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Article

Genome-Wide Association Study in Pigmentation as One of Skin Aging Characteristics

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Abstract. Skin aging is a physiological process marked by changes in the skin's structure, giving rise to the characteristics of skin aging, such as pigmentation. Genome-Wide Association Studies (GWAS) identify genetic profiles that play a role in skin aging characteristics such as pigmentation. This study aimed to gather information about candidate SNPs and genes related to pigmentation characteristics of skin aging across different populations. We systematically searched relevant articles published in PubMed and ProQuest in the last ten years. Out of 212 articles screened, seven studies pertinent to our research are included in the analysis. Results indicated that in European and East Asian populations, several gene candidates such as *IRF4*, *MC1R*, *ASIP*, *BNC2*, *PPARGC1B*, *RAB11FIP2*, and *CYP1A* associated with SNPs that are known to have functions related to skin aging. However, further comprehensive analysis is needed to understand the functional correlation between SNP or gene candidates and pigmentation. In addition, the diversity of the subjects in the GWAS is still concerning. The future comprehensive analysis of GWAS, which involves underrepresented ones, is needed to broaden the knowledge of skin aging mechanisms across different populations.

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1. Introduction

Aging is a physiological process experienced by every living thing, including humans, in which the body cells change, such as cell death and protein interstitial matrix loss. The aging process of an individual can show various characteristics, one of them being aging skin. Skin aging has several aspects, among which the most found are wrinkles, pigmentation, and decreased moisture [1-2]. These features can appear on mature skin with various age ranges, generally after someone is 25-30 years old [3]. Multiple factors, such as lifestyle, geographic location, skincare, and hereditary genetic factors, can influence aging characteristics. Hence, skin aging is a multifactorial phenotype affected by various factors, including extrinsic and intrinsic factors [3-4].

Intrinsic and extrinsic factors of skin aging are interconnected and together produce the appearance of aging skin characteristics, such as wrinkles, pigmentation, and decreased moisture. In terms of these aging characteristics, genetic, racial, and hormonal factors can significantly influence skin changes. Research conducted to determine the characteristics of wrinkles and pigmentation in two different races population shows that racial differences are one of the main factors of aging characteristics [5-6]. A study by Richard et al., (2005) [5] showed that Asian people tend to exhibit characteristics of hyperpigmentation compared to wrinkles. In contrast, wrinkles appeared more common in the Caucasian population [5]. Moreover, a newer study conducted in 2022 using artificial intelligence to detect aging skin characteristics also supports the hypothesis of aging skin differences between the European and Asian populations [7].

Apart from being a multifactorial trait, skin aging characteristics are also known to be polygenic. Polygenic traits are influenced by several genes simultaneously. In the context of skin aging, for example, it is known that genes such as *MC1R*, *OCA2*, and *BNC2* influence the process of collagen degradation and changes in melanogenesis [8-9]. The characteristic of aging itself is a phenotype that is multifactorial and polygenic. A multifactorial trait is a trait whose appearance is influenced by various factors, including intrinsic and extrinsic factors. Meanwhile, polygenic traits are a term for a trait whose formation can be affected by different genes [8-10].

Various studies have been conducted to determine the genetic profile that plays a role in skin aging, primarily through a genomic approach. The term genomics itself has a different meaning compared to genetics. World Health Organization (WHO) states that the field of genetics is a study that studies the inheritance of genetic material. Meanwhile, genomics is a field of study investigating the function of various genes carried out using different techniques. Hence, genetic studies tend to study a single gene, while genomic studies are more comprehensive regarding function and interrelationships between genes. However, these two fields of study are closely related since both study the same object [11]. Various genomic studies on skin aging have been carried out using different techniques. One of them is Genome-Wide Association Study (GWAS).

GWAS is a research method widely used to determine the genetic factors affecting the appearance of polygenic or multifactor phenotypes such as skin aging. Additionally, GWAS can map the genetic structure of a polygenic phenotype by identifying genetic variants that have a significantly higher frequency in groups with phenotypes/disease compared to the healthy/without phenotype groups [12]. Until now, GWAS have been carried out on various populations with various sample sizes so that the genes that tend to have a relationship and play a role in the skin aging process can be identified.

However, the association studies' results will likely differ due to differences in genetic structure and the emerging characteristics of skin aging in different populations [13]. The population diversity in GWAS will lead to several hypotheses regarding the genes associated with skin aging characteristics. This review will briefly discuss GWAS in skin aging, focusing on the pigmentation aspect of aging skin along with several genes presumably related to skin aging pigmentation

2. Materials and Method

This article review used Preferred Reporting Item for the Systematic Reviews and Meta-Analysis (PRISMA) method [14]. Keywords such as skin aging, Genome-Wide Association Study/GWAS, and pigmentation were used for article selection in two publication databases, PubMed (https://pubmed.ncbi.nlm.nih.gov) and ProQuest (https://www.proquest.com). A total of 212 articles (PubMed: 12 articles, ProQuest: 200 articles) found were then selected and filtered based on the relevance of the title, abstract, and the entire article with the questions addressed. After choosing the papers, seven reports that discussed genomic association studies with skin aging factors, especially pigmentation characteristics, were used. Figure 1 shows the flowchart of the articles included in this study.

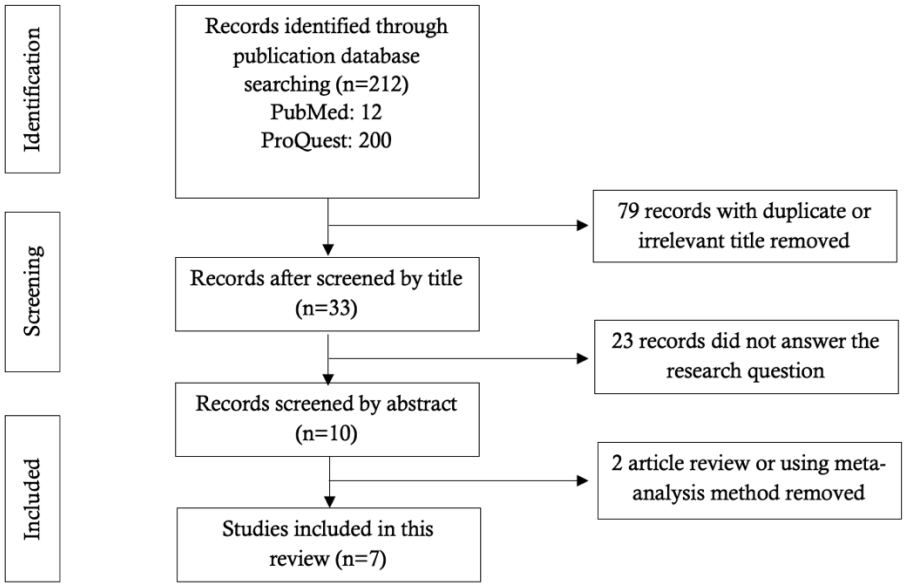

Figure 1. PRISMA diagram of the article inclusion

3. Results and Discussion

The criteria of the several studies included in this review are listed in Table 1. Studies included in this review were published within the last ten years (2013-2022). Two papers were conducted on the European population, while the other five were conducted on East Asian populations, mainly Chinese, Japanese, and Korean. GWAS on skin aging study conducted by Clerc et al., (2013) [15] shows an association between SNP rs322456-AA and photoaging characteristics, especially wrinkle and sagging. But still, it is not associated with the presence of solar lentigines, indicating that the SNP is not associated with pigmentation disorders.

A study conducted by Jacobs et al., (2015) [16] with a larger sample size of 2844 individuals in the Netherlands did not detect any association between skin aging characteristics and genes known to be associated with photoaging by Clerc et al., (2013) [15]. However, this study shows that there is an association between SNPs present near the position of several new genes, such as SNP rs12203592 (*IRF4* gene), rs35063026 (*MC1R* gene), rs6059655 (*RALY/ASIP* gene), and rs62543565(C) (*BNC2* gene) with the formation of pigmented spots [16].

Unlike the two previous studies conducted on Caucasian populations, the research undertaken by Gao et al., (2017) [17] to our knowledge, is the first GWAS research in skin aging conducted in East Asia. This research used the skin aging scale measurement and demonstrated that the SNP rs10733310 is associated with pigmentation. Candidate gene studies showed that the SNP rs10733310

was associated with the *BNC2* gene, the same gene detected by Jacobs et al., (2015) [16] in the Asian population. Another research in China by Liu et al., (2019) [18] involved 1534 individuals and showed an association between SNP rs1048943, located in the exon of the *CYP1A1* gene, and pigmented spots on cheeks. Else, a study conducted in East Asia by Endo et al., (2018) [19] against 11,378 individuals in the population in Japan. This research aims to determine the association between genotype profile and skin aging phenotype, including age spots and freckles. This study shows an association between the SNPs rs251468 (*PPARGC1B* gene), rs61866017, and rs35563099 (*RAB11FIP2* gene) with the formation of age spots and freckles on aging skin.

Other studies conducted in East Asia include research by Oh Kim et al., (2021) [20] against 1079 individuals in Korea. This research shows that there is an association between several SNPs related to the *TSN1* (rs11685354), *NCLN* (rs34466224), *CDC42BPA* (rs4653497), and *OCA2* (rs74653330) genes with aging skin pigmentation characteristics. In contrast to previous studies that used standardized or self-report phenotype rating scales, this study used skin aging phenotype analysis tools such as the Mexameter for hyperpigmentation. Then the latest study, which is a replication of the study in Korea, carried out by Cha et al., (2022) [21], showed that there were *TSN1* and *UNCX* genes that were replicated and had significant association values. Studi ini menunjukkan bahwa terdapat keragaman gen-gen yang ditemukan berkaitan dengan karakteristik pigmentasi penuaan kulit pada populasi yang berbeda.

Table 1. The Criteria of Selected Articles

First Author, Published Year	Population	Number of Subjects	Outcome (SNPs or genes related to pigmentation)
Sigrid Le Clerc, 2013	European	502 French adults in middle-age	Association between SNP rs322456-AA with photo-aging, but not correlated with pigmentation.
Leonnie C. Jacobs, 2015	European	2.844 European (>45years of age)	Association between *IRF4*, *MC1R*, *RALY/ ASIP*, and *BNC2* gene with pigmented spots.
Wenshan Gao, 2016	Chinese	502 Chinese women (32–85 years of age)	SNP rs10733310, associated with the *BNC2* gene, correlated with skin pigmentation.
Yu Liu, 2018	Chinese	1534 Chinese women (31-86 years of age)	Association between SNP rs1048943 located in the exon of the *CYP1A1* gene with pigmented spots.
Chihiro Endo, 2018	Japanese	11.311 subjects	Association between the SNPs rs251468 (*PPARGC1B* gene), rs61866017, and rs35563099 (*RAB11FIP2* gene) with the formation of age spots and freckles
Jung Oh Kim, 2021	Korean	1.079 Korean with an average of 40.81 years of age	Association of several SNPs related to the *TSN1* (rs11685354), *NCLN* (rs34466224), *CDC42BPA* (rs4653497), and *OCA2* (rs74653330) genes with aging skin pigmentation
Mi-Yeon Cha, 2022	Korean	261 with an average of 45.10 years of age	*TSN1* and *UNCX* genes that were replicated and had significant association values

Several studies have successfully obtained gene candidates associated with pigmentation characteristics in skin aging within different populations. However, there is not enough information just knowing the association of one phenotype to its genetic variation. One of the problems concerning the GWAS is the complexity of interpreting the significance of the associations obtained to produce a significant clinical impact, especially the complex traits whose majority of variants remain uncovered [12][22].

One reason is the linkage disequilibrium phenomenon, where a detected SNP can be inherited with other SNPs without influencing the observed phenotype. In addition, the associated SNPs are not necessarily SNPs contained in a gene, where 90% of SNPs found to be associated with phenotypes in GWAS studies are known to be in the non-coding region of the sequences in the genome [12][22-23]. In addition, even though the area where the SNP is located is known, it is necessary to find out more about the role of the variant. For example, when a variant is located within the enhancer region, this does not necessarily indicate a change in the function of the enhancer itself [12, 24]. Therefore, further functional analysis needs to be carried out to obtain more comprehensive information regarding the association of SNPs with phenotypes.

One of the procedures that can be carried out to overcome this problem is using a range of machine learning-based computational tools developed for gene functional analysis, such as GWAVA and JARVIS [24]. GWAVA and JARVIS is a tool that integrates various genomic and epigenomic annotations to support the prioritization of non-coding regions [25-27]. Another procedure is SNP enrichment analysis, used for detecting which cell type is the most relevant to the phenotype or the one with the most related gene representations. This approach can be carried out by integrating GWAS with other studies, such as gene expression Quantitative Trait Loci (eQTL) mapping [12]. Based on the functional analysis in several previous GWAS articles included in this study, several genes such as *IRF4*, *MC1R*, *ASIP*, *BNC2*, *PPARGC1B, RAB11FIP2, CYP1A* associated with SNPs that are known to have functions related to skin aging mechanism. Here, we tried to discuss the role of several genes in skin aging pigmentation based on previous studies.

The Interferon Regulatory Factor 4 (*IRF4*) gene is a gene found on chromosome number 6 (6p25.3) and has many roles in lymphoid malignancy, such as multiple myeloma [28-29]. The *IRF* gene acts as a lymphoid transcription factor and the primary regulator of the development of various immune cells, especially several processes such as differentiation, maturation, and B cell signaling [30]. An association study of *IRF4* variants in multiple myeloma patients showed that the *IRF4* gene increases the risk of multiple myeloma [31]. Another study in skin cancer patients also showed that SNP rs12203592, located in the *IRF4* gene associated with pigmentation, considered *IRF4* to limit the immune response as one of the symptoms of melanoma skin cancer [32]. In addition, the *IRF4* variant is also known to be associated with the number of nevi counts in age-specific melanoma patients [33].

The Melanocortin 1 receptor (*MC1R*) gene is one of the genes known to be related to skin pigmentation and has been well characterized. MC1R is located on the long arm of chromosome 16 (16q24), encoding the α-melanocyte-stimulating hormone (α-MSH) receptor protein. When α-MSH binds to the MC1R receptor, it causes stimulation of melanogenesis [34-35]. One study on the Hispanic population showed that the *MC1R* has an essential role in the appearance of pigmentation characteristics. Individuals with specific alleles categorized as high-risk tend to have skin quickly burned by sun exposure [36]. Studies of the association of *MC1R* variants with melanoma risk have shown that specific variants of the *MC1R* have a higher pigmentation effect in women than men, which also increases the risk of developing melanoma [37].

Agouti signaling protein (*ASIP*) gene is located on the long arm of chromosome 20 (20q11.22) encoding ASIP protein. The ASIP protein can affect hair pigmentation and has an antagonist role with α -MSH against melanocortin [38]. A study conducted by Peter et al., (2002) [39] in healthy subjects shows that polymorphisms of the *ASIP* gene may play a role in the appearance of hair pigmentation characteristics and eye color. Apart from being based on an association study conducted

by Taylor et al., (2015) [40], it is known that the TG haplotype has a close relationship with poor melanoma survival ability.

The Basonuclin 2 (*BNC2*) gene's position is on the short arm of chromosome 9 (9p22.3). Based on candidate gene studies conducted by Jacobs et al., (2013) [41], the *BNC2* gene plays a role in encoding a protein that functions in skin color saturation. In addition to *BNC2* gene expression, studies on light-to-dark melanocyte cell lines conducted by Visser et al., (2014) [42] showed higher expression of *BNC2* in dark melanocyte cells. However, the detailed mechanisms and functions of the *BNC2* gene on skin pigmentation are still unknown. The Peroxisome proliferator-activated receptor coactivator 1 beta (*PPARGC1B*) gene's position is on the long arm of chromosome 5 (5q32).

The *PPARGC1B* gene stimulates several transcription factors, such as PPARG, expressed in skin cells, such as keratinocytes and melanocytes. Several studies related to PPARG allow for a relationship between *PPARGC1B* and pigmentation. One of the studies by Lee et al., (2007) [43] on melanocyte culture cells showed that PPARG plays a role in melanocyte cell migration and human skin pigmentation. In addition, based on a study finding by Meylan et al., (2021) [44], a low expression of the Thioredoxin-interacting protein gene regulated by PPARG in melanocytes plays a role in melanoma progression.

The RAB11 Family Interacting protein (*RAB11FIP2*) gene's location is on the long arm of chromosome 10. RAB11b is a protein that mediates the transfer of melanin from melanocytes to keratinocytes. This is one of the crucial processes in the skin when exposed to sunlight to protect the skin from UV rays [45]. In addition, Moreisas et al., (2020) [46] showed that decreased levels of RAB11 act as one of the exocysts that encourage the exocytosis process of melanin pigment. Another gene named Oculocutanous albinism 2 (*OCA2*) gene, known to be associated with pigmentation, is located on the long arm of chromosome 15 (15q12). The *OCA2* gene encodes a transport protein that modulates melanosomal pH, so melanogenesis occurs [47].

Based on previously conducted association studies, it is known that *OCA2* is also closely related to skin pigmentation disorders such as melanoma. The cytochrome P450 gene family 1 subfamily A member 1 (*CYP1A1*) gene's position is on the long arm of chromosome 15 (15q24.1). *CYP1A1* encodes the cytochrome450 (CYP450) enzyme superfamily that regulates the metabolism and synthesis of molecules such as cholesterol, steroids, and lipids. Based on in vivo studies, it is known that CYP1A1 enzymatic activity involves in the occurrence of skin inflammation through the AHR signaling pathway [48]. CYP1A1 is known to regulate AHR, which functions as a regulator of skin barrier function, keratinocyte differentiation, and skin pigmentation [49].

Skin aging pigmentation can occur through various signaling pathways triggered by extrinsic or intrinsic factors (Figure 2). One track is the Reactive Oxygen Species (ROS) increasing due to antioxidant degradation caused by external exposure factors and natural aging [4]. ROS can be formed due to metabolic processes in mitochondria or exposure to UV light which causes photooxidation. After ROS formation, cytokine receptors on the cell surface, as well as keratinocyte and fibroblast cell growth factors, will activate transcription factor such as activator protein-1 (AP-1) and Nuclear factor kappa B (NF-kb).

The active of AP-1 and NF-kB causes a decrease in collagen production and changes in pigmentation [1][50]. Another pathway involves MC1R, which is associated with pigmentation, according to a study by Jacobs et al., (2015) [16]. MC1R receptor will be activated by α-melanocyte-stimulating hormone (α -MSH), which increases due to the upregulation of its precursor, pro-opiomelanocortin (POMC), because of exposure to external factors. The activation of MC1R causes melanocyte activation and improves melanogenesis and pigmentation [51-53].

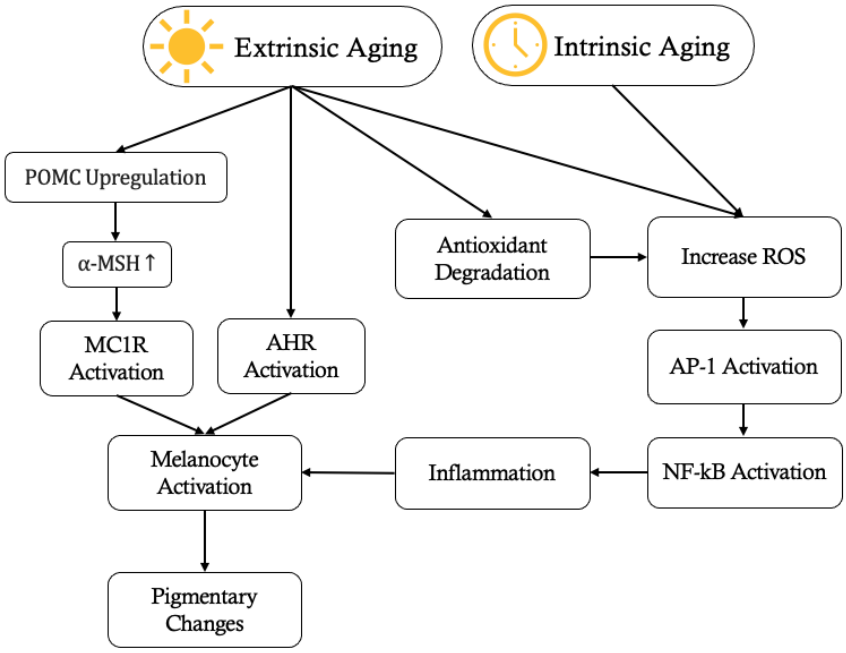

Figure 2. Mechanism of Pigmentary Changes in Skin Aging [50-53]

Besides the functional role of the genes in the skin aging mechanism, it is also concerning that most of the GWAS were conducted in the European population. In 2009, research showed that 96% of the GWAS research had European respondents [54], encouraging non-European countries to conduct GWAS research. Seven years later, in 2016, there was progress where non-European GWAS research increased from 4% to 19% [55] and continued to grow, although it has also decreased again in recent years [56]. In 2017, 86% of the genetic discovery through GWAS was carried out in Europe, while Asia followed with a proportion of 9.92%. Other populations such as African American, Hispanic, and African only show a ratio of 0.3-1.9% [56-57]. The difference in the proportion shows the inequality that occurs in the GWAS research subjects themselves.

The GWAS is crucial to be carried out in various populations for several reasons, such as differences in risk variants and allele variations across populations. The difference in risk variants and allele variations can happen because of the complex forces of migration, genetic recombination, genetic drift, and natural selection when an allele is passed on to the next generations in the population [27]. Conducting GWAS studies in diverse populations will help provide data on risk variants and allele variations so clinicians can determine a clinical approach to a phenotype according to unique genetic data. In addition, more various GWAS will impact the possibility of finding new variants associated with the same phenotype [58-59].

GWAS research exploring the association between genotype profiles and skin aging characteristics such as pigmentation has been conducted in various populations worldwide. Several studies conducted in the East Asia region have succeeded in adding references to GWAS studies other than references from Europe. In the context of pigmentation-related genes, this is depicted by the diversity of SNPs and genes candidate obtained from each study with different populations allegedly associated with pigmentation. The diversity of the findings bodes well for various GWAS studies. However, GWAS studies in other underrepresented populations, such as Africans, Hispanics, and Southeast Asians, are still needed. On a larger scale, GWAS studies conducted in more diverse populations will advance precision medicine and make better predictions on specific diseases or phenotypes. Additionally, clinical decisions aimed at patients are more efficient and effective according to biological data.

4. Conclusion

Through GWAS conducted in various populations, it has been known that several SNPs variations are related to skin aging characteristics such as pigmentation. The different populations showed different gene candidates associated with pigmentation. However, further comprehensive analysis needs to be conducted to understand the functional correlation of the genes. GWAS in skin aging has been carried out mainly in Europe and East Asia. Meanwhile, to our knowledge, no publication has been found regarding GWAS conducted on populations in Southeast Asia.

Therefore, GWAS research focusing on skin aging in an underrepresented population such as Southeast Asia is necessary to determine how the genetic profile is related to specific skin aging features in its people. A comprehensive and diverse understanding of gene function related to skin aging characteristics will broaden the knowledge of skin aging's mechanism and become basic research to encourage the development of precision skincare applications.

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