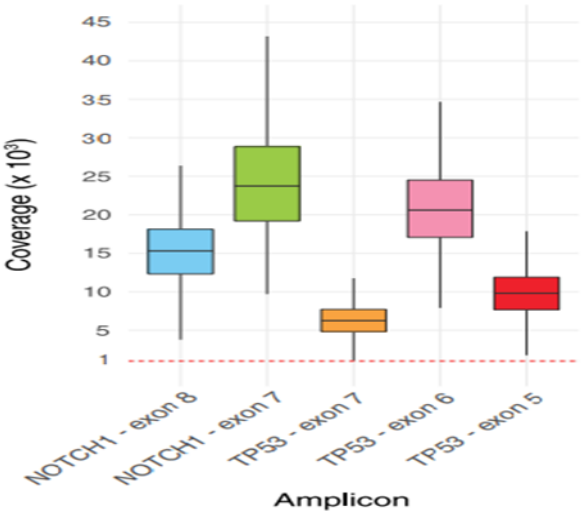

Figure 1: Sequencing Depth Across the 5 Amplicons, Each Sequenced to a Minimum Coverage of 1000x

risk, data from the National Health Interview Survey were used, with additional modeling of skin tone, mutations, and family history based on a 1038-subject cohort.

Results:

Somatic mutations in TP53 and NOTCH1 were analyzed in 1038 subjects to assess their role in skin cancer risk. These genes were selected due to their frequent mutations in cutaneous squamous cell carcinoma (cSCC), as identified in a recent meta-analysis. Sequencing of target regions in TP53 (exons 5–7) and NOTCH1 (exons 7–8) revealed 909 mutation occurrences, with 131 distinct mutations identified in Figure 1. The most frequent mutation, TP53:R248W, was found in 10.6% of subjects. A majority of mutations (83%) had low variant allele frequencies (VAFs), with 87% exhibiting UV signature C→T transitions, particularly in a CC dinucleotide context. Mutation presence correlated with skin cancer risk factors, including age, skin tone, and personal or family history of skin cancer. Older individuals, those with lighter skin tones, and those with a personal or family history of skin cancer were more likely to harbor mutations. Of the subjects, 8.4% had mutations in both TP53 and NOTCH1, while 25.2% had mutations in TP53 alone. Multivariate analysis showed that including somatic mutation count significantly improved skin cancer risk prediction, with a model AUC of 0.79. Adding family history further increased model accuracy (AUC 0.84), leading to the development of the DNA-SCAR model, which incorporates age, skin tone, mutation count, and family history. The model was validated across skin tones, achieving an AUC of 0.88, with higher accuracy for darker-skinned individuals (AUC 0.9). DNA-SCAR demonstrated good calibration when compared with previously reported skin cancer incidence rates, particularly for non-Hispanic Whites by age 70, where the predicted risk closely matched observed rates.

Discussion:

In the current study, TP53 mutations were detected in 34% of subjects, 2.6 times more frequently than NOTCH1 mutations, which were observed in 13% of subjects. This contrasts with earlier studies on somatic mutations in non-cancerous skin, where NOTCH1 mutations were reported to be 2–3 times more prevalent than TP53 mutations.[3] The higher prevalence of TP53 mutations in the current study supports the hypothesis that UV radiation (UVR) exposure may increase the frequency of TP53 mutations, as previous research has shown elevated TP53 mutation rates in sun-exposed areas compared to paired unexposed regions. In contrast, NOTCH1 mutations did not exhibit significant differences between sun-exposed and unexposed regions.[4]

Conclusion:

Somatic mutations in apparently healthy, sun-exposed skin contribute to increased skin cancer risk, providing additional risk information beyond traditional factors. The noninvasive collection of skin samples via adhesive patches enhances the clinical utility of this approach.

Somatic mutations in sun-exposed skin increase skin cancer risk.

Reference:

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Clinical and Genetic Spectrum of Patients with Palmoplantar Keratoderma

Introduction:

Palmoplantar keratodermas (PPK) are a group of disorders characterized by thickening of the skin, particularly the stratum corneum on the palms and soles. These conditions can be hereditary or acquired, with differentiation based on family history, involvement patterns, extension beyond palms and soles, and associated abnormalities in teeth and nails.[1] PPK presents in several clinical forms, including punctate, diffuse, focal, or striate hyperkeratosis. It can be isolated, part of generalized skin diseases, or associated with syndromes that involve extracutaneous manifestations. Despite advances in understanding the genetic basis, most knowledge comes from case reports and small series, with limited research on unselected cohorts. Further large-scale studies are needed to better understand its spectrum and improve diagnostic approaches.[2] Therefore, this study aimed to examine the clinical and genetic characteristics of patients with PPK.

Methods:

This cohort study included participants with newly diagnosed or follow-up patients with PPK, excluding acquired PPK or those under 18 years. Family members were also invited. Participants were classified as probands (initial patients) and relatives. Data were collected via interviews by the principal investigator, covering clinical features (e.g., age at onset, symptoms, family history), and clinical examinations (in person or via images). PPK subtypes were classified based on hyperkeratosis patterns (punctate, diffuse, focal, striate). Genetic testing included (1) in-house exome/genome panels for 52 probands, (2) focused AAGAB gene analysis for 14 probands with punctate PPK, and (3) prior testing for 10 probands. Relatives were tested via Sanger sequencing or the in-silico panel. Variants were analyzed using various software tools and databases, with segregation analysis when possible.

Results:

A total of 142 participants (76 probands, 66 relatives; 63% female, 37% male; median age 52 years) were enrolled. The most common PPK subtype was punctate (55%), followed by diffuse (34%), focal (7%), and striate (4%) (Figure 1). Age at onset ranged from 0 to 47 years, with punctate PPK having a median onset of 19 years and diffuse PPK 5.3 years. Most probands had bilateral involvement (92%), with common symptoms including pain (68%),

excessive sweating (37%), odor (45%), and fungal infections (24%). A genetic punctate PPK having a median onset of 19 years and diffuse PPK 5.3 years. Most probands had bilateral involvement (92%), with common symptoms including pain (68%), excessive sweating (37%), odor (45%), and fungal infections (24%).A genetic diagnosis was made in 83% of probands (63 of 76), with AAGAB c.370C>T being the most common variant (39 probands). Other variants were identified in DSG1 (8), KRT1 (3), and others. Nine genes followed autosomal dominant inheritance, while 4 were autosomal recessive. Testing of relatives identified disease-causing variants in 54 additional participants, bringing the total number of genetically diagnosed individuals to 117 (82% of the cohort). All AAGAB mutations were linked to punctate PPK, with a median onset of 18 years. DSG1 mutations showed a variable disease course, while DSP mutations were associated with symptom improvement. Pain, sweating, odor, and fungal infections were common across the cohort.

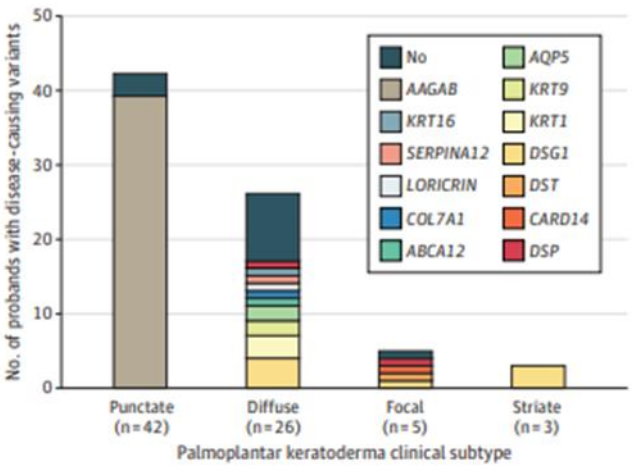

Figure 1. Clinical Subtypes and Molecular Genetic Diagnosis in 76 Families with Palmoplantar Keratoderma

Discussion:

The genetic evaluation of PPK patients yielded an 83% diagnostic rate, likely influenced by the higher participation of patients with affected family members. This supports the hereditary nature of the condition. In contrast, a Finnish study of 64 patients with various PPK subtypes reported a 48% diagnostic yield, highlighting a higher diagnostic rate in this cohort.[3] Punctate palmoplantar keratoderma (PPK) was the predominant clinical subtype, with the AAGAB variant, c.370C>T, identified in 83% of cases as a founder variant. This aligns with existing literature, supporting AAGAB mutations as the primary genetic cause of isolated punctate PPK and reinforcing the established understanding of its molecular pathogenesis.[4,5]

Conclusion:

This study highlighted the clinical and genetic diversity of palmoplantar keratoderma (PPK) in a large Danish cohort. Genetic diagnoses were made in 83% of cases, with novel variants expanding the known spectrum. Punctate PPK was linked to AAGAB, while nonpunctate PPK involved 12 genes, including DSP, associated with cardiomyopathy. Genetic testing is crucial for identifying patients at risk of cardiac complications and ensuring proper management.

Genetic testing is key to accurately diagnosing palmoplantar keratoderma (PPK) and identifying individuals at risk for cardiac complications, particularly in non-punctate PPK linked to DSP.

Reference:

1. Singh R et al. Acquired palmoplantar keratodermas: A study of clinical, histopathological and patch test findings. Journal of Pakistan Association of Dermatologists. 2020 Oct 1;30(3):388-95.
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Case Report on Vitiligo Universalis Repigmentation After Hemodialysis

Introduction:

Vitiligo is an autoimmune skin condition causing chronic depigmentation, commonly affecting the hands and face, and impacting approximately 0.2–1.8% of the global population.[1] Its exact pathogenesis remains unclear, though genetic, immunological, and neurological factors are believed to contribute, with immune-mediated destruction of melanocytes as a potential cause. The condition has an unpredictable course, with depigmentation either stabilizing or progressing over time. Vitiligo universalis (VU) is a severe variant with widespread involvement. Only two cases have reported spontaneous repigmentation of VU following hemodialysis.[2] This was an unique case of a patient with stable VU for over 14 years who experienced unexpected repigmentation after starting hemodialysis.

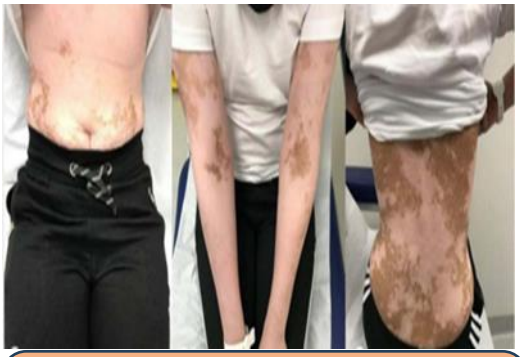

Figure 1: Signs of Skin Repigmentation on the Back, Abdomen, and Arms

Case presentation:

A 25-year-old woman with a history of vitiligo universalis and systemic lupus erythematosus (SLE) presented with nephrotic syndrome. She had been undergoing hemodialysis (HD) three times a week for six months prior to her visit to the dermatology clinic, where she reported the development of new brown spots (Figure 1). The patient was diagnosed with vitiligo at age 10, and the condition progressively advanced over the subsequent years, ultimately affecting more than 95% of her body surface area (BSA). For the past 15 years, she had remained fully depigmented until November 2018, when HD was initiated due to deteriorating lupus nephritis. In the weeks following the start of HD, the patient noticed the emergence of new areas of pigmentation on her face, arms, thighs, abdomen, and back. After 11 months of continuous

HD, repigmentation continued to increase, despite resistance to topical depigmentation treatments (Figure 2). On physical examination, complete repigmentation was noted on the bilateral thighs and back, and to a lesser extent on the face, abdomen, and arms. Overall, repigmentation covered more than 70% of her BSA, compared to only 5% before starting HD. The patient was on a regimen of thyroxine (150 mg), nifedipine (60 mg), and prednisolone (5 mg) and reported no significant changes to her medical treatment or condition during this period.

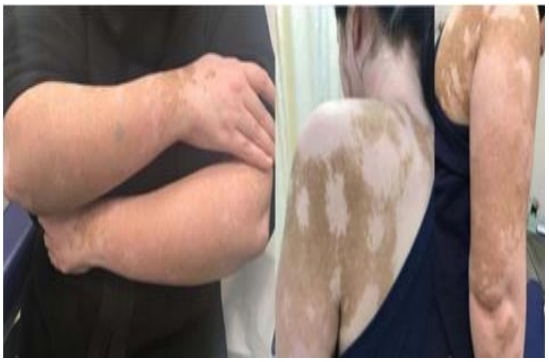

Figure 2: Evidence of Skin Regimentation on the Forearms and Shoulders

Discussion:

This case study reported a rare case of repigmentation in vitiligo universalis following hemodialysis (HD), contributing to the limited literature on this phenomenon. This finding aligns with previous reports by Farahbakhsh et al. and Rekik et al., which also observed repigmentation in vitiligo patients post-HD, suggesting that HD may reactivate melanocyte function.[3,4] Additionally, this study supports Moon et al.'s study indicating that high-flux hemodialysis (HF-HD) and hemodiafiltration (HDF) improve skin pigmentation by clearing uremic toxins that impair melanocyte activity.[5]

Conclusion:

The repigmentation of vitiligo universalis following hemodialysis (HD) represents a rare and poorly understood phenomenon. Potential contributing factors include the removal of middle-molecular-weight substances, melanocyte reactivation, and immune modulation. Further studies are needed to elucidate the precise mechanisms and explore the therapeutic potential of HD for vitiligo patients.

Hemodialysis may trigger repigmentation in vitiligo universalis, possibly through immune modulation and melanocyte reactivation.

Reference:

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