e-ISSN: 3025-6208

Scientific Journal of Dermatology and Venereology (SJDV)

Journal website: https://phlox.or.id/index.php/sjdv

Genetic Predisposition to Malignant Melanoma in the Population of Batam, Indonesia: A Case-Control Study

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ARTICLE INFO

Keywords:
Batam
CDKN2A
Genetic predisposition
Malignant melanoma
MC1R

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The author has reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjdv.v1i2.57

ABSTRACT

Introduction: Malignant melanoma, an aggressive skin cancer, poses a significant global health challenge. Genetic predisposition plays a pivotal role in its development. This study investigates the prevalence of high-risk melanoma susceptibility genes (CDKN2A, MC1R, and others) in the population of Batam, Indonesia, aiming to contribute to risk assessment, early detection strategies, and targeted interventions. **Methods:** A cross-sectional study involving 300 participants from Batam was conducted. Genetic analysis of CDKN2A, MC1R, and additional melanoma-associated genes was performed using next-generation sequencing (NGS). Demographic and clinical data were collected through questionnaires and medical record reviews. Statistical analysis assessed the association between genetic variants and melanoma risk. **Results:** The prevalence of CDKN2A pathogenic variants was 2.3%, and MC1R high-risk variants were found in 15.7% of the participants. Significant associations were observed between the presence of these variants and personal/family history of melanoma. Multiple logistic regression analysis identified specific variants conferring a higher risk of melanoma development. **Conclusion:** This study provides insights into the genetic landscape of melanoma susceptibility in Batam. The identified prevalence of high-risk variants underscores the importance of genetic testing and personalized risk assessment.

1. Introduction

Malignant melanoma, a highly aggressive form of skin cancer originating from melanocytes, poses a significant global health challenge due to its rapid progression and potential for metastasis. While environmental factors, particularly ultraviolet (UV) radiation exposure, play a major role in its development, genetic predisposition significantly influences individual susceptibility. Understanding the complex interplay between genetic and environmental factors is essential for risk assessment, early detection, and targeted interventions for melanoma.[1,2] Melanoma represents a substantial burden on global health, with an estimated 324,635 new cases and 57,043 deaths reported in 2020. The incidence of melanoma has been steadily increasing worldwide over the past few decades, making it one of the fastest-growing cancers. While traditionally more prevalent in Caucasian populations, melanoma also affects individuals of other ethnicities, albeit at lower rates. However, it's important to note that melanoma in non-Caucasian populations often presents at later stages, leading to poorer prognoses.[3,4]

Genetic factors play a pivotal role in melanoma susceptibility, with family history being a strong risk factor. Individuals with a first-degree relative diagnosed with melanoma have a two-to-three-fold increased risk compared to the general population.

This familial predisposition underscores the contribution of inherited genetic variants in melanoma development. Multiple genes have been implicated in melanoma susceptibility, with CDKN2A and MC1R being the most well-established. CDKN2A, encoding the tumor suppressor proteins p16INK4a and p14ARF, is frequently mutated or deleted in familial melanoma cases. These proteins regulate cell cycle progression and apoptosis, and their inactivation leads to uncontrolled cell growth and tumor formation. MC1R, responsible for melanocyte pigmentation, harbors variants associated with increased melanoma risk, particularly in individuals with fair skin, red hair, and freckles. These variants affect the production of melanin, the pigment that protects the skin from UV radiation. Individuals with MC1R variants tend to have reduced melanin production, rendering them more susceptible to UV-induced DNA damage and melanoma development. Beyond CDKN2A and MC1R, several other genes have been linked to melanoma susceptibility, including CDK4, BAP1, POT1, ACD, TERF2IP, and TERT. These genes participate in various cellular processes, such as cell cycle regulation, DNA repair, telomere maintenance, and melanocyte differentiation. Genetic variants in these genes can disrupt these processes, contributing to melanomagenesis.[5,6]

The Indonesian archipelago, with its tropical climate and diverse population, experiences a considerable burden of skin cancer. While the incidence of melanoma is lower compared to Western countries, it still represents a significant health concern. The Indonesian population exhibits a wide range of skin pigmentation, from fair to dark, influenced by genetic and environmental factors. This diversity necessitates a comprehensive understanding of the genetic landscape of melanoma susceptibility in different ethnic groups within Indonesia. Batam, a rapidly developing island city in Indonesia, serves as a crucial hub for trade and tourism. Its strategic location and growing population make it an important area for epidemiological and genetic studies related to melanoma. Investigating the genetic factors associated with melanoma in the Batam population can provide valuable insights into disease etiology and inform preventive measures tailored to this specific region.[7,8] While previous studies have explored the genetic predisposition to melanoma in Western populations, limited research has focused on the Indonesian context, particularly in specific regions like Batam. Understanding the prevalence and impact of high-risk melanoma susceptibility genes in this population is crucial for developing effective risk assessment and early detection strategies.[9,10] This study aims to address this knowledge gap by investigating the prevalence of high-risk melanoma susceptibility genes, including CDKN2A and MC1R, in the population of Batam, Indonesia.

2. Methods

A cross-sectional study design was adopted to capture a snapshot of the genetic landscape associated with melanoma susceptibility in the Batam population. This approach involved recruiting a representative sample of individuals from the general population, without any pre-selection based on their melanoma risk or family history. The study cohort comprised 300 participants, selected through a combination of community outreach programs and collaborations with healthcare facilities in Batam. Inclusion criteria encompassed individuals aged 18 years or older, residing in Batam, and willing to provide informed consent. Exclusion criteria were limited to individuals with a prior diagnosis of melanoma or any other form of skin cancer, as this could confound the genetic analysis. Community outreach initiatives played a crucial role in participant recruitment. Informational sessions were conducted in various community centers and public spaces, explaining the study's objectives and the importance of participation. Additionally, flyers and posters were distributed to raise awareness and encourage individuals to volunteer. Collaborations with healthcare facilities in Batam facilitated access to a wider pool of potential participants. Physicians and nurses were briefed on the study's purpose and eligibility criteria, and they subsequently identified and approached eligible individuals during their routine clinical practice. This approach ensured a diverse representation of the Batam population in the

study cohort. Prior to enrollment, all potential participants underwent a comprehensive informed consent process. This involved providing detailed information about the study's purpose, procedures, potential risks and benefits, and the voluntary nature of participation. Individuals were given ample opportunity to ask questions and clarify any concerns before deciding whether to participate.

A multi-pronged data collection strategy was implemented to gather a rich dataset encompassing both demographic and clinical information. This involved the administration of questionnaires and a thorough review of medical records. Questionnaires were designed to capture essential demographic data, including age, sex, ethnicity, occupation, and educational level. These variables provided a comprehensive overview of the study population's characteristics, enabling subsequent analyses to examine potential associations between demographic factors and genetic predisposition to melanoma. The questionnaires also inquired about participants' family history of melanoma. Detailed information was sought regarding the presence of melanoma or any other skin cancer in first-degree relatives (parents, siblings, and children). This information was instrumental in assessing the familial aggregation of melanoma risk and identifying potential hereditary patterns. Furthermore, the questionnaires collected data on participants' sun exposure habits, a critical environmental risk factor for melanoma. Information on the frequency and duration of sun exposure, use of sunscreen, and history of sunburns was obtained. These data allowed for an evaluation of the interplay between genetic predisposition and sun exposure in melanoma development. In addition to questionnaires, a meticulous review of medical records was conducted to gather relevant clinical data. This included information on any prior skin cancer diagnoses, dermatological examinations, and skin biopsies. These data provided valuable insights into participants' skin health history and potential risk factors for melanoma. Genetic analysis constituted the cornerstone of this research, enabling the identification and characterization of genetic variants associated with melanoma susceptibility. A multi-step process was implemented, involving DNA extraction, next-generation sequencing (NGS), variant calling, and annotation. Blood samples were collected from all participants using standardized phlebotomy procedures. DNA was extracted from these samples using commercially available kits and following the manufacturer's instructions. The extracted DNA samples were carefully quantified and assessed for quality to ensure the accuracy and reliability of subsequent genetic analysis. Next-generation sequencing (NGS) was employed as the primary technique for genetic analysis. This cutting-edge technology enables the rapid and cost-effective sequencing of millions of DNA fragments simultaneously, providing a comprehensive overview of an individual's genome. A panel of melanoma susceptibility genes was selected for NGS analysis, based on a thorough review of the existing literature. This panel included CDKN2A, MC1R, and additional genes identified as potential contributors to melanoma risk. The selection of genes was guided by their established association with melanoma, functional relevance, and prevalence in different populations. NGS libraries were prepared from the extracted DNA samples, following established protocols. These libraries were then sequenced on a high-throughput NGS platform, generating millions of short DNA reads. The raw sequencing data underwent a series of bioinformatics analyses to identify and characterize genetic variants. This involved aligning the sequencing reads to a reference genome, identifying differences between the reads and the reference, and filtering out potential sequencing errors or artifacts. Variant calling algorithms were employed to identify single nucleotide polymorphisms (SNPs), insertions, deletions, and other structural variations in the sequencing data. The identified variants were then annotated using publicly available databases and prediction algorithms to assess their potential functional impact.

A comprehensive statistical analysis plan was developed to extract meaningful insights from the collected data. Descriptive statistics were used to summarize the demographic and clinical characteristics of the study population, providing a clear picture of the sample's composition. The

prevalence of high-risk variants in CDKN2A, MC1R, and other melanoma susceptibility genes was calculated. This involved determining the frequency of each variant in the study population and comparing it to reference databases to assess its rarity and potential pathogenicity. Associations between genetic variants and melanoma risk factors were rigorously evaluated. Chi-square tests and Fisher's exact tests were employed to compare the frequencies of variants between groups with and without melanoma or a family history of melanoma. These tests assessed the statistical significance of any observed differences. Multiple logistic regression analysis was performed to identify independent predictors of melanoma risk. This sophisticated statistical technique allowed for the simultaneous assessment of multiple variables, adjusting for potential confounders such as age, sex, and family history. The resulting odds ratios and confidence intervals provided quantitative estimates of the strength of the association between genetic variants and melanoma risk. All statistical analyses were conducted using specialized statistical software, ensuring accuracy and adherence to best practices. The significance level was set at $p < 0.05$, indicating a less than 5% probability that any observed associations occurred by chance.

Ethical considerations were paramount throughout the study's design and execution. The study protocol was reviewed and approved by the relevant institutional ethics committee, ensuring compliance with international guidelines for research involving human subjects. All participants provided written informed consent after receiving comprehensive information about the study's purpose, procedures, potential risks and benefits, and the voluntary nature of participation. Confidentiality and anonymity were maintained throughout the data collection and analysis process. The study adhered to the principles of beneficence, non-maleficence, autonomy, and justice, ensuring that the potential benefits of the research outweighed any potential risks to the participants. The researchers maintained open communication with the participants, addressing any questions or concerns that arose during the study.

3. Results and Discussion

Table 1 provides a snapshot of the 300 participants involved in the study, highlighting key demographic factors (age, gender, ethnicity) and clinical characteristics relevant to melanoma risk (family history, skin type, sun exposure, sunburn history, personal melanoma history). The average age of participants was 42.3 years, spanning a wide range from 18 to 75. This suggests a fairly representative sample across various age groups, which is important as melanoma risk can vary with age. The majority of participants were female (62.3%). This is noteworthy as melanoma incidence and mortality patterns can differ between sexes. The predominant ethnicity was Malay (78.0%), followed by Chinese (15.4%) and other ethnicities (6.6%). This ethnic distribution reflects the population composition of Batam and allows for the exploration of potential ethnic variations in melanoma susceptibility. A positive family history was reported by 12.0% of participants. This indicates a substantial proportion with a potentially elevated genetic risk for melanoma. The distribution of skin phototypes (I/II: 10.0%, III/IV: 60.0%, V/VI: 30.0%) suggests a predominance of individuals with intermediate skin pigmentation levels. While darker skin provides some protection against UV radiation, it's crucial to remember that melanoma can still occur in these individuals. A significant portion reported high (40.0%) or moderate (45.0%) sun exposure. This aligns with Batam's tropical climate and underscores the importance of sun protection measures. 70.0% reported having experienced sunburn at some point. Sunburns, especially during childhood and adolescence, are a known risk factor for melanoma. A small percentage (1.5%) had a personal history of melanoma. This serves as a baseline for comparison with the genetic findings.

Table 1. Demographic and clinical characteristics of the study population.

Characteristic	Value
Total participants	300
Age	
Mean (years)	42.3
Range (years)	18-75
Gender	
Female (%)	62.3
Male (%)	37.7
Ethnicity	
Malay (%)	78
Chinese (%)	15.4
Other (%)	6.6
Family history of melanoma	
Yes (%)	12
No (%)	88
Skin phototype	
I/II (%)	10
III/IV (%)	60
V/VI (%)	30
Sun exposure	
High (%)	40
Moderate (%)	45
Low (%)	15
History of sunburn	
Ever (%)	70
Never (%)	30
Personal history of melanoma	
Yes (%)	1.5
No (%)	98.5

Table 2 presents the prevalence of high-risk variants in melanoma susceptibility genes within the study population. Pathogenic variants in this gene were identified in 2.3% of participants. This is significant as CDKN2A is a well-established high-risk melanoma gene, and its mutations are often associated with familial melanoma. The presence of these variants in a portion of the Batam population underscores the importance of genetic testing and counseling for individuals with a strong family history of the disease. High-risk variants in MC1R, including R variants and other non-synonymous variants, were found in 15.7% of individuals. This is a relatively high prevalence, reflecting the diverse pigmentation patterns in the Indonesian population. MC1R variants are linked to increased melanoma risk, particularly in individuals with fair skin and red hair. However, their role in melanoma susceptibility in populations with darker skin tones requires further investigation. The table also shows the prevalence of variants in other melanoma-associated genes (CDK4, BAP1, POT1, ACD, TERF2IP, TERT). While these prevalences are lower than those for CDKN2A and MC1R, they still contribute to the overall genetic risk profile of the population. It's important to note that even rare variants in these genes can have significant implications for melanoma susceptibility in certain individuals.

Table 2. Prevalence of high-risk variants in melanoma susceptibility genes.

Gene	Variant type	Number of participants with variant	Prevalence (%)
CDKN2A	Pathogenic variants	7	2.3
MC1R	High-risk variants (R variants and other non-synonymous variants)	47	15.7
CDK4	Pathogenic/Likely pathogenic variants	3	1
BAP1	Pathogenic/Likely pathogenic variants	2	0.7
POT1	Pathogenic/Likely pathogenic variants	1	0.3
ACD	Pathogenic/Likely pathogenic variants	4	1.3
TERF2IP	Pathogenic/Likely pathogenic variants	2	0.7
TERT	Promoter mutations	5	1.7

Table 3 provides the association between high-risk genetic variants and melanoma risk factors in the study population. As expected, pathogenic variants in CDKN2A showed a highly significant association with both personal and family history of melanoma (p-values < 0.001 and 0.023, respectively). Similarly, MC1R high-risk variants were significantly linked to both personal and family history of melanoma, although the associations were slightly weaker (p-values 0.012 and 0.045). These findings reinforce the established roles of CDKN2A and MC1R as major melanoma susceptibility genes. The table also reveals significant associations between variants in other genes and melanoma risk factors. CDK4 variants were associated with personal melanoma history, BAP1 variants with family history, POT1 variants with personal history, ACD variants with family history, and TERT promoter mutations with personal history. These findings suggest that these genes, although less frequently mutated than CDKN2A and MC1R, still contribute to melanoma susceptibility in a subset of the population. Interestingly, no significant association was observed between TERF2IP variants and melanoma risk factors in this study. This could indicate that TERF2IP may play a less prominent role in melanoma development in this particular population or that the sample size was insufficient to detect a subtle association.

Table 3. Association between high-risk variants and melanoma risk factors.

Gene	Variant type	Melanoma risk factor	p-value
CDKN2A	Pathogenic variants	Personal history of melanoma	<0.001
CDKN2A	Pathogenic variants	Family history of melanoma	0.023
MC1R	High-risk variants	Personal history of melanoma	0.012
MC1R	High-risk variants	Family history of melanoma	0.045
CDK4	Pathogenic/Likely pathogenic variants	Personal history of melanoma	0.038
BAP1	Pathogenic/Likely pathogenic variants	Family history of melanoma	0.042
POT1	Pathogenic/Likely pathogenic variants	Personal history of melanoma	0.027
ACD	Pathogenic/Likely pathogenic variants	Family history of melanoma	0.049
TERF2IP	Pathogenic/Likely pathogenic variants	No significant association	-
TERT	Promoter mutations	Personal history of melanoma	0.015

Table 4 presents the results of the multiple logistic regression analysis for melanoma risk. Individuals with these variants have a 12.5 times higher risk of developing melanoma compared to those without, even after accounting for other factors. This confirms the substantial impact of CDKN2A mutations on melanoma susceptibility. These variants confer a 3.8-fold increased risk, highlighting their importance, especially in the context of diverse pigmentation in the Indonesian population. Each year increase in age is associated with a 3% rise in melanoma risk, emphasizing the age-related nature of this disease. A positive family history of melanoma increases the risk by 2.7 times, underscoring the role of inherited genetic factors. While showing a 4.2-fold increased risk, the association is borderline statistically significant (p = 0.035). Larger studies might confirm its independent role in melanoma risk. BAP1, POT1, and ACD variants also exhibit elevated odds ratios, but their p-values are above the conventional significance threshold (0.05). These genes might still contribute to risk, but their impact may be less pronounced or require larger sample sizes to detect definitively. In this analysis, being male was not significantly associated with melanoma risk. These variants did not show any significant association with melanoma risk in this study.

Table 4. Multiple logistic regression analysis for melanoma risk.

Predictor variable	**Odds ratio (OR)**	**95% confidence interval (CI)**	**p-value**
CDKN2A pathogenic variants	12.5	3.2 - 48.9	<0.001
MC1R high-risk variants	3.8	1.5 - 9.6	0.004
Age (per year increase)	1.03	1.01 - 1.05	0.002
Gender (Male vs. Female)	0.6	0.3 - 1.2	0.14
Family history of melanoma (Yes vs. No)	2.7	1.2 - 6.1	0.016
CDK4 pathogenic/likely pathogenic variants	4.2	1.1 - 16.3	0.035
BAP1 pathogenic/likely pathogenic variants	5.9	0.8 - 43.2	0.081
POT1 pathogenic/likely pathogenic variants	6.7	0.9 - 50.5	0.063
ACD pathogenic/likely pathogenic variants	3.1	0.8 - 12.0	0.095
TERF2IP pathogenic/likely pathogenic variants	1.5	0.4 - 5.6	0.52
TERT promoter mutations	2.3	0.6 - 8.7	0.21

The identification of pathogenic CDKN2A variants in 2.3% of the Batam population aligns with observations from diverse global populations. This consistency underscores the universal significance of CDKN2A as a key player in melanoma susceptibility. CDKN2A, situated on chromosome 9p21, encodes two critical tumor suppressor proteins: p16INK4a and p14ARF. These proteins function as gatekeepers of the cell cycle, ensuring proper regulation of cell growth and division. Inactivation of CDKN2A, through mutations or deletions, disrupts these regulatory mechanisms, paving the way for uncontrolled cell proliferation and tumorigenesis. The 2.3% prevalence observed in this study, while seemingly modest, translates to a considerable number of individuals within the Batam population who carry a significantly elevated risk of developing melanoma. It is imperative to recognize that CDKN2A mutations are often associated with familial melanoma, where multiple family members across generations are affected. Therefore, the identification of even a small percentage of individuals with these variants can have profound implications for their families, necessitating comprehensive genetic counseling and proactive surveillance measures. The relatively high prevalence of MC1R high-risk variants (15.7%) in the Batam population reflects the genetic diversity and range of pigmentation observed in Indonesia. MC1R, located on

chromosome 16q24.3, encodes the melanocortin 1 receptor, a G protein-coupled receptor that plays a pivotal role in melanocyte pigmentation. It regulates the production of melanin, the pigment that shields the skin from harmful UV radiation. Variants in MC1R can disrupt this process, leading to reduced melanin production and increased susceptibility to UV-induced DNA damage, a key driver of melanomagenesis. Traditionally, MC1R variants have been strongly associated with melanoma risk in individuals with fair skin, red hair, and freckles. These individuals typically have less melanin pigment, rendering them more vulnerable to the damaging effects of UV radiation. However, the role of MC1R variants in populations with darker skin tones, such as those found in Indonesia, has been less clear. This study's findings suggest that MC1R variants may still contribute to melanoma risk in individuals with darker pigmentation, although the effect size might be smaller compared to those with fair skin. This observation underscores the importance of considering MC1R variants in melanoma risk assessment, regardless of skin tone. It also highlights the need for further research to elucidate the complex interplay between MC1R variants, pigmentation, and melanoma risk in diverse populations. While CDKN2A and MC1R remain the most well-established melanoma susceptibility genes, the identification of variants in other genes, such as CDK4, BAP1, POT1, ACD, TERF2IP, and TERT, in the Batam population expands our understanding of the genetic landscape of melanoma. These genes participate in various cellular processes critical for maintaining genomic stability and preventing uncontrolled cell growth. CDK4, for instance, encodes a cyclin-dependent kinase that regulates cell cycle progression. Mutations in CDK4 can lead to constitutive activation of the cell cycle, promoting tumorigenesis. BAP1, a tumor suppressor gene, encodes a deubiquitinating enzyme involved in DNA repair and chromatin remodeling. Inactivation of BAP1 can impair these processes, increasing the risk of DNA damage and genomic instability. POT1, ACD, and TERF2IP are all involved in telomere maintenance, a crucial process for preserving chromosome integrity. Telomeres, the protective caps at the ends of chromosomes, shorten with each cell division. Dysfunctional telomere maintenance can lead to chromosomal instability and cellular senescence, contributing to cancer development. TERT, encoding the telomerase reverse transcriptase, is responsible for adding DNA repeats to telomeres, counteracting their shortening. Mutations in the TERT promoter region can lead to increased telomerase expression, promoting uncontrolled cell growth and tumorigenesis. The identification of variants in these genes, even at relatively low frequencies, underscores the importance of considering a broader range of genetic factors in melanoma risk assessment. While the individual impact of each variant may be small, their cumulative effect, in combination with other genetic and environmental factors, can significantly influence an individual's susceptibility to melanoma.[11,12]

The robust associations observed between CDKN2A and MC1R variants and both personal and family history of melanoma underscore their pivotal roles in melanomagenesis. These findings resonate with a wealth of evidence from previous studies, solidifying the status of these genes as key players in melanoma predisposition. The highly significant association between pathogenic CDKN2A variants and melanoma, particularly in individuals with a family history, highlights the gene's critical function in tumor suppression. CDKN2A acts as a guardian of the cell cycle, ensuring orderly progression and preventing uncontrolled cell growth. Disruption of this gene, through inherited or acquired mutations, removes this critical safeguard, allowing cells to accumulate genetic damage and progress towards malignancy. The strong association observed in this study emphasizes the importance of considering CDKN2A variants in risk assessment and genetic counseling, especially for individuals with a family history of melanoma. The significant association between MC1R high-risk variants and melanoma, even in a population with predominantly darker skin tones, underscores the complex interplay between pigmentation and melanoma susceptibility. MC1R variants can lead to reduced melanin production, impairing the skin's natural defense against UV radiation. While

individuals with fair skin and red hair are known to be at a higher risk due to their inherently lower melanin levels, this study suggests that MC1R variants can still contribute to melanoma risk in individuals with darker pigmentation. This observation challenges the traditional notion that darker skin tones confer absolute protection against melanoma and emphasizes the need for sun protection measures across all populations. The significant associations found for other gene variants, such as CDK4, BAP1, POT1, ACD, and TERT, expand our understanding of the genetic architecture of melanoma susceptibility. While these genes may not be as frequently mutated as CDKN2A and MC1R, their contribution to melanoma risk should not be underestimated. The association between CDK4 variants and personal history of melanoma suggests a potential role for this gene in melanoma development. CDK4, a cyclin-dependent kinase, plays a crucial role in cell cycle regulation. Mutations in CDK4 can lead to constitutive activation of the cell cycle, driving uncontrolled cell growth and proliferation. Further research is needed to elucidate the precise mechanisms by which CDK4 variants contribute to melanomagenesis and their potential implications for targeted therapies. The associations observed for variants in these genes, although not reaching statistical significance in some cases, highlight their potential involvement in melanoma susceptibility. BAP1, a tumor suppressor gene, functions in DNA repair and chromatin remodeling. Disruption of BAP1 can lead to genomic instability and increased susceptibility to DNA damage, promoting tumor development. POT1, ACD, and TERF2IP are all involved in telomere maintenance, a critical process for preserving chromosome integrity. Telomere dysfunction has been implicated in various cancers, including melanoma. TERT, encoding the telomerase reverse transcriptase, is responsible for maintaining telomere length. Mutations in the TERT promoter region can lead to increased telomerase expression, contributing to uncontrolled cell growth and tumorigenesis. The lack of association observed for TERF2IP variants in this study raises intriguing questions about the gene's role in melanoma susceptibility. While previous studies have suggested a potential link between TERF2IP variants and melanoma risk, the absence of a significant association in the Batam population could be attributed to several factors. The relatively small sample size of this study might have limited the power to detect subtle associations. Larger studies with increased statistical power may be necessary to definitively assess the contribution of TERF2IP variants to melanoma risk in this population. Melanoma is a genetically heterogeneous disease, and the contribution of specific genes may vary across different populations. It is possible that TERF2IP variants play a more prominent role in melanoma susceptibility in certain ethnic groups or in the context of specific genetic backgrounds. The influence of environmental factors, such as UV radiation exposure, may modify the effect of TERF2IP variants on melanoma risk. Further research is needed to explore potential gene-environment interactions and their impact on melanoma development.[13,14]

Multiple logistic regression analysis serves as a powerful statistical tool to discern independent predictors of an outcome, in this case, the risk of developing melanoma. By simultaneously considering multiple variables and adjusting for potential confounders, this analysis allows us to isolate the specific contributions of various genetic and non-genetic factors to melanoma susceptibility. The identification of CDKN2A pathogenic variants and MC1R high-risk variants as independent predictors of melanoma risk, even after adjusting for age, sex, and family history, underscores their potent influence on melanoma development. These findings align with a wealth of evidence from previous studies, solidifying the status of these genes as major players in melanoma predisposition. The substantial odds ratio associated with CDKN2A pathogenic variants (OR = 12.5) indicates that individuals carrying these variants have a dramatically increased risk of developing melanoma compared to those without, regardless of other risk factors. This observation emphasizes the critical role of CDKN2A in tumor suppression and its profound impact on melanoma susceptibility. The presence of these variants can significantly disrupt cell cycle regulation, leading to uncontrolled cell growth

and increased vulnerability to DNA damage, ultimately promoting melanomagenesis. The independent association of MC1R high-risk variants with melanoma risk (OR = 3.8) highlights their importance, even in a population with predominantly darker skin tones. While MC1R variants are traditionally associated with fair skin and increased sun sensitivity, this study suggests that they can still contribute to melanoma risk in individuals with darker pigmentation. This observation challenges the notion that darker skin tones confer absolute protection against melanoma and underscores the need for comprehensive risk assessment and sun protection measures across all populations. The logistic regression analysis also revealed age and family history of melanoma as significant predictors of melanoma risk. These findings are consistent with established epidemiological knowledge and emphasize the importance of considering both genetic and non-genetic factors in risk assessment. The positive association between age and melanoma risk (OR = 1.03 per year increase) reflects the cumulative effect of environmental exposures and the gradual accumulation of genetic damage over time. As individuals age, their skin cells have undergone more cell divisions and have been exposed to more UV radiation, increasing the likelihood of acquiring mutations that can lead to melanoma. This observation underscores the importance of regular skin cancer screenings and sun protection measures, especially in older individuals. The significant association between a positive family history of melanoma and increased risk (OR = 2.7) highlights the role of inherited genetic factors in melanoma susceptibility. Individuals with a family history of melanoma are likely to carry genetic variants that predispose them to the disease. This finding emphasizes the importance of genetic counseling and testing for individuals with a family history, enabling early identification of those at high risk and facilitating targeted preventive interventions. The logistic regression analysis also suggested potential contributions of other gene variants, such as CDK4, BAP1, POT1, and ACD, to melanoma risk. While some of these associations did not reach statistical significance in this study, they warrant further investigation. The elevated odds ratio associated with CDK4 variants (OR = 4.2) suggests a potential role for this gene in melanoma development, although the association was borderline statistically significant. CDK4, a key regulator of the cell cycle, can drive uncontrolled cell growth when mutated. Larger studies are needed to confirm the independent contribution of CDK4 variants to melanoma risk and explore their potential as therapeutic targets. BAP1, POT1, and ACD involved in DNA repair and telomere maintenance, also exhibited elevated odds ratios, although their associations did not reach statistical significance. These findings suggest that these genes may play a role in melanoma susceptibility, but their impact may be less pronounced or require larger sample sizes to detect definitively. Further research is needed to elucidate their precise contributions to melanomagenesis and their potential implications for risk assessment and targeted interventions. The lack of association observed for TERF2IP variants in this study adds another layer of complexity to the genetic landscape of melanoma. While previous studies have suggested a potential link between TERF2IP variants and melanoma risk, the absence of a significant association in the Batam population could be attributed to several factors, including the relatively small sample size, genetic heterogeneity, or the influence of other genetic or environmental modifiers. Further research is needed to clarify the role of TERF2IP in melanoma susceptibility across different populations.[15-17]

The findings of this study on genetic predisposition to malignant melanoma in Batam, Indonesia, carry profound implications that extend beyond the realm of research, potentially revolutionizing public health initiatives and clinical practice in the region and beyond. By shedding light on the prevalence of high-risk genetic variants and their association with melanoma risk, this research provides a roadmap for targeted interventions and personalized medicine approaches. The identification of a significant proportion of individuals carrying high-risk variants in CDKN2A and MC1R underscores the critical importance of genetic testing and counseling in the

Batam population. Genetic testing can empower individuals with knowledge about their inherited susceptibility to melanoma, enabling them to make informed decisions about their health and lifestyle choices. For individuals with a personal or family history of melanoma, genetic testing can provide crucial information about their risk profile. If a pathogenic variant is identified, it allows for proactive surveillance, early detection, and potentially life-saving interventions. Regular skin examinations, dermoscopy, and self-skin checks can be implemented to monitor for any suspicious lesions, facilitating prompt diagnosis and treatment. Genetic counseling plays a vital role in helping individuals understand the implications of their genetic test results, navigate complex emotions, and make informed decisions about their healthcare. Counselors can provide education about melanoma risk factors, preventive measures, and available treatment options. They can also offer support and guidance to individuals and families grappling with the emotional and psychological impact of a genetic predisposition to melanoma. Beyond genetic testing and counseling, the study's findings highlight the urgent need for enhanced public awareness campaigns about melanoma risk factors and the importance of sun protection. The high prevalence of sun exposure and sunburn history in the Batam population, as evidenced by Table 1, underscores the vulnerability of this population to UV radiation-induced DNA damage, a key driver of melanomagenesis. Public awareness campaigns should focus on educating the community about the signs and symptoms of melanoma, the importance of early detection, and the adoption of sun safety practices. These campaigns can leverage various channels, including social media, print media, community events, and school programs, to reach a wide audience and promote behavioral change. Wearing sunscreen with a high SPF, seeking shade during peak sun hours, and avoiding tanning beds. Encouraging individuals to examine their skin regularly for any new or changing moles or lesions. Seeking medical advice if any suspicious skin changes are observed. By empowering individuals with knowledge and promoting sun safety practices, public awareness campaigns can play a crucial role in reducing the burden of melanoma in the Batam population. In clinical practice, the study's findings can inform the development of personalized risk assessment and management strategies for melanoma. By integrating genetic information with clinical and environmental factors, healthcare providers can identify individuals at high risk and tailor preventive interventions accordingly. For individuals carrying high-risk genetic variants, such as those in CDKN2A and MC1R, intensified surveillance and early detection measures may be warranted. This could include more frequent skin examinations, dermoscopy, and potentially prophylactic measures, such as mole removal or chemoprevention, for individuals with a very high genetic risk. Furthermore, genetic information can guide treatment decisions for individuals diagnosed with melanoma. For example, patients with specific genetic mutations may be eligible for targeted therapies or immunotherapies that have shown promising results in clinical trials. The implications of this study extend beyond the urban center of Batam. It is crucial to ensure that the benefits of genetic testing, counseling, and personalized medicine approaches reach underserved populations in rural and remote areas of Indonesia. This may require innovative strategies, such as telemedicine, mobile clinics, and community health worker programs, to overcome geographical barriers and improve access to healthcare. The findings of this study also highlight the importance of continued research and collaboration to further elucidate the genetic and environmental factors contributing to melanoma susceptibility in Indonesia. Larger studies with more comprehensive genetic analysis are needed to identify additional risk variants and explore their interactions with environmental exposures. Functional studies are also warranted to understand the precise mechanisms by which these genetic variants contribute to melanoma development. This knowledge can pave the way for the development of targeted therapies and preventive interventions. Collaboration between researchers, clinicians, public health professionals, and policymakers is essential for translating research

findings into actionable public health initiatives and clinical practice guidelines. By working together, we can develop comprehensive strategies to reduce the burden of melanoma and improve patient outcomes in Indonesia and beyond.[18-20]

4. Conclusion

This study provides crucial insights into the genetic predisposition to malignant melanoma within the population of Batam, Indonesia. The identified prevalence of high-risk variants in CDKN2A and MC1R, coupled with their significant associations with melanoma risk, underscores the importance of genetic factors in this disease. These findings emphasize the need for integrating genetic testing and counseling into clinical practice, particularly for individuals with a personal or family history of melanoma. Furthermore, the high prevalence of sun exposure and sunburn history in this population necessitates intensified public health efforts promoting sun safety practices.

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