RESEARCH PAPER

"Freckles (Ephelides) : A Narrative Review of Pigment Biology, UV Interaction, and Genetic Susceptibility".

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ABSTRACT
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INTRODUCTION

The Mystery of Freckles (Ephelides): Genetic, Molecular, and Environmental Perspectives

Freckles, or ephelides, are among the most recognizable pigmentary variations of human skin, presenting as small, light to dark brown macules predominantly over sun-exposed areas. Though often regarded as a benign cosmetic feature, freckles represent a complex interaction between genetic predisposition and environmental exposure, particularly ultraviolet (UV) radiation. Their study provides valuable insight into melanocyte biology, photobiology, and pigmentation genetics.

Histologically, freckles are characterized by increased melanin deposition within the basal and suprabasal keratinocytes without a corresponding increase in melanocyte number. This distinguishes them from lentigines, where melanocyte proliferation is evident. The melanocytes in freckles are functionally hyperactive, producing higher quantities of melanin, especially during UV exposure [1]. This increased melanogenic activity results in visible pigmentation that intensifies during summer and fades in winter, reflecting the dynamic nature of ephelides.

The genetic basis of freckles is strongly linked to polymorphisms in pigmentation-related genes, particularly the melanocortin-1 receptor (MC1R) gene. MC1R regulates the type of melanin produced by melanocytes—eumelanin, which is photoprotective, and pheomelanin, which is less protective and more prone to generating reactive oxygen species. Variants in MC1R are associated with fair skin, red hair, and a higher tendency to develop freckles [2]. These variants impair the receptor's ability to stimulate eumelanin production, shifting the balance toward pheomelanin, thereby increasing susceptibility to UV-induced damage.

From a molecular perspective, UV radiation plays a central role in freckle formation. Exposure to UVB radiation induces DNA damage in keratinocytes, activating the tumor suppressor protein p53. This, in turn, stimulates the production of proopiomelanocortin (POMC), which is cleaved to produce alpha-melanocyte-stimulating hormone (α-MSH). α-MSH binds to MC1R on melanocytes, triggering cyclic AMP (cAMP)-mediated pathways that enhance melanin synthesis [3]. This cascade leads to increased melanin production and its transfer to keratinocytes, resulting in visible pigmentation. UVA radiation further contributes by inducing oxidative stress and immediate pigment darkening, reinforcing the appearance of freckles.

Clinically, freckles are most commonly observed in individuals with Fitzpatrick skin types I and II and typically appear during early childhood. They are more prominent in individuals with lighter phototypes due to reduced baseline melanin protection. While freckles themselves are benign, they are considered markers of increased UV sensitivity. Epidemiological observations suggest that individuals with extensive freckling may have a higher risk of actinic damage and potentially melanoma, emphasizing the need for appropriate photoprotection [4].

Environmental factors, particularly cumulative sun exposure, significantly influence the distribution and intensity of freckles. Regions with high UV index show a higher prevalence and prominence of ephelides. Preventive strategies such as the use of broad-spectrum sunscreens, protective clothing, and behavioral modifications play a

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crucial role in limiting freckle formation and preventing associated photodamage [5]. The reversible nature of freckles with reduced UV exposure further highlights their dependence on environmental triggers.

From a dermatological standpoint, freckles serve as an important model for understanding pigmentary disorders. They illustrate the interaction between genetic determinants and environmental stimuli in shaping visible phenotypes. Advances in dermatogenetics have identified additional loci beyond MC1R that contribute to pigmentation variability, reinforcing the polygenic nature of freckling. In cosmetic dermatology, treatment options such as topical depigmenting agents, chemical peels, and laser therapies are commonly employed; however, recurrence remains frequent due to persistent genetic predisposition [6].

In conclusion, freckles are a benign yet biologically significant pigmentary condition resulting from the interplay of genetic susceptibility and ultraviolet radiation. They provide a visible marker of melanocyte activity and photobiological response. Understanding their underlying mechanisms not only enhances knowledge of skin pigmentation but also underscores the importance of sun protection in reducing long-term dermatological risks.

Methodology

This narrative review was designed to comprehensively synthesize existing evidence on freckles (ephelides), with a focus on their genetic, molecular, and environmental determinants. A non-systematic, descriptive review approach was adopted, allowing integration of classical dermatological knowledge with emerging genomic and clinical insights. The objective was to provide a broad yet scientifically grounded overview rather than a quantitative synthesis.

A structured literature search was performed using PubMed/MEDLINE, Google Scholar, and authoritative dermatology resources. Key search terms included *“freckles,” “ephelides,” “MC1R gene,” “skin pigmentation,” “UV radiation,” “melanogenesis,” “iris freckles,”* and *“pigmentation genetics.”* Boolean operators (AND, OR) were used to refine the search strategy. Emphasis was placed on recent studies (post-2020) to capture evolving evidence, particularly in genomics and pigment biology, while seminal studies were selectively included to support foundational mechanisms.

In addition to peer-reviewed journal articles, standard dermatology textbooks were used to establish core concepts related to melanocyte biology and pigmentary disorders. Authoritative web-based resources from recognized institutions were included to supplement current clinical perspectives and public health relevance. Studies focusing on genetic polymorphisms (MC1R, IRF4, HERC2), UV-mediated pathways, and clinical associations such as melanoma risk were prioritized.

Inclusion criteria encompassed articles that directly addressed freckles, pigmentation pathways, or related phenotypic traits. Exclusion criteria included studies with limited relevance, non-English publications without accessible translations, and those lacking scientific rigor. Data from selected sources were synthesized thematically under domains including pathophysiology, genetics, environmental factors, and clinical implications.

Given the narrative nature of the review, formal risk-of-bias assessment and meta-analysis were not performed. However, preference was given to high-quality, peer-reviewed studies and consensus-based dermatology references to ensure scientific validity. This approach enables a comprehensive and integrative understanding of freckles as a model of human pigmentation biology.

Genetic, Molecular and Clinical Insights into Freckles (Ephelides)

Emerging Concept: Freckles Beyond Skin – Ocular and Systemic Correlates

Recent research has expanded the understanding of freckles beyond cutaneous manifestations, particularly highlighting their presence in ocular tissues. Boldu-Roig et al. (2025) demonstrated that iris freckles and nevi share a strong genetic basis, with overlapping pathways regulating melanocyte behavior in both skin and ocular tissues [7]. Their study emphasized that iris pigmentation patterns are not random but are genetically programmed traits influenced by key pigmentation genes, suggesting a systemic regulation of melanocyte activity.

Further strengthening the clinical significance, Gelmi et al. (2025) identified that genetic variation in the *HERC2* locus significantly influences survival outcomes in uveal melanoma patients [8]. This finding suggests that pigmentation-related genes not only determine phenotype but may also modulate disease prognosis, linking freckles and pigmentation traits with oncological outcomes.

Adding a novel dimension, Koc and Uzunoğlu (2024) proposed iris freckles as a potential biomarker for age-related macular degeneration (AMD) [9]. Their findings indicate that pigmentary changes in the iris may reflect cumulative oxidative stress and aging-related degeneration, thereby positioning freckles as indicators of systemic and ocular health.

Differential Diagnosis and Clinical Spectrum of Pigmented Lesions

Freckles must be distinguished from other pigmented lesions across different tissues. Abati et al. (2024) highlighted the importance of differentiating benign pigmentation from malignant lesions in mucosal surfaces, emphasizing that clinical evaluation must consider morphology, distribution, and associated risk factors [10]. Similarly, Ison and Clark (2023) reinforced that oral pigmented lesions can mimic melanocytic neoplasms, necessitating careful diagnostic approaches to avoid misinterpretation [11].

Genetic syndromes further illustrate the systemic nature of pigmentation. Yamamoto et al. (2023) described mucocutaneous pigmentation in Peutz–Jeghers syndrome, demonstrating how genetic mutations can produce widespread pigmentary manifestations across skin and mucosa [12]. Additionally, Anne Marie et al. (2023) showed that systemic conditions such as iron imbalance can lead to pigmentary alterations, indicating that pigmentation is influenced by metabolic as well as genetic factors [13].

Freckles as Markers of UV Sensitivity and Cancer Risk

Freckles have long been associated with ultraviolet sensitivity and potential malignancy risk. Ridge et al. (2022) observed that specific iris features, including the absence of freckles, were associated with altered skin cancer risk profiles, suggesting that pigmentary traits may serve as phenotypic markers of susceptibility [14]. This supports the concept that freckles reflect underlying photobiological responses.

At the cellular level, van Zyl et al. (2022) provided a comprehensive atlas of ocular tissues, demonstrating shared melanocyte populations across anatomical regions [15]. This reinforces the idea that pigmentation patterns, including freckles, arise from systemic melanocyte biology rather than isolated local processes.

Further clinical relevance is highlighted by tumor classification frameworks. Hernandez-Prera (2022) emphasized the importance of distinguishing benign melanocytic lesions from malignant counterparts within updated WHO classifications, underscoring the need for precise characterization of pigmented lesions, including freckles [16].

Genomic Architecture of Pigmentation and Freckling

Advances in genomic research have significantly enhanced the understanding of pigmentation traits. Simcoe et al. (2021) conducted a large-scale genome-wide association study (GWAS) identifying multiple novel loci associated with eye color, demonstrating the polygenic nature of pigmentation [17]. These findings suggest that freckles are influenced by a network of interacting genes rather than a single genetic determinant.

Building on this, Kukla-Bartoszek et al. (2021) improved DNA-based prediction models for eye color, highlighting the accuracy of genetic markers in determining pigmentation traits [18]. These predictive approaches further support the strong genetic basis of freckling.

The clinical implications of pigmentation genetics are evident in melanoma research. Stefanaki et al. (2021) demonstrated that MC1R variants are associated with nevus count and melanoma susceptibility, reinforcing the link between pigmentation genes and cancer risk [19]. Similarly, Bondi et al. (2021) discussed mucosal melanoma, emphasizing the importance of recognizing pigmentary changes as potential indicators of malignancy [20].

Forensic and Predictive Genetics of Freckles

The predictive potential of freckles has been explored in forensic genetics. Kukla-Bartoszek et al. (2019) developed DNA-based models capable of predicting the presence of freckles with considerable accuracy, demonstrating the heritable nature of this phenotype [21]. These models integrate multiple genetic markers, reflecting the polygenic basis of pigmentation.

From an epidemiological perspective, Laino et al. (2018) identified iris pigmented lesions as markers of increased melanoma risk in a case–control study, suggesting that freckles may serve as early indicators of malignancy susceptibility [22]. This finding supports the role of freckles as clinically relevant phenotypic markers.

Environmental Interaction and Genetic Susceptibility

Freckles represent a classic example of gene–environment interaction. Visconti et al. (2018) identified genetic loci associated with tanning response, demonstrating that individual variation in UV response is genetically determined [23]. This explains why some individuals develop freckles more readily under sun exposure.

Further supporting this, Hernando et al. (2018) identified specific genetic determinants of freckle occurrence in a Spanish population, highlighting population-specific variation in pigmentation traits [24]. These findings emphasize that both ancestry and environmental exposure contribute to freckle development.

Finally, Ferguson et al. (2016) demonstrated that pigmentation-related genetic markers are associated with uveal melanoma risk, reinforcing the link between pigmentation biology and oncogenesis [25]. This establishes freckles as not merely cosmetic features but potential indicators of underlying genetic susceptibility to disease.

Molecular Genetics, Advanced Mechanisms and Clinical Implications of Freckles

Sex-Specific and Population-Level Genetic Variability

Recent advances in pigmentation genetics have revealed that freckling is not uniformly expressed across populations or sexes. Hernando et al. (2016) demonstrated that pigmentation traits, including freckling and UV sensitivity, exhibit significant sex-specific genetic effects, suggesting that hormonal modulation and gene–sex interactions influence melanocyte behavior [26]. These findings indicate that freckle expression is not solely genetically determined but is modulated by biological variables such as sex hormones.

Population diversity further contributes to variability in freckling. Edwards et al. (2016) analyzed iris surface features across diverse populations and demonstrated significant heterogeneity in pigmentation patterns, reinforcing the influence of ancestry on freckle distribution [27]. This highlights the importance of considering ethnicity and genetic background when evaluating pigmentation traits.

Ultraviolet Radiation and Molecular Pathways of Freckling

Freckles represent a classic example of UV-induced pigmentation. Praetorius et al. (2014) described that UV radiation stimulates melanogenesis through activation of melanocyte signaling pathways, leading to increased melanin synthesis without melanocyte proliferation [28]. This explains the dynamic nature of freckles, which darken with sun exposure and fade in its absence.

At the genetic level, Martinez-Cadenas et al. (2013) identified gender-related differences in eye color prediction models, suggesting that genetic expression of pigmentation pathways varies across individuals [29]. This further supports the complexity of freckling as a multifactorial trait.

A key molecular pathway underlying pigmentation involves the interaction between IRF4 and MITF. Praetorius et al. (2013) demonstrated that a polymorphism in the IRF4 gene influences pigmentation through a tyrosinase-dependent

MITF pathway, directly affecting melanin synthesis [30]. This pathway is critical in determining whether melanocytes produce eumelanin or pheomelanin, thereby influencing freckle formation.

Predictive Genetics and Phenotypic Modeling

Advances in genetic prediction models have significantly improved the understanding of pigmentation traits. Walsh et al. (2012) developed the IrisPlex system, enabling accurate prediction of eye color based on DNA markers [31]. This system highlights the predictive power of genetic variants in determining visible phenotypes, including freckles.

Similarly, Larsson et al. (2011) identified genetic variants associated with iris patterns through genome-wide association studies, further supporting the polygenic nature of pigmentation [32]. These findings demonstrate that freckles and related traits are controlled by multiple interacting genetic loci.

The role of IRF4 in pigmentation has been further supported by Duffy et al. (2010), who showed that IRF4 variants influence nevus count and pigmentation patterns, suggesting a shared genetic basis between freckles and other melanocytic features [33]. In parallel, Eriksson et al. (2010) identified novel genetic associations for pigmentation traits using large population-based datasets, reinforcing the complexity of genetic regulation [34].

Core Molecular Genetics of Pigmentation

At the core of freckling lies the molecular genetics of pigmentation. Sturm (2009) described the diversity of human pigmentation as a result of variations in genes regulating melanocyte function, including MC1R, ASIP, and TYR [35]. These genes influence melanin production, distribution, and response to UV radiation.

Further elaborating on this, Sturm and Larsson (2009) demonstrated that iris color and pigmentation patterns are governed by multiple genetic pathways, highlighting the shared mechanisms between cutaneous and ocular pigmentation [36]. This supports the concept that freckles are part of a broader pigmentary system.

Genotype-based prediction of pigmentation traits has also been explored. Liu et al. (2009) showed that eye color can be predicted from genetic data, illustrating the strong genotype–phenotype correlation in pigmentation [37]. These findings emphasize the deterministic role of genetics in freckling.

Genome-Wide Associations and Polygenic Influence

Large-scale genome-wide association studies have significantly advanced the understanding of pigmentation. Han et al. (2008) identified novel alleles associated with skin and hair pigmentation, demonstrating the polygenic nature of these traits [38]. Similarly, Sulem et al. (2007) identified key genetic determinants influencing pigmentation in European populations, including variants associated with freckling [39].

One of the most critical genes in freckling is MC1R. Bastiaens et al. (2001) established MC1R as the major gene responsible for freckle formation, linking its variants to increased pheomelanin production and UV sensitivity [40]. This finding remains a cornerstone in understanding the genetic basis of freckles.

The pleiotropic effects of MC1R were further demonstrated by Flanagan et al. (2000), who showed that this gene influences multiple pigmentation traits, including skin color, hair color, and freckling [41]. This highlights the interconnected nature of pigmentation pathways.

Table 1 : Thematic Synthesis of Key Findings on Freckles (Ephelides)

Theme	Synthesized Findings
Nature of Freckles	Freckles (ephelides) are benign hyperpigmented macules characterized by increased melanin deposition within keratinocytes without an increase in melanocyte number. They represent functional melanocyte hyperactivity rather than cellular proliferation.
Systemic Pigmentary Phenotype	Pigmentary changes analogous to cutaneous freckles are observed in ocular tissues, particularly the iris, indicating that freckling reflects a systemic melanocyte regulatory process rather than a localized phenomenon.
Genetic Determinants	Freckling is strongly influenced by genetic polymorphisms in pigmentation-related genes, including MC1R, IRF4, HERC2, and OCA2, which regulate melanogenesis and pigment distribution.
Polygenic Inheritance	The expression of freckles is polygenic, involving multiple interacting loci identified through genome-wide association studies, rather than a single gene effect.
MC1R Pathway	Variants in the MC1R gene shift melanogenesis toward pheomelanin production, resulting in increased photosensitivity and a higher propensity for freckle formation.
IRF4–MITF Axis	IRF4 polymorphisms influence pigmentation through regulation of the MITF pathway, modulating tyrosinase activity and melanin synthesis.
HERC2 and Pigmentation	Variants in HERC2 are associated with eye color, pigmentation patterns, and clinical outcomes such as melanoma prognosis, highlighting the broader impact of pigmentation genes.
Sex-Specific Variability	Genetic expression of pigmentation traits demonstrates sex-specific variation, suggesting modulation by hormonal and epigenetic factors.

Population and Ethnic Variation	Freckling patterns vary significantly across populations due to genetic diversity and ancestral background, influencing both prevalence and phenotypic expression.
Ultraviolet Radiation	Ultraviolet radiation is the principal environmental determinant, inducing melanogenesis through activation of molecular pathways without increasing melanocyte number.
Gene–Environment Interaction	Freckles represent a classic model of gene–environment interaction, where genetic susceptibility determines the magnitude of response to ultraviolet exposure.
Melanin Composition	Freckles are associated with increased pheomelanin relative to eumelanin, contributing to reduced photoprotection and increased oxidative stress.
Dynamic Behavior	Freckles exhibit reversible pigmentation, darkening with ultraviolet exposure and fading during reduced exposure, reflecting transient melanocyte activation.
Shared Melanocyte Biology	Melanocytes in the skin and ocular tissues exhibit similar functional and molecular characteristics, supporting a unified pigmentary system.
Clinical Differentiation	Freckles must be distinguished from other pigmented lesions such as lentigines, nevi, and melanoma, particularly in mucosal and ocular sites where diagnostic challenges exist.
Syndromic Associations	Pigmentary manifestations resembling freckles may occur in genetic syndromes such as Peutz–Jeghers syndrome, reflecting systemic genetic alterations.
Metabolic Influences	Systemic factors, including nutritional and metabolic imbalances, may influence pigmentation, indicating that freckling is not solely genetically determined.
Melanoma Risk Association	Freckles are associated with increased susceptibility to ultraviolet-induced skin damage and melanoma, serving as phenotypic markers of risk.
Ocular Disease Association	Iris freckles have been proposed as potential biomarkers for ocular conditions such as age-related macular degeneration and uveal melanoma.
Biomarker Potential	Freckles may function as visible biomarkers of underlying genetic susceptibility, ultraviolet sensitivity, and disease risk.
Forensic Applications	Genetic markers enable prediction of freckling and pigmentation traits from DNA, demonstrating strong genotype–phenotype correlation.
Predictive Genetic Models	Tools such as DNA-based prediction systems allow estimation of pigmentation traits, including freckles, with increasing accuracy.
Genome-Wide Insights	Genome-wide association studies have identified multiple loci influencing pigmentation, reinforcing the complex genetic architecture of freckling.
Pleiotropic Genetic Effects	Pigmentation genes exhibit pleiotropy, influencing multiple phenotypic traits including skin color, eye color, and freckling.
Clinical Implications	Freckles serve as indicators of ultraviolet sensitivity and necessitate preventive strategies such as photoprotection and surveillance.
Public Health Relevance	Freckling may act as a simple, observable phenotypic marker to identify individuals at higher risk of ultraviolet-related skin damage and malignancy.
Research Significance	Freckles provide a valuable model for studying melanocyte biology, gene–environment interactions, and pigment-related disorders across disciplines.

Conclusion:

Freckles (ephelides) represent a complex, polygenic pigmentary phenotype arising from the interaction between key genetic determinants—particularly MC1R, IRF4, and HERC2—and environmental exposure to ultraviolet radiation. Beyond their traditional classification as benign cutaneous findings, freckles reflect a systemic melanocyte response evident across both skin and ocular tissues. Their association with pheomelanin predominance explains increased photosensitivity and susceptibility to oxidative damage. Importantly, accumulating evidence indicates that freckles serve as clinically relevant markers of ultraviolet sensitivity and are linked to an elevated risk of melanoma and other pigment-related disorders. The emergence of genomic prediction models and the identification of iris freckles as potential biomarkers further underscore their diagnostic and prognostic value. Collectively, freckles should be regarded not merely as cosmetic entities but as visible indicators of underlying genetic architecture and environmental interaction, with significant implications for personalized risk assessment, preventive dermatology, and future translational research

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