MICRO LABS LIMITED

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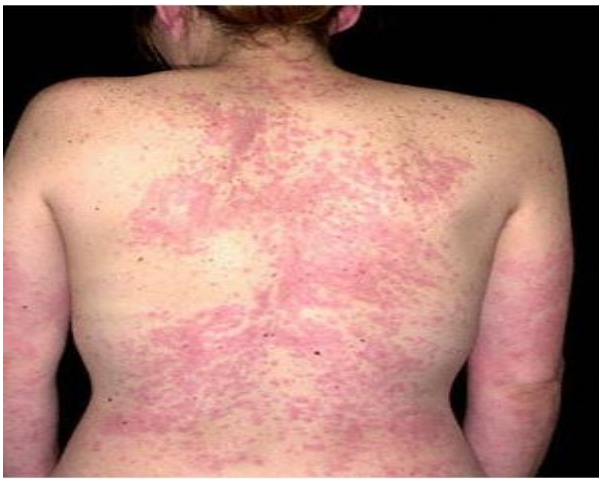
Relationship Between Urticaria and Immune Cells: A Bidirectional Mendelian Randomization Analysis

Introduction:

Urticaria is a common mast cell-driven condition characterized by wheals, angioedema, or both, with an approximate lifetime prevalence of 20%.[1] It significantly impacts quality of life due to persistent itching and unpredictable flare-ups. Various triggers, including drugs, foods, infections, stress, and endocrine changes, contribute to its onset. Genetic factors are central to susceptibility, with immune responses, particularly Type I hypersensitivity and IgE involvement, driving inflammation and symptom manifestation. However, the direct causal relationship between immune cells and urticaria remains unclear, highlighting the need for further investigation into the underlying mechanisms.[2] So, this study used bidirectional Mendelian randomization to explore the causal relationship between immune cells and urticaria.



Urticaria

Methods:

This study utilized bidirectional Mendelian randomization (MR) to examine the causal relationship between immune cells and urticaria. Genome-wide Association Study (GWAS) data for immune cells were obtained from the GWAS Catalog, which included 3,757 cases and 3,027 controls, representing 731 immunophenotypes. The urticaria data were sourced from the FinnGen database, consisting of 5,066 individuals with urticaria and 212,464 controls, with 16,380,466 SNPs. Urticaria diagnoses were based on the ICD-10 M13 code. To identify instrumental variables (IVs), a P-value threshold of $<1 \times 10^{-5}$ was used. The clump program was applied to prune SNPs based on linkage disequilibrium ($r^2 < 0.01$, window size > 10,000 kb). IVs with F-statistics <10 was excluded to avoid weak instruments, ensuring the validity of the MR analysis. This process was applied to both direct and reverse MR analyses.

Results:

A two-sample Mendelian Randomization (MR) analysis was conducted to explore the causal relationship between urticaria and immune cells, identifying 31 immunophenotypes linked to urticaria. Eighteen immunophenotypes were associated with increased risk, and 13 with protective effects. Four immunophenotypes were found to have a causal relationship with urticaria: HLA DR+ CD4+AC (OR 1.0341, p = 0.0076), CD45 on CD8br (OR 1.0137, p = 0.0033), HLA DR on plasmacytoid DC (OR 1.0424, p = 0.0047), and CD8dim NKT

%lymphocyte (OR 0.9495, p = 0.0082) in Table 1. Sensitivity analyses, including MR-Egger intercept tests, scatter and funnel plots, and leave-one-out analysis, confirmed the validity and stability of these findings, with no evidence of horizontal pleiotropy or significant changes when individual SNPs were excluded. In reverse MR analyses, urticaria showed a negative causal effect on CD8dim NKT %lymphocyte (OR 0.878, p = 0.030), with no significant reverse causality observed for other immunophenotypes, further supported by robustness tests.

Immune Phenotype	Odds Ratio (OR)	95% Confidence Interval (CI)	p-value
HLA DR+ CD4+AC	1.0341	1.0089–1.0599	0.0076
CD45 on CD8br	1.0137	1.0046–1.0231	0.0033
HLA DR on plasmacytoid DC	1.0424	1.0128–1.0729	0.0047
CD8dim NKT %lymphocyte	0.9495	0.9137–0.9867	0.0082
CD8dim NKT %lymphocyte (Reverse MR)	0.878	0.781–0.988	0.030

Table 1. Causal relationship to urticaria in different immunophenotypes

Discussion:

This study identifies immune cell phenotypes linked to urticaria risk, showing that HLA DR+ CD4+ T cells, CD45+ CD8+ T cells, and HLA DR+ plasmacytoid DCs increased risk, while CD8dim NKT lymphocytes are protective. These findings align with prior study on immune involvement in skin diseases but contrast with studies focusing on gut microbiota and genetic factors, emphasizing the complex immune role in urticaria.[3] Limitations such as the lack of biological validation and a focus on European populations suggest the need for more diverse and experimental studies to confirm these results.[2]

Conclusion:

Mendelian randomization analysis revealed that increased HLA DR+ CD4+ T cells, CD45 on CD8+ T cells, and HLA DR on plasmacytoid dendritic cells elevate urticaria risk, while higher CD8dim NKT cell percentage reduces the risk, suggesting potential immune-targeted therapies.

Immune cell markers influence urticaria risk, with specific markers offering potential targets for future therapies.

Reference:

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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

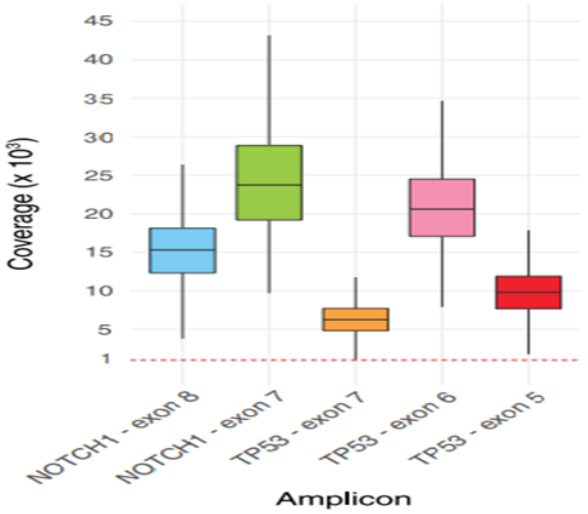

Figure 1: Sequencing Depth Across the 5 Amplicons, Each Sequenced to a Minimum Coverage of 1000x

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:

1. Khan NH et al. Skin cancer biology and barriers to treatment: Recent applications of polymeric micro/nanostructures. J Adv Res. 2021 Jun 16;36:223-247.
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4. Wei L et al. Ultradeep sequencing differentiates patterns of skin clonal mutations associated with sun-exposure status and skin cancer burden. Sci Adv. 2021;7: eabd7703.

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.

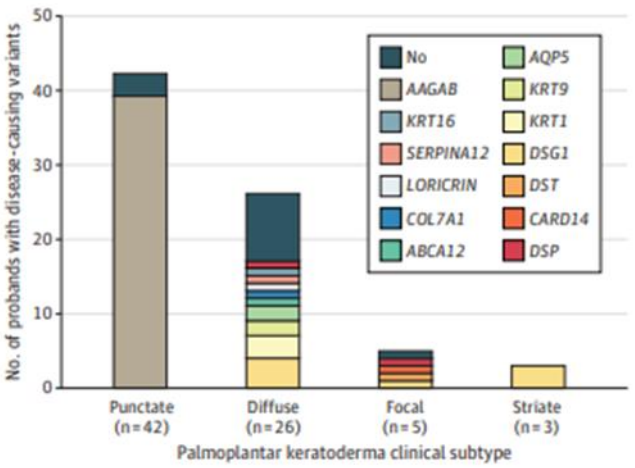

Figure 1. Clinical Subtypes and Molecular Genetic Diagnosis in 76 Families with Palmoplantar Keratoderma

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 Necrotizing Cellulitis Following Cosmetic Blepharoplasty

Introduction:

Periorbital necrotizing fasciitis (PNF) is a rare form of necrotizing cellulitis affecting the subcutaneous tissue around the eyes, occurring less frequently than infections in other regions such as the legs or perineum due to the face's robust vascularization. Unlike preseptal cellulitis, which can be treated with medication, PNF requires surgical debridement and antibiotics for management. Necrotizing cellulitis is an uncommon complication of aesthetic surgery,[1] with liposuction and blepharoplasty being the most frequently associated procedures. However, PNF following blepharoplasty is exceptionally rare, with only six reported cases to date.[2] This case discusses PNF following cosmetic lower blepharoplasty.

Case Presentation:

A 52-year-old woman presented with swollen eyelids and painful red eyes for 2 days following transconjunctival inferior blepharoplasty. She had no significant medical history. On examination, visual acuity was 7/10 in the right eye and 5/10 in the left. Intraocular pressure was elevated at 26 mmHg (right) and 47 mmHg (left). Bilateral erythematous, indurated eyelid oedema was noted, along with limited extraocular muscle movement, especially in the left eye (Figure 1). Examining the conjunctiva under a slit lamp showed chemosis and hyperemia, but no anterior segment inflammation. MRI confirmed bilateral orbital cellulitis,

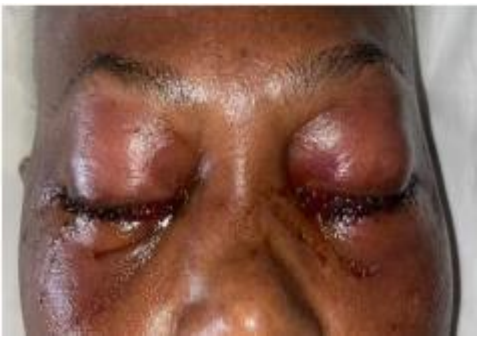

Figure 1. Eyelid oedema and erythema on day one of treatment

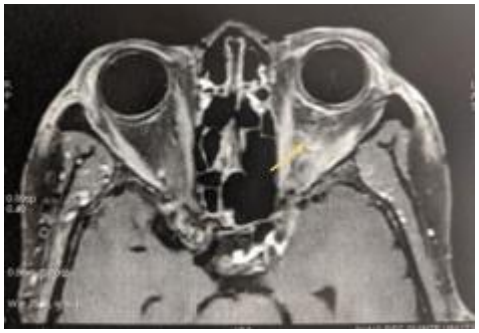

Figure 2. MRI showing bilateral soft tissue infiltration, extending into the left orbit.

with extension into the left orbit (Figure 2). The patient was treated with intravenous cefuroxime (200 mg/kg/day), metronidazole (1500 mg/day), acetazolamide (1500 mg/day), and topical beta-blockers. Drainage of subciliary and subconjunctival fluid was performed on day 2, revealing Staphylococcus epidermidis resistant to all beta-lactams. Despite initial treatment, swelling worsened, and a follow-up MRI showed further extension of cellulitis. Three doses of intravenous methyl prednisolone (500 mg) were administered between days 4 and 7, leading to significant improvement, with visual acuity increasing to 8/10 (right) and 7/10 (left), and intraocular pressure normalizing (11 mm Hg right, 13 mm Hg left). The patient's eyelid swelling and chemosis reduced, with residual mild periorbital oedema and limited upward gaze. A final MRI confirmed resolution of cellulitis. The patient was discharged on oral amoxicillin/clavulanic acid and prednisone, and fully recovered after 10 days.

Discussion:

This case presents the first reported instance of post-blepharoplasty PNF caused by Staphylococcus epidermidis, contrasting with previous reports of Streptococcus pyogenes, a more virulent pathogen. The moderate clinical presentation supports the literature suggesting that pathogen virulence correlates with the severity of the infection.[2] While standard management of PNF typically involves broad-spectrum antibiotics and extensive debridement, the infection was effectively treated with drainage surgery alone compared with the more aggressive approaches seen in previous cases.[2]

Conclusion:

This is the first reported case of necrotizing cellulitis caused by Staphylococcus epidermidis. Rapid diagnosis is essential to prevent treatment delays, especially following blepharoplasty.

Rapid diagnosis of *Staphylococcus epidermidis*-induced necrotizing cellulitis after blepharoplasty is crucial to prevent treatment delays.

Reference:

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