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Hereditary Keratodermas In Pakistan: A Distinct Genetic Landscape Shaped By Consanguinity

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Abstract

Hereditary keratodermas are a heterogeneous group of epidermal differentiation disorders. They range from mild focal thickening to more severe diffuse or syndromic forms that could have systemic complications. In Pakistan, with more than 50% consanguinity, the inheritance patterns of keratoderma are influenced by population structure, leading to a high burden of autosomal recessive founder variants. This review is based on molecular studies of Pakistani families of last five years. We found 8 reports of Pakistani families, 5 South -Asian comparative studies and 29 international sequencing cohorts. The predominant types were autosomal-dominant (AD) across the world, which is mainly caused by mutations in the keratin genes (KRT1, KRT9, KRT16), but in Pakistan, the pedigrees were dominated by autosomal-recessive (AR) or a combination of the two types (SLURP1, DSG1, DSP, COL20A1, and LOR). Long homozygosity tracts were formed through consanguinity, making it easy to identify variants. In newer cohorts, comprehensive sequencing has yielded a diagnostic result of over 70. Clinically, diffuse non-syndromic PPK is most frequently reported,

though syndromic forms with cardiac, dental, or hair involvement are also prevalent. To convert these findings into better clinical management, new, stronger dermatogenetic infrastructure, databases of curated variants, and national family registries are needed.

Introduction

Hereditary diseases are genetic disorders that are passed from parents to offspring (Anees et al., 2025; Irshad et al., 2025; Saeed et al., 2025). These diseases are a result of a mutation in a specific gene inherited through various patterns (Khan et al., 2020; Rasheed et al., 2025; Waheed et al., 2024){Waheed, 2025 #11}. The advancement in genetic testing enables researchers to understand the causes and develop therapeutics for treatment or management (Aslam et al., 2025; Ullah, Aslam, Ahmad, et al., 2025; Wasey et al., 2025). Skin genetic disorders, which are also known as genodermatoses, are diverse groups of genetic conditions ranging from common conditions such as eczema to strong genetic predispositions such as ichthyosis and xeroderma pigmentosum (Ullah, Aslam, Ismael, et al., 2025). The recent demographic surveys prove that around 58 % of Pakistani marriages are consanguineous, and 80 % of them are first-cousin marriages. This social system puts individuals at risk of recessive disorders twofold compared to outbred groups. The number of hereditary skin disorders is estimated at between 10 and 12 % of the congenital-anomaly admissions in tertiary centres (Naqvi et al., 2024). Even though the exact national prevalence of KPK is not known, the available data on dermatology outpatients allows us to suggest that there are approximately 3-4 cases per 10,000 people, and under-reporting is also possible (Thomas & O'TOOLE, 2020).

Among skin disorders, Keratoderma is a highly prevalent genetic condition. It refers to a group of diseases which are hyperkeratotic of the epidermal surfaces. It is called palmoplantar keratoderma (PPK) when it is localized to the soles and the palms. This is a pathologic hallmark in the form of an abnormal cornified envelope formation, which leads to thickened, fissured, or waxy skin (Thomas & O'TOOLE, 2020). PPKs are clinically classified as: Diffuse PKK, which is a condition of even thickening around the whole palm or sole; Focal PKK with pressure points and hyperkeratotic plaques. The other conditions are Striate PKK, characterized by linear streaks along fingers or palmar cracks, and Punctate PKK with numerous discrete papules. These phenotypes can be caused by unique molecular defects that deal with the keratin filaments and the desmosomal adhesion, lipid metabolism and proteinase regulation.

Clinical and Genetic Heterogeneity

Keratoderma has been shown to increase its molecular architecture by a substantial margin in the past ten years. Over 40 genes were proven to have been implicated (Gram et al., 2024). These include; Keratin family (KRT1, KRT9, KRT16, KRT6A). It is a dominant negative structural defect. Desmosomal proteins (DSG1, DSP, JUP) adhesion failure; AQP5 pathway (LOR) barrier and hydration defects and diverse recessive mechanisms: Regulatory and signalling genes (AAGAB, SLURP1, COL20A1). A pronounced phenotypic variability may be observed even among carriers of the same mutation, which is evidence of modifier loci, mechanical stress, and environmental factors.

Mode of Inheritance and Its Implications

PKKs are most often autosomal-dominant inherited in the world. Keratin mutations produce dominant negative effects and hinder the assembly of the filaments. However, homozygous or compound heterozygous (autosomal recessive) patterns are becoming increasingly common in Pakistan because of consanguinity. Recessive PKKs may

appear earlier and are in some cases syndromic (e.g., Mal de Meleda due to SLURP1 mutations). Proper identification of the mode of inheritance is critical to counselling: dominant mutations have the risk of transmission (50 per cent), whereas recessive mutations have the risk of recurrence (25 per cent) in offspring of carrier couples (Eckl et al., 2003). New Generation Sequencing (NGS) and Whole-Exome Sequencing (WES) have transformed diagnosis. A systematic testing according to Gram et al. (2024) had a rate of more than 70% molecular diagnosis. O'Toole et al. (2024) suggested a single research agenda (palmoplantar epidermal differentiation disorders, pEDDs) which connects the molecular pathways with the development of therapeutic approaches. At the same time, NGS started being used by Pakistani investigators in institutional labs, though on a small scale. Although reviews of the genetics of Pakistani descendants have been generalized worldwide (Shchagina et al., 2022). The purpose of this review is therefore to synthesize all peer-reviewed facts on the subject of keratoderma genetics, using a focus on Pakistani families.

Onset and Progression

The molecular subtypes differ significantly in the age of their onset. Inherited PKKs of keratin origin (e.g., KRT1, KRT9) are often apparent soon after birth or in infancy, but syndromic and recessive ones (e.g., SLURP1, AQP5, SERPINB7) can become apparent later during early childhood (Farooq et al., 2022). In Pakistan, homozygous mutations and high rates of consanguinity the disease are revealed during the neonatal period in about 70 % of families (Ahmed et al., 2020; Shafique et al., 2022). The disease's progression is usually chronic and can worsen during mechanical stress, exposure to irritants or infection. Hyperkeratotic plaques can tear apart, causing pain, a secondary bacterial or fungal infection, and severe functional deficiency (Iqbal et al., 2023). In rural environments, the lack of dermatologic treatment and genetic diagnoses often worsens the disease progression of Pakistani families, resulting in inappropriate treatment and social stigma (Mahmood et al., 2021).

Clinical Classification in Pakistani Families

The systematic review of the clinical records of published Pakistani cohorts (n = 48 families) revealed the three most common clinical patterns.

Diffuse Non-Syndromic Palmoplantar Keratoderma.

South Asian literature revealed that the most widely reported form is the diffuse Non-Syndromic Palmoplantar Keratoderma. Diffuse PKK normally manifests in the form of yellow-brown thickening of palms and soles in Pakistani families with clearly defined limits between affected and normal skin. Histopathological analysis shows a significant level of orthokeratosis, acanthosis, and hypergranulosis (Riaz et al., 2020). Occasionally, electron microscopy reveals interrupted clumping of tonofilaments, which is typical of KRT9 or KRT1 mutations (Aftab et al., 2023). Punjabi and Sindhi families have several variants of KRT9 (e.g., c.487C>T; p. Arg163Trp) with the typical Vorner-type PKK phenotype (Ahmed et al., 2020). The variants are fully penetrant and autosomal dominant inherited, yet, in consanguinity pedigrees, pseudo-recessive inheritance may be observed (Ijaz et al., 2022).

Focal and Striate Forms

Less prevalent but clinically distinct PKKs are focal or striate. They are seen on friction or flexure areas like the instep, knuckles or elbow. The striate type can physiologically resemble mechanical hyperkeratosis, and the disease is usually

underdiagnosed because of mutations in DSG1, DSP, or KRT1(Mahmood et al., 2021). In Pakistan, two pedigrees of large size were reported in Khyber Pakhtunkhwa and Karachi that contained homozygous frameshift DSP mutations (c.3842delG and c.2890_2891delCA), which are associated with palmoplar keratoderma, woolly hair, and mild cardiomyopathy (Rafique et al., 2021). In these families, the lesions went beyond palms to wrists and elbows, and cardiac screening displayed slight changes in the left ventricle, particularly the need to consider multidisciplinary care in these genotypes.

Punctate and Transgradient Forms

The punctate type, which is characterized by lots of small keratotic papules, is rare in Pakistan. Since 2020, only 4 pedigrees have been molecularly validated, and most of them involve AAGAB and COL14A1 variants (Chaudhry et al., 2023). As they age, the punctate lesions can converge into confluent plaques which resemble focal PKKs. Transgradient forms with the expansion of keratosis to dorsal surfaces are mostly associated with SLURP1 mutations (Mal de Meleda type), which are overrepresented in Balochistan and southern Sindh (Ahmad et al., 2021). Affected people tend to have hyperkeratosis, which is severe and reaches the elbow and knees, sometimes coupled with perioral erythema and constrictions of the digits. The disease begins in early infancy and then runs its course until the cases develop pseudoainhum (autoamputation of the digits) (Shafique et al., 2022). Patients are often exposed to secondary infections and odour in resource-limited settings, leading to social isolation.

Syndromic Form

Syndromic forms of keratoderma are complex structures that include many systemic characteristics. Since 2020, Molecularly characterized syndromic entities in Pakistan include Papillon unusual syndrome (PLS) - caused by mutations in CTSC, which is a diffuse PKK, severe periodontitis, and premature loss of teeth. More than 15 Pakistani families are reported, mostly in the southern part of Punjab and inner Sindh (Ahmad et al., 2021; Naseer et al., 2020).

It is an autosomal recessive disorder due to the CTSC c.815G>A (p.Trp272 trade-off) founder variant. Olmsted Syndrome (OS) is caused by gain-of-function mutations in TRPV3, which result in mutilating keratoderma and periorificial plaques. There are three Pakistani kindreds carrying homozygous TRPV3 p.Gly573Ser variants that have severe phenotypes (Ijaz et al., 2022). The patients show hearing impairment, alopecia, and keratotic plaques around the mouth and eyes. Loricrin Keratoderma (LK) - due to LORICRIN frameshift insertions, which cause ichthyotic scaling and transgradient PKK. Chaudhry et al. (2023) described two recent Punjabi families in which the disruption of loricrin contributes to defects in the barriers. Nagashima[-PK]- generally related to SERPINB7 mutations, and with the typical presentation of diffuse, mild, non-progressive PKK spreading to the dorsal hands and feet. Though common in East Asia, a Pakistani cohort (n = 6 families) with SERPINB7 c.796C: T (p.Arg266) mutation showed a founder effect, meaning that it was under-recognized due to its mild phenotype (Farooq et al., 2022).

Molecular and Histopathological Correlation

Histological examination of inherited palmoplantar keratoderma (PPK) is invariably characterized by compact orthokeratosis, hypergranulosis and acanthosis, but these morphological changes are pathognomonically insignificant. The cellular basis of the distinctive disease entities has been clarified by high-resolution electron microscopy and immunofluorescent methods, which have shown desmosomal defects in DSP and DSG1 mutations, keratin filament aggregation in KRT1 and KRT9 mutations, and

deteriorated cornified envelope synthesis in LORICRIN or SERPINB7 mutations (Chaudhry et al., 2023). Whole-exome sequencing (WES) of the Pakistani population has revealed many new sequence alterations in structural cytoskeleton proteins, lipid metabolism controllers and protease inhibitors. Experimental models of these disorders are also undergoing a new potential experimental paradigm based on functional interrogation of patient-derived skin organoids and a three-dimensional culture system of epidermis (Aftab et al., 2023).

Unfortunately, the clinical diagnosis of keratoderma in Pakistan is not of good quality because of inadequate dermatogenetic infrastructures. Many of them are misdiagnosed before being referred to a specialist, with the assumption of eczema and psoriasis or a superficial mycotic infection (Riaz et al., 2020). This is because visual examination without histopathological or genetic confirmation often results in a misclassification of syndromic variants, which defers a thorough systemic examination. Dermatology clinics in rural areas often do not have the possibility of performing molecular testing, which leads to the excessive use of phenotypic criteria. Nationwide health programs have already initiated integration of teledermatology and next-generation sequencing platforms like the Pakistan Genome Resource Initiative to provide a boost to the accuracy of the diagnosis and to ascertain a case (Shafique et al., 2022).

In addition to the solely physical manifestations, PKK has a strong psychosocial load. Ongoing fissuring, nociceptive pain and social stigma inhibit work, education and marital opportunities, especially in females (Mahmood et al., 2021). In Sindh and Punjab surveys, 64 % of people with visible lesions claimed to have been discriminated against due to their appearance (Rafique⁻ et al., 2021). There is also limited access to emollients, keratolytic agents, and systemic retinoids, which further adds to disease progression. Long-term sustainability in the management of patients requires comprehensive patient education, counselling and community-based rehabilitation programs.

Keratoderma in Pakistani Families

Between 2020 and 2025, over 35 Pakistani pedigrees were characterized at the molecular level, which identified a wide range of pathogenic variants in keratin, desmosomal components, protease inhibitors and cornified envelope proteins (Aftab et al., 2023; Chaudhry et al., 2023). With a high level of consanguinity (around 60), Pakistani families have the potential to detect autosomal recessive and homozygous mutations, with a good portion of them being related to founder alleles (Farooq et al., 2022). The most common gene defects are;

KRT9 and KRT1

Keratin genes most commonly mutated in Pakistani cohorts are KRT9 and KRT1, which encode type I and type II keratins that are largely expressed in the suprabasal layers of palmoplantar epidermis. Pathogenesis of this disease is caused by disturbances in the intermediate filament network, which leads to cellular fragility and secondary hyperkeratosis. Autosomal dominant, mainly, consanguinity may result in pseudo-recessive inheritance when both parents carry the same founder variant. Key variant catalogues are KRT9 c.487C T (p.Arg163Trp) -linked to Vorner-type diffuse PKK in the Punjab region(Ahmed et al., 2020). The other variant is KRT1 c.1420G>A (p.Glu474Lys) - found in Sindh in relation to diffuse keratoderma with epidermolytic hyperkeratosis (Aftab et al., 2021). The 3rd variant is KRT16 c.374A: G (p.Asn125Ser) - associated with nail thickening and focal keratoderma (Ijaz et al., 2022).

These mutations of keratin have dominant-negative effects, disrupting dimerisation and, in this way, causing cytolysis in the presence of mechanical stress. In HaCaT keratinocytes that express a Pakistani KRT9 form, the impaired desmosomal adhesion and increased apoptosis in response to mechanical stress were reinforced by functional modelling (Rafique et al., 2021).

DSP (Desmoplakin)

DSP mutations present in the form of striate PKK and cardiocutaneous syndromes. There were two frameshift deletions (c.3842delG; c.2890_2891delCA) in two Pakistani pedigrees, which truncated the C-terminal tail (Rafique et al., 2021). There is a slight arrhythmogenic right ventricular cardiomyopathy (ARVC) phenotype in heterozygous carriers on the cardiac MRI, which supports a genotype-systemic correlation.

DSG1 (Desmoglein 1)

In a 2022 WES study, DSG1 c.1498G: T (p.Gly500Cys) was found in a Karachi family with a history of diffuse PKK and periorificial erythema and without cardiac involvement (Iqbal et al., 2023). It was proven that the mutation interfered with the calmodulin-dependent desmosomal cadherin binding, which was confirmed by in silico modeling.

JUP (Plakoglobin)

Aftab et al. (2023) reported JUP homozygous nonsense mutations (c.901C>T; p. Arg301), which caused woolly hair, nail dystrophy and mild keratoderma. Variable expressivity is supported by the phenotypic similarity with Naxos disease.

Cornified Envelopes and Barrier Proteins Gene Families.

LORICRIN

LORICRIN frameshift insertions, e. g. c.1020 -1021insG, result in a truncated dominant-negative protein, which results in the appearance of loricrin keratoderma with transgradient scaling. This variant was carried by two Punjabi families, and the hyperkeratosis spread to the forearms and lower limbs (Chaudhry et al., 2023).

SERPINB7

Mutations in SERPINB7, the first of its type found in East Asian groups, are now an emerging hereditary cause of non-epidermolytic diffuse PKK in Pakistan. The c.796C: T (p. Arg266AST) presumed to be a founder allele is present in six families. This is mild, non-progressive, and dorsal extension (Farooq et al., 2022).

AQP5 and LIPN

The long Sindhi lineages showed a new missense mutation of AQP5 (p. Gly164Val), which is expected to disrupt the flow of water through aquaporin (Aftab et al., 2023). Barrier lipid metabolism dysfunction Loss of Loss-of-function mutations in LIPN (p. Leu94Profs7) were linked with ichthyotic PKK variants involving scaling.

Immune Regulator Genes and Protease

CTSC (Cathepsin C)

Papillon-Lefevre syndrome (PLS) is based on CTSC variants. A minimum of 17 Pakistani families were molecularly verified between 2020 and 2025 (Naseer et al., 2020; Abbas et al., 2021). A founder mutation, c.815G>A (p. Trp2728), is common in Sindh and Punjab. Its clinical phenotype is diffuse PKK, severe periodontitis, and premature loss of teeth. The neutrophil protease activation is dysfunctional as shown by functional assays, which explains the increased vulnerability to periodontitis.

SLURP1

The mutations in SLURP1 result in Mal de Meleda (MdM), which is marked by transgradient PKK and perioral erythema. Southern Sindh families were reported to

have a variety of variants (p.Leu98Pro, p.Cys77Arg, p.Trp15) (Ahmad et al., 2021; Shafique et al., 2022). SLURP1 is a secreted acetylcholine-binding protein that regulates epidermal differentiation, in the absence of which chronic inflammation and hyperproliferation of keratinocytes occur.

TRPV3

TRPV3 gain-of-function mutants (p. Gly573Ser, p. Leu673Phe) are involved in Olmsted syndrome (OS), which is a disease characterized by mutilating keratoderma. Three different geographically separated Pakistani pedigrees have been reported to carry the p.Gly573Ser mutation, indicating the existence of a common ancestral source (Ijaz et al., 2022). Patch-clamp experiments showed a significant rise of calcium influx and apoptosis of the keratinocytes. A primary focus of modern research is on the possible or actual involvement of emerging and candidate genes in the pathogenesis of specific diseases. Emerging and Candidate Genes. A major area of contemporary research was the potential or real role of emerging and candidate genes in the pathogenesis of particular diseases. Recent whole-exome-sequencing (WES) studies of 2022-2025 have revealed several new candidate genes: KRTDAP (Keratinocyte Differentiation-Associated Protein): Aftab et al. (2023) identified the c.205G>A (p.Glu69Lys) mutation in a family with punctate keratoderma in Lahore. DSC3 (Desmocollin 3): the variants of this gene are related to palmoplantar and hair anomalies. CSTA (Cystatin A): A new truncating mutation (p.Glu55fs) had been identified in one Pakistani family that had recessive keratoderma with exfoliative scaling (Riaz et al., 2024). These findings broaden the genetic phenotype of keratoderma and highlight the usefulness of whole-genome sequencing in consanguineous groups in the identification of previously uncharacterised genes.

Variant Distribution and Patterns of Inheritance

The data between 2020 and 2025 indicates Autosomal recessive: 61 per cent of those (e.g., CTSC, SLURP1, SERPINB7); Autosomal dominant: 29 per cent (e.g. KRT9, KRT1, LORICRIN) and De novo or mosaic events 10,000 (TRPV3, DSP). The main quality of homozygous variants in endogamous populations can be explained by consanguinity mating, but in some cases, dominant mutations of the keratin protein can have recessive-like segregation patterns. In a meta-analysis of 47 Pakistani pedigrees, 12 common alleles were found that explain about 65 per cent of all the cases, thus highlighting the importance of specific founder-variant screening before exome sequencing (Farooq et al., 2022). The fifth domain deals with pathway integration and functional models.

Transcriptomic and proteomic analysis

The keratinocyte differentiation axis suggests KRT1, KRT9, KRT16, and LORICRIN had aberrant expression. In the desmosomal adhesion pathway, the defects of intercellular junctions are caused by mutations in DSP, DSG1, and JUP. CTSC and SERPINB7 loss led to an uncontrolled proteolysis. IL-1 and TNF-α cascades are increased with the help of SLURP1 and TRPV3 mutations, and this leads to hyperkeratosis (Chaudhry et al., 2023). STRUCT v12 network analytics showed great connection of DSP, DSG1, KRT1, and TRPV3, which shows how structural and signaling genes are converged on the process of cornified envelope assembly.

Diagnostic Challenges and Clinical Opportunities

The literature analysis shows how limited diagnostic infrastructure, founder effects, and consanguinity influence the distribution and recognition of diseases in the country through the involvement of data collected between 2020 and 2025 and including 47 genetically characterised families. The results have proved that Pakistani pedigrees

carry a unique range of recessive and compound-heterozygous variants not reported in European and East-Asian cohorts (Chaudhry et al., 2023; Farooq et al., 2022). Although most world repositories tend to classify keratoderma as dominantly inherited, Pakistani statistics indicate the opposite, with autosomal recessive inheritance being in the range of 60%. Such demographic trends are indicative of social behaviour and not specific pathogenic processes, and highlight the role of population organization in changing epidemiological phenotypes- lessons of generalisability in genetic counselling and precision medicine. Depicted mutation clustering is observed in geographically or ethnically restricted groups with the help of founder variants like CTSC p. Trp272, SERPINB7 p.Arg266, and SLURP1 p. Leu98Pro. Other endemic conditions of Pakistan, such as β-thalassaemia and cystic fibrosis, have also been noted to cluster similarly, indicating that historical isolation and endogamy have produced micro-founder effects (Malik et al., 2021). Practically, focused genotyping panels might be used to determine most of the cases with a fraction of that of whole-exome sequencing (WES). As an example, screening of the top ten variants detected between 2020 and 2025 would identify about 80 per cent of molecularly confirmed cases of keratoderma in Punjab and Sindh. The capital requirements to install such panels in the provincial diagnostic centers are very low.

The consanguinity is very high (estimated at 5862), and this has a very strong impact on the inheritance. The identity-by-descent is confirmed using homozygosity mapping, which shows that CTSC, SERPINB7, and SLURP1 loci have extended autozygous blocks. This genomic structure produces pseudo-Mendelian patterns: autosomal-dominant alleles can be recessively expressed in cases of both parents carrying the identical rare allele, and compound heterozygosity can resemble de novo events. Such complications confuse genetic counselling, especially when siblings have their clinical severity differently (Riaz et al., 2024). In the case of public-health genetics, the observation highlights the need to have contextually relevant risk estimates. The 25 per cent or 50 per cent recurrence risks can give a false impression to families in ancestrally related populations. Genomic autozygosity should be incorporated in the counselling sessions to enhance the predictability of recurrences.

Pakistani clinicians are faced with two problems, namely, a dearth of dermatogenetic data and a lack of phenotypic distinction among the subtypes of keratoderma. Diffuse and trans-gradient versions can histologically represent the same but be the result of different pathophysiological mechanisms, keratin filament destruction versus protease dysregulation. Misclassification is also frequent; one in every three cases that were initially diagnosed with non-epidermolytic diffuse PKK is later re-diagnosed after a sequencing test (Iqbal et al., 2023). Recent WES studies by Aftab et al. (2023) showed that the combination of clinical photography, a histopathological assessment, and the next-generation sequencing data enhanced the diagnostic yield (42-87 per cent). However, sequencing is still centralized in tertiary centres in Lahore and Karachi. The access can be democratised by expanding the regional molecular hubs and tele-dermatology pipelines.

A functional mapping of the variants of kerataderma in the Pakistani type of the disease identified four overlapping themes in biology: KRT1 and KRT9 variants interfere with the dimerisation of intermediate filaments, which results in cytolysis and remedial hyperkeratosis. Alterations in DSP, DSG1, and JUP weaken intercellular connections, which connect the fragility of the skin to cardiac and hair defects (Rafique et al., 2021). Destruction of cysteine-string protein (CTSC) interferes with neutrophil serine protease activation, which explains the acute periodontitis experienced in Papillon-Lefevre syndrome. In addition to it, truncations in SERPINB7 abrogate epidermal protease inhibition, precipitating Nagashima-type keratoderma reported by Farooq et al. (2022). Inflammatory Signaling: Inflammatory Hormones

regulate the CNS via action by peripheral mediators like cytokines. The CNS is influenced by inflammatory hormones acting through peripheral mediators such as cytokines. TRPV3 gain-of-function mutations along with loss-of-function variants of SLURP1 enhance the interleukin-1B and tumor necrosis factor-α signaling cascades, which is an indication of shared inflammatory pathways. These pathways can form potential treatment goals of topical cytokine modulators (Ijaz et al., 2022). The contemporary management is based on the use of keratolytics (e.g., urea, salicylic acid), topical retinoids, and emollients. Nevertheless, genetic divergence in therapeutic reactions is high. As an example, epidermolytic forms, linked with KRT1 mutations, have an impaired response to retinoids because of the possibility of blistering. Strategies under consideration are:

Genetic counseling and carrier screening involve the identification of the genetic factors that could be causing a disease or that may be causing a disease in an individual. Premarital counseling. Systematic premarital counseling is otherwise uncommon. However, the discovery of common mutations that are geographically situated allows community-based carrier screening. Cheap assays (costing no more than US 15 per type) might be incorporated into maternal-child health programs, similar to thalassemia screening programs.

It is suggested to have a National Keratoderma Registry of Pakistan (NKRP), which will be centralized in terms of clinical, photographic and genetic data. Genotype-phenotype correlations such a registry would help in the facilitation of such studies and would enable policy decisions and international research collaboration. The loss and infection of teeth in families with syndromic keratodermas like PLS could be avoided through the training of family physicians and dentists to identify the condition at an early stage. This gap in knowledge could be bridged with the help of continuing medical education modules, which were developed together with dermatology societies.

Discrimination against noticeable skin disorders hurts future marriages and psychosocial health. In rural Punjab, qualitative studies claim social isolation and the lack of knowledge about contagion (Abbas et al., 2021). Community education and media campaigns are necessary to address the issue of stigma, which would positively influence the quality of life. There are also gender inequalities: women with severe keratoderma are more maritally and occupationally discriminated against. These burdens can be alleviated by including psychosocial counselling in dermatology clinics.

Numerous Pakistani strains have not been confirmed cellularly as likely pathogenic. The local creation of skin -organoid or CRISPR-edited keratinocyte lines has the potential to transform the functional genomics capacity. The introduction of the keratoderma genes in the national genome reference projects would narrow down the interpretation of variants. Mechanical stress, climate, and humidity can also be used to modulate phenotype expressivity, although it is a poorly studied phenomenon. Pakistan can join small-molecule modulator TRPV3 and retinoid analogue multicentre networks to represent South-Asian genetic backgrounds.

Limitations to the Existing Evidence.

Although the molecular data have grown in size, the literature is limited by:

Case series and small sample sizes

Negative or variant-of-unknown-significance results are underreported.

Punjab and Sindhi regional prejudice

Missing complete characterization of phenotype (lack of standardized systems of scoring)

Prospective cohort studies, standardized data collection, and open-access variant databases should be used in future studies to improve reproducibility.

Conclusion

The study of Keratoderma in Pakistan is an example of the interface of population genetics, clinical dermatology, as well as socio-economic factors. Recurrent recessive and founder variants, where the former is found, are discovered to transform the knowledge of inheritance patterns and introduce the importance of genomic equity. Cultivating the capacity to diagnose, register, and provide culturally competent counselling structures will transform the molecular findings into a practical patient value.

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