Population- and haplotype-dependent variation around *TYR* rs1126809: An in silico study for melanoma risk research

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The common missense variant rs1126809 in the *TYR* gene, encoding a key enzyme in melanin synthesis, is linked to both albinism and melanoma susceptibility. Although its role in hypopigmentation as part of a risk haplotype is established, its function in melanoma is less understood. To investigate population- and haplotype-dependent associations surrounding *TYR* rs1126809 that may suggest directions for future studies on melanoma risk and melanocyte biology, we analyzed melanoma GWAS summary statistics using FUMA to identify lead SNPs in linkage disequilibrium with rs1126809 and assessed their regulatory potential using chromatin state data from melanocytes, keratinocytes, and fibroblasts. Haplotype structures were examined in European, American, and South Asian populations using LDlink. rs1126809 emerged as lead SNP in the *TYR* locus. Thirty SNPs were in high linkage disequilibrium, 6 of which reside in melanocyte-specific regulatory regions. These variants form population-specific haplotypes that may modulate TYR expression. In Europeans and Americans, 2 distinct haplotypes carrying the risk allele showed different linked SNP profiles, suggesting haplotype-dependent effects. The findings suggest that variations surrounding *TYR* rs1126809 may exhibit population- and haplotype-dependent patterns relevant to melanoma risk, pointing to previously unreported directions for future research and refinement of polygenic risk modeling.

Keywords: Cancer genetics, Epigenetics, GWAS, Melanocytes, Melanoma

INTRODUCTION

The role of common missense variants in human diseases remains a subject of ongoing debate. Although these variants rarely cause disease on their own, they can contribute to complex traits or act as genetic modifiers. Their biological impact is often subtle but meaningful and may vary between populations owing to differences in genomic background, haplotype structure, and regulatory context. This variability highlights the need to view variant pathogenicity not as a binary classification but as a continuum influenced by multiple factors (Banerjee et al, 2025; Ponzoni et al, 2020). As an example, in polygenic risk score models, common missense variants are often incorporated; however, their effect sizes are difficult to estimate accurately using standard additive approaches because they may be modulated by interactions with nearby variants or by epigenetic factors (Mastrangelo et al, 2025). Therefore, the investigation of variant–variant interactions that can influence gene regulation and phenotype is critical to advance the disease-causing role of common missense variants (Kuznetsov et al, 2023).

A well-known example of this debate with dermatology aspects is the common missense variant rs1126809 in the tyrosinase (*TYR*) gene; *TYR* encodes an enzyme critical for melanin synthesis. The variant rs1126809 causes a change from arginine (R) to glutamine (Q) at amino acid position 402 (chr11-89017961 G>A, c.1205G>A, p.Arg402Gln, NM_000372.5) and occurs with a frequency of 0.16–0.27 in Europeans (gnomAD, https://gnomad.broadinstitute.org). The potential disease-causing role of this variant has been investigated and debated by approximately 90 previous studies, suggesting that this variant is a hypomorphic allele: it is not fully pathogenic alone but significantly reduces TYR expression and, therefore, its enzyme activity (Dolinska et al, 2017; Jagirdar et al, 2014; Lasseaux et al, 2018; Tripathi et al, 1992a, 1992b). In vitro functional studies also suggested that in cultured human melanocytes, the TYR enzyme carrying the variant rs1126809 is degraded more quickly at 37 °C than at 32 °C, whereas wide beside-type TYR does not show this temperature sensitivity (Halaban et al, 2000, 1988; Jagirdar et al, 2014; Tripathi et al, 1992b).

Regarding the most recent disease associations of the *TYR* rs1126809 variant, Michaud et al (2022) demonstrated that the risk alleles of 3 common variants of the *TYR* gene, including the rs1126809 missense one, are part of a risk haplotype in albinism. This risk haplotype in homozygous form or in heterozygous form with a rare heterozygous pathogenic variant can significantly contribute to the development of albinism (Michaud et al, 2022; Nagy et al, 2025).

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Abbreviation: LD, linkage disequilibrium

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Furthermore, another study investigated the synergistic role of the variant *TYR* rs1126809 with another common variant (rs74653330) in the *OCA2* (oculocutaneous albinism type 2) gene and found that dual heterozygosity of the variant *TYR* rs1126809 with the investigated variant *OCA2* rs74653330 significantly increased the odds of diagnosing albinism and is associated with the development of worse visual acuity and thicker retina (Green et al, 2024; Nagy et al, 2024).

In addition to the well-established role of *TYR* in monogenic albinism, this gene also contributes to the susceptibility of additional skin diseases such as melanoma. The germline genetic background of melanoma is composed of variants of predisposing genes with high penetration and susceptibility genes with moderate or low penetration (Bokor et al, 2025; Gerstenblith et al, 2010). The variant *TYR* rs1126809 is associated with modest increases in the risk of cutaneous malignant melanoma (OR = 1.21) (GWAS Catalog, https://www.ebi.ac.uk/gwas/, references). The *TYR* gene is a known low-penetrance melanoma-associated gene, and the rs1126809 variant is included in the calculation of the polygenic risk score for melanoma (PGS Catalog; Rashkin et al, 2020).

In summary, *TYR* rs1126809 SNP is considered a variant not being pathogenic itself in albinism but being part of a haplotype that contributes to the disease. The question emerged of whether it would be possible to identify an rs1126809-linked haplotype as a genetic risk factor for melanoma. Therefore, we performed a thorough in silico analysis using databases of "omics" studies and analysis tools, which may bring us closer to understanding the complex genetic architecture of melanoma. For that, we analyzed the melanoma summary statistics of a pan-cancer GWAS and investigated the variants, which are in linkage disequilibrium (LD) with the *TYR* rs1126809 variant.

RESULTS

Identification of SNPs linked to *TYR* rs1126809 in epigenetically relevant regions

FUMA analyzed the summary statistics of the GWAS of melanoma in silico to annotate, prioritize, and functionally interpret the SNPs (n = 10,003,934) in the statistics. FUMA performed SNP2GENE mapping and defined genomic risk loci on the basis of LD structure and functional annotations. A total of 153 independent significant polymorphisms (SNPs) and 31 lead SNPs were identified from the melanoma GWAS summary statistic by FUMA. These SNPs were grouped into 15 genomic risk loci (Figure 1).

One of the genomic loci was located on chromosome 11 (positions 88,486,635–89,058,101), where the SNP *TYR* rs1126809 emerged as the leading variant within the region of the *TYR* gene. By generating a regional association plot, SNPs (n = 30) were found to have an LD ($r^2 > 0.7$) with the lead *TYR* rs1126809 variant (Figure 2). Of these, only the *TYR* rs1126809 is an exonic variant, whereas all the other SNPs are intronic ones. Among the SNPs in this region, the *TYR* rs1126809 (Combined Annotation Dependent Depletion score: 29.4) and *TYR* rs72963135 (Combined Annotation Dependent Depletion score: 10.8) had the highest predicted deleteriousness according to Combined Annotation Dependent Depletion scores.

To further assess the regulatory potential of the *TYR* rs1126809–linked variants, we in silico analyzed epigenomic annotations from the Roadmap Epigenomics Project, including data from epigenomes corresponding to the types of melanocytes, keratinocytes, and fibroblast cells (Table 1). Of the SNPs (n = 30) in LD with *TYR* rs1126809, 6 SNPs were located in epigenetically relevant regions such as active promoter or proximal enhancer elements in melanocytes. On the contrary, in keratinocytes and fibroblasts, these 6 SNPs were located within epigenetically repressed regions. Therefore, in silico analysis of melanoma GWAS summary statistics by FUMA identified 6 *TYR* SNPs in epigenetically relevant regions (rs10765196, rs72963135, rs17793678, rs11018524, rs11018522, and rs12270717) in melanocytes, which are in LD with the lead *TYR* rs1126809 SNP. These variants are likely to play a significant role in the regulation of *TYR* expression in melanocytes. These 6 SNPs in epigenetically relevant regions may contribute to the susceptibility of melanoma through melanocyte-specific mechanisms.

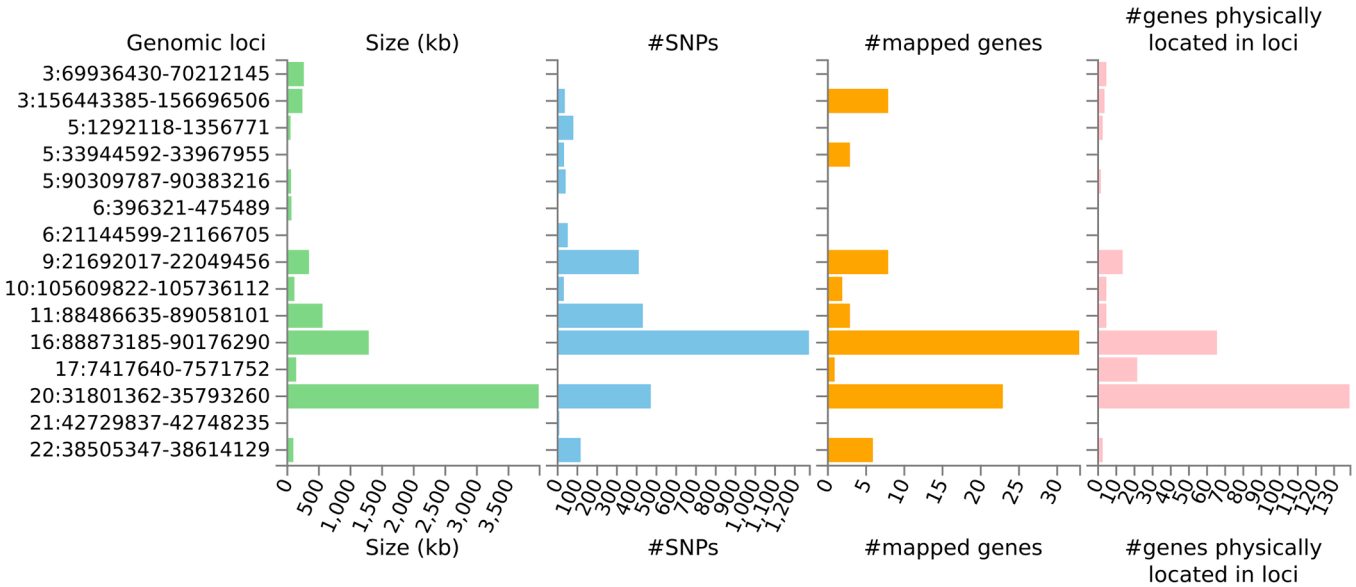

Figure 1. In silico analysis of the melanoma GWAS summary statistics identified 15 genomic risk loci.

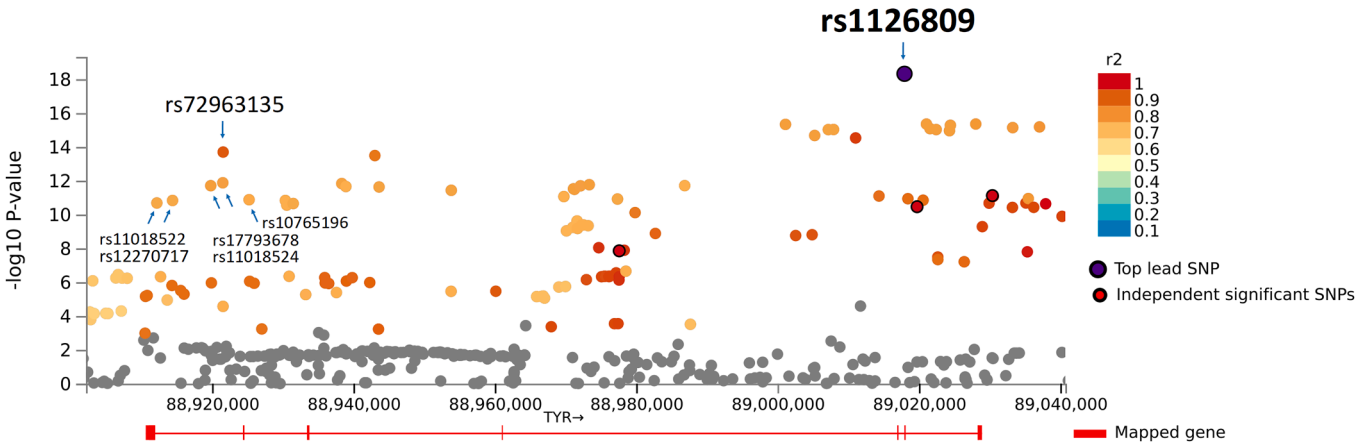

Figure 2. Regional association plot of the genomic loci on chromosome 11 that contain the *TYR* rs1126809 variant as the top leading SNP. Arrows indicate SNPs that are located in epigenetically relevant regions (Table 1).

Table 1. The List of SNPs that Are in LD with the *TYR* rs1126809 Variant and their Location in Epigenetically Relevant Regions in Keratinocytes (E057 and E058), Fibroblasts (E055 and E056), and Melanocytes (E059 and E061)

			Roadmap Epigenomics Project, Epigenome ID					
			Keratinocyte	Keratinocyte	Fibroblast	Fibroblast	Melanocyte	Melanocyte
Selected SNP	**r2**	**CADD**	**E057**	**E058**	**E055**	**E056**	**E059**	**E061**
rs12270717	**0.73**	**1.06**	15	15	15	15	**1**	**1**
rs11018522	**0.74**	**3.32**	15	15	15	15	**1**	**3**
rs11018524	**0.76**	**0.07**	15	15	15	15	**3**	**3**
rs17793678	**0.75**	**0.94**	15	15	15	15	**1**	**1**
rs72963135	**0.90**	**10.78**	15	15	15	15	**1**	**1**
rs10765196	**0.73**	**0.17**	15	15	15	15	**1**	**3**
rs11018528	0.73	7.60	15	15	15	15	5	6
rs12791412	0.73	1.95	15	15	15	15	5	6
rs12789914	0.73	1.45	15	15	15	15	5	6
rs7107143	0.74	3.67	15	15	15	15	5	6
rs10830240	0.75	0.92	15	15	15	15	5	4
rs12286618	0.72	0.68	15	15	15	15	5	5
rs72963168	0.84	0.20	15	9	15	15	8	4
rs11018534	0.75	1.06	15	15	15	15	5	5
rs11018536	0.75	6.01	15	15	15	15	5	4
rs7358418	0.71	4.08	15	15	15	15	7	6
rs7939929	0.71	2.60	15	15	15	15	5	4
rs12365043	0.76	0.61	15	15	15	15	5	4
rs11018545	0.76	1.42	15	15	15	15	5	6
rs7940368	0.71	2.24	15	15	15	15	5	6
rs10765199	0.71	6.28	15	15	15	15	5	6
rs10765200	0.71	1.25	15	15	15	15	5	6
rs10765201	0.72	0.07	15	15	15	15	5	6
rs7358330	0.75	6.87	15	15	15	15	5	6
rs6415994	0.72	3.38	15	15	15	15	5	6
rs1939262	0.72	0.22	15	15	15	15	5	6
rs7933594	0.72	1.49	15	15	15	15	5	6
rs11018546	0.76	0.13	15	15	15	15	5	6
rs10501698	0.74	6.79	15	15	15	15	5	6
rs1393350	0.94	1.89	15	15	15	15	5	4
rs1126809	1	29.40	15	15	15	15	5	4

Abbreviations: CADD, Combined Annotation Dependent Depletion; ID, identification; LD, linkage disequilibrium.

The in silico identified SNPs linked to *TYR* rs1126809 in epigenetically relevant regions in melanocytes are highlighted in bold. Chronological annotation codes: 1 refers to active promoter, 2–3 refer to proximal enhancer, 4–7 refer to distal enhancer, 8–9 refer to weakly active region, 10–12 refer to transcription related, and 13–15 refer to heterochromatin or repressed region.

Table 2. The Haplotypes of the TYR rs1126809 Lead SNP and the 6 SNPs in Epigenetically Relevant Regions in Europeans, Americans, and South Asians

			Haplotypes among									
			Europeans (CEU, TSI, FIN, GBR, IBS)				Americans (MXL, PUR, CLM, PEL)				South Asians (GIH, PJL, BEB, STU, ITU)		
Rs Number	Reference Allele Frequency	Nonreference Allele Frequency										
rs12270717	0.73	0.27	T	**C**	C	**T**	T	**C**	C	**T**	T	**C**	C
rs11018522	0.73	0.27	C	**T**	T	**C**	C	**T**	T	**C**	C	**T**	T
rs11018524	0.73	0.26	C	**T**	T	**C**	C	**T**	T	**C**	C	**T**	T
rs17793678	0.73	0.26	C	**T**	T	**C**	C	**T**	T	**C**	C	**T**	T
rs72963135	0.75	0.24	C	**A**	C	**C**	C	**A**	C	**C**	C	**A**	C
rs10765196	0.72	0.27	G	**C**	C	**G**	G	**C**	C	**G**	G	**C**	C
rs1126809	0.74	0.25	G	**A**	G	**A**	G	**A**	G	**A**	G	**A**	G
Haplotype frequency by LDlink			0.71	**0.23**	0.03	**0.01**	0.77	**0.11**	0.09	**0.01**	0.90	**0.05**	0.04

CEU denotes Utah residents with Northern and Western European ancestry; TSI denotes Toscani in Italy; FIN denotes Finnish in Finland; GBR denotes British in England and Scotland; IBS denotes Iberian in Spain; MXL denotes Mexican ancestry in Los Angeles; PUR denotes Puerto Rican in Puerto Rico; CLM denotes Colombian in Medellin, Colombia; PEL denotes Peruvian in Lima, Peru; GIH denotes Gujarati Indian in Houston, TX; PJL denotes Punjabi from Lahore, Pakistan; BEB denotes Bengali in Bangladesh; STU denotes Sri Lankan Tamil in the United Kingdom; and ITU denotes Indian Telugu in the United Kingdom (LDlink, https://ldlink.nci.nih.gov).

Bold faces is used to highlight the A risk allele of rs1126809 and its associated haplotypes.

Haplotype frequencies of SNPs linked to *TYR* rs1126809 in epigenetically relevant regions between different populations

After identifying SNPs located in epigenetically active regions in melanocytes, we investigated the haplotype structures formed by these variants in different populations. In particular, the risk "A" allele of the *TYR* rs1126809 SNP is found primarily in European, American, and South Asian populations, whereas the nonrisk "G" allele predominates in other populations around the world. To note, the risk "A" allele is completely absent in African populations; therefore, we did not perform our analysis in those databases. To explore potential population-specific patterns in genetic risk, we examined how haplotypes involving these SNPs in epigenetically relevant regions are structured in combination with the risk allele "A" in the aforementioned populations.

According to data from LDlink (https://ldlink.nci.nih.gov), in Europeans, *TYR* rs1126809 and the 6 linked SNPs in epigenetically relevant regions in melanocytes form 4 distinct haplotypes (Table 2).

Most individuals carry a haplotype, in which the *TYR* rs1126809 variant is present with its nonrisk "G" allele. On the contrary, 0.24 of the individuals carry a haplotype in which *TYR* rs1126809 appears with its risk allele "A". Interestingly, among those who carry the risk allele of "A" of *TYR* rs1126809, 0.94 carry the nonreference alleles of 6 linked SNPs (rs10765196, rs72963135, rs17793678, rs11018524, rs11018522, and rs12270717) in epigenetically relevant regions, whereas 0.06 carry the reference alleles of these variants at these positions. These findings suggest that the functional impact of the "A" risk allele of the variant *TYR* rs1126809 may vary depending on the haplotype of the nearby SNPs in epigenetically relevant regions, highlighting the possibility of haplotype-dependent genetic effects.

In Americans, 0.12 of the individuals carry the risk allele "A" of the variant *TYR* rs1126809, and the rest carry the nonrisk allele "G" of this variant. To note, among those who carry the risk allele "A" of the *TYR* rs1126809, 0.96 carry the nonreference alleles of the 6 linked SNPs in epigenetically relevant regions, whereas only 0.04 carry the reference alleles of these variants at these positions (Table 2).

These findings suggest a similar haplotype-dependent genetic effect of the risk variant 'A' allele *TYR* rs1126809 in the investigated American populations, as observed in the European ones.

In South Asian populations, only 0.05 of the individuals carry the risk allele "A" of the *TYR* variant rs1126809. Carriers of alleles *TYR* rs1126809 "A" have only 1 haplotype of linked SNPs in epigenetically relevant regions; therefore, we can exclude the possibility of a haplotype-dependent modifying effect (Table 2).

DISCUSSION

In this study, we report on the results of an in silico survey of the melanoma summary statistics of a pan cancer GWAS study to reveal the role of the common missense *TYR* variant (rs1126809) in the susceptibility to melanoma. Its association with rare and complex human diseases is well-known (Bokor et al, 2025; Lasseaux et al, 2018; Michaud et al, 2022); however, this is still a highly debated variant in the literature: alone itself, it is not pathogenic but still significantly contributes to albinism through risk haplotypes and to melanoma as a risk variant (Bokor et al, 2025; Lasseaux et al, 2018; Michaud et al, 2022).

Analyzing the GWAS data, we have listed SNPs (n = 30) in LD with the variant *TYR* rs1126809 and investigated their potential functional relevance. Within this group of SNPs, we have identified 6 variants that are located in epigenetically relevant positions in melanocytes and suggest that the genotype of these variants may influence the expression of the *TYR* gene. Using LDlink, among European and American populations, we detected 2 major haplotypes associated with the risk allele of the *TYR* rs1126809 variant: in one haplotype, the nonreference alleles of the SNPs in epigenetically relevant regions were present, and in the other, the reference alleles of the SNPs in epigenetically relevant regions were

found. On the basis of our results, we hypothesize that carrying the reference or nonreference alleles of epigenetically relevant SNPs in Europeans and Americans could influence the effect of the risk allele of the *TYR* rs1126809 variant. Thus, our results suggest population- and melanocyte-specific haplotype-dependent modifier effects of the linked SNPs in epigenetically relevant regions on the *TYR* rs1126809 variant. Because the pigmentation background of the melanocyte donors in the Roadmap dataset is unknown, future studies using ancestry-defined melanocyte models will be important to confirm these findings.

Our data also raise the question of whether disease-associated SNPs identified by previous GWASs alone are useful to take them into account in the polygenic risk calculation (Lambert et al, 2019). Our results confirm the previous assumption (Nicolas et al, 2025) that the identification and clinical use of the rare and functionally relevant haplotypes could not only rewrite the way we think about complex diseases but also could contribute to the development of a clinically relevant polygenic risk calculation.

To our best knowledge, this study reanalyzed the haplotype context of a common missense variant (*TYR* rs1126809) with an already proven disease susceptibility role established by GWAS. Our results not only further strengthen the evidence for its pathogenic role but also revealed, to our knowledge, a previously unreported, population-specific, haplotype-dependent modifying effect of the linked SNPs located in epigenetically relevant regions in melanocytes. This represents a perspective that may bring us closer to understanding the true pathogenic nature of an individual common missense variant. Our study demonstrated that the integrated applied approach using 'omics' data on lead SNP and its linked variants can identify SNPs located in regions with active chromatin status in the cell type (melanocyte), which is most relevant in the pathogenesis of melanoma.

The results of our in silico analysis have twofold translational potential: (i) this approach may be relevant in designing in vitro functional studies to understand the role of the broader genomic context of a susceptibility SNP in disease pathogenesis; moreover, (ii) results of a thorough in silico analysis using the demonstrated approach may be incorporated into polygenic risk calculation. In this study, we investigate a *TYR* SNP associated with albinism and melanoma susceptibility, and our hypothesis-generating in silico results suggest population- and haplotype-dependent patterns surrounding TYR rs1126809, which may point toward mechanistic links between pigmentation-related gene regulation and melanoma susceptibility that require further functional validation. However, this approach can be broadly applied to explore the complex genomic and epigenomic context of any susceptibility factor related to any multifactorial polygenic disease.

MATERIALS AND METHODS

The melanoma summary statistics were obtained from the pan-cancer GWAS by Rashkin et al (2020), which included 20,524 melanoma cases and 372,381 controls of European ancestry (total n = 417,127). The summary statistics were downloaded from the GWAS Catalog (https://www.ebi.ac.uk/gwas/, accessed on May 3, 2025). All investigations were in silico analysis of summary statistics data using FUMA (https://fuma.ctglab.nl), which incorporates 18 biological data repositories and tools to process summary statistics of GWAS and provide a variety of annotations. All methods were carried out in accordance with the Declaration of Helsinki.

Genome-wide significance was defined using the conventional threshold of $P < 5 \times 10^{-8}$, consistent with standard GWAS practice. The in silico analyses employed in this study have been described extensively in the literature (Watanabe et al, 2017); therefore, only a brief overview of the FUMA SNP2GENE pipeline is provided in this study. In this framework, SNPs are annotated with predicted biological functions and mapped to genes on the basis of positional information, expression quantitative trait locus, and chromatin interaction data.

Using the GWAS summary statistics, independent significant SNPs and their surrounding genomic loci were identified according to the underlying LD structure, allowing the definition of lead SNPs and genomic risk loci. Independent significant SNPs as well as SNPs in LD with these variants were annotated for functional consequences on gene structure (on the basis of Ensembl gene build 85 using ANNOVAR [Wang et al, 2010]), predicted deleteriousness (Combined Annotation Dependent Depletion scores [Kircher et al, 2014]), and potential regulatory function (RegulomeDB scores [Boyle et al, 2012]). In addition, chromatin state annotations were derived from the 15-state ChromHMM core model (Ernst and Kellis, 2012). Effects on gene expression were assessed using expression quantitative trait locus data across multiple tissue types and 3-dimensional chromatin interactions inferred from Hi-C data (Schmitt et al, 2016), covering 127 tissue and cell types from the Roadmap Epigenomics Consortium (Roadmap Epigenomics Consortium et al, 2015).

Epigenomic data specific to melanocytes (E059 and E061; primary foreskin melanocytes) were obtained from the Roadmap Epigenomics Project (https://egg2.wustl.edu/roadmap/web_portal/meta.html, accessed on May 16, 2025). Donors were male in both samples; ethnicity was reported as unknown in the metadata. The absence of detailed ancestry or pigmentation information represents a limitation when interpreting melanocyte-specific regulatory patterns.

Population definitions were based on the 1000 Genomes Project reference panels used by LDlink. These classifications originate from the original 1000 Genomes Project sampling framework and are based on database-defined population labels rather than self-reported or investigator-observed race or ethnicity. The "European" group includes CEU, TSI, FIN, GBR, and IBS; the "American" group comprises admixed populations from Central and South America (MXL, PUR, CLM, and PEL); and the "South Asian" group includes GIH, PJL, BEB, STU, and ITU. These population labels reflect the 1000 Genomes Project sampling framework and do not necessarily capture the full ancestral composition of the individuals.

ETHICS STATEMENT

All the performed analyses were carried out in silico on a publicly available GWAS summary statistic. The study protocol was approved by the Hungarian National Public Health Center, in adherence with the Helsinki guidelines.

DATA AVAILABILITY STATEMENT

Datasets related to this article can be found at the Public Results Database hosted at FUMA GWAS (https://fuma.ctglab.nl/browse/631425).

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CONFLICT OF INTEREST

The authors state no conflict of interest.

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AUTHOR CONTRIBUTIONS

Conceptualization: NN; Investigation: AAB, NN; Supervision: NN; Writing – Original Draft Preparation: MS, NN

DECLARATION OF GENERATIVE ARTIFICIAL INTELLIGENCE (AI) OR LARGE LANGUAGE MODELS (LLMs)

During the preparation of this manuscript, Writefull Revise AI was used exclusively for language editing and improvement of clarity. This was an institutional instance of Writefull Revise (https://revise-u-szeged-hu.writefull.ai/), which is designed solely for automated language editing. The system does not allow users to provide prompts; after logging into the account, the manuscript is uploaded and the language editing is performed automatically. Users may only choose whether to accept or reject the suggested language edits. All scientific content, interpretations, and conclusions were reviewed, edited, and approved by the authors, who take full responsibility for the final manuscript.

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