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ORIGINAL PAPER

Association between miR-202, miR-211, and miR-1238 gene polymorphisms and risk of vitiligo

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Abstract

Vitiligo, as a common pigment defect in the skin, hair, and mucous membranes, results from the destruction of melanocytes. Recent investigations have shown that miRNA dysregulation contributes in the pathogenesis of vitiligo. Therefore, in this research, our aim is to explore the relationship between miR-202 rs12355840, miR-211 rs8039189, and miR-1238 rs12973308 polymorphisms and susceptibility to vitiligo. A total number of 136 vitiligo patients and 129 healthy individuals as a control group were included in this research. The salting out approach was implemented to extraction genomic DNA. The genetic polymorphisms of miR-202 rs12355840, miR-211 rs8039189, and miR-1238 rs12973308 were determined using PCR–RFLP approach. The findings revealed that miR-202 rs12355840 polymorphism under codominant (CT and TT genotypes), dominant, recessive, overdominant, and also allelic models is correlated with increased risk of vitiligo. In addition, codominant, dominant, overdominant, as well as allelic models of miR-211 rs8039189 polymorphism decrease risk of vitiligo. No significant relationship was observed between the miR-1238 rs12973308 polymorphism and susceptibility to vitiligo. The miR-211 rs8039189 polymorphism may serve a protective effect on vitiligo development and miR-202 rs12355840 polymorphism may act as a risk factor for vitiligo susceptibility.

Keywords Vitiligo · miR-202 · miR-211 · miR-1238 · Polymorphism

Introduction

Vitiligo is an acquired disorder of pigmentation that results from the destruction of melanocytes or a loss of their function [1]. The global prevalence of vitiligo is mostly about 0.5–2%, but this statistic can vary up to about 4.7% in Nigeria and more than 8% in India [2]. Based on natural history and clinical presentation, there are two basic forms of vitiligo: segmental vitiligo with unilateral skin distribution pattern includes 10–15% of cases, and non-segmental vitiligo with bilateral and symmetrical distribution, which includes 80% of cases, and also contains general, acrofacial, or mixed types. Recent studies have shown that there is a common mechanism between these two forms [3].

Clinically, the white spots on the skin in vitiligo patients are not as severe as the symptoms of other diseases that involve the skin; however, vitiligo may reduce the quality of life [4]. The exact cause of vitiligo is unclear; however, several hypotheses have been proposed for its pathogenesis, including some autoimmune diseases, metabolic abnormalities, oxidative stress, genetic factors,

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and environmental triggers [3]. Studies conducted on twins illustrate the important role of genetics and environment in the etiology of the disease [5, 6]. A large number of genes have been discovered that contribute to the risk of vitiligo, and the protein products of such genes play a role in regulating the function of melanocytes, regulating immunity, and apoptosis [7–9]. For example, it has been determined that the protein coded by the forkhead box protein 3 (FPXP3) gene is involved in regulating the activity of T cells, and its defect plays a role in vitiligo disease and the development of an autoimmune condition [10, 11]. It has also been reported that some genes, such as MIFT, which is the main gene responsible for controlling melanocyte differentiation, and LEF1 gene, which plays a role as a pigment regulator in melanocytes, have a reduced expression level in the lesional skin of vitiligo patients compared to non-lesional skin, patients show vitiligo. In addition, the difference in MIFT expression in the lesional skin of vitiligo patients is less compared to the skin of healthy individuals [12]. Changes in the expression of some pro-inflammatory cytokines such as IL6, IL2, IL8, IL10, and INF-γ have been shown in vitiligo as an autoimmune disease. It has also been determined that CD8+ T cells and autoantibodies in destruction of melanocytes plays a role in vitiligo skin [13–18]. In a study conducted by Rätsep et al., it was found that IL22 is significantly related to the active stage of vitiligo and may lead to the destruction of melanocytes by stimulating inflammation [19]. High levels of superoxide dismutase (SOD) and low levels of catalase (CAT) in the skin of vitiligo patients indicate an increase in oxidative stress in vitiligo, and research has shown that the accumulation of reactive oxygen species in melanocytes can lead to melanocyte damage [20, 21].

The theory of autoimmune diseases has received more attention due to the connection between vitiligo and other autoimmune disorders, such as systemic lupus erythematosus, Hashimoto's thyroiditis, multiple sclerosis, rheumatoid arthritis, and primary Sjogren's syndrome [22, 23]. Genetically, vitiligo is a multifactorial disease with a polygenic inheritance pattern, with 75–83% of the attributed risk related to the genetic component, and the remaining 20% is related to environmental factors [9]. More than 150 genes have been identified that affect skin, hair, and eye pigmentation. Many vitiligo-related pathogenic genes have been identified, most of them associated with autoimmune diseases and key regulatory pathways, such as melanin biosynthesis, TLR14 signaling, apoptosis, vitamin D metabolism, inflammatory pathways, and oxidative stress response [24–26].

Many regions of the human genome encode non-coding RNAs (ncRNAs) that are not translated into proteins. Various studies have identified some types of ncRNAs, including miRNAs, lncRNAs, and circular RNAs, as regulatory factors of vitiligo [27]. miRNAs with a length of about 22 nucleotides are connected to the RISC complex and this combination finally acts on its target by suppressing the transcription or degradation of mRNA. In several studies, expression of miRNAs has been reported to be different with respect to the health state [28–30]. For example, it has been found that the expression of some miRNAs is different in many types of cancers such as colorectal cancer, melanoma, breast cancer, thyroid cancer, and osteosarcoma [31–35]. In addition, various researches have shown that some miRNAs also play a role in autoimmune diseases such as systemic lupus erythematosus, type 1 diabetes, rheumatoid arthritis, and vitiligo [36–40].

miRNAs play a role in important processes such as differentiation, oxidative stress, genomic stability, angiogenesis, and cell cycle control [41–45]. Due to the destruction of melanocytes under the increase of oxidative stress, the role of miRNAs in regulation of oxidative stress and the biology of melanocytes in vitiligo has been the focus of extensive research [2, 27].

As an illustrative example, it was observed that miR-211 gene expression is reduced in vitiligo skin samples and PIG3V, which is a vitiligo cell line. This gene is responsible for regulating oxidative stress and energy metabolism in mitochondria and is effective in melanin homeostasis [46]. In other studies, it has been observed that the expression of miR-155 in the T cells of people with vitiligo is reduced, and after the suppression of miR-155, a significant decrease in the number and function of regulatory T cells is observed [46]. It has also been observed that the expression of miR-21-5p was higher in patients with vitiligo with respect to the control group [47, 48]. Another study has shown a significant difference in the expression of miR-766-3p, miR-630, miR-202-3p, and miR-1238-3p in people with vitiligo compared to healthy people [49].

The study of single nucleotide polymorphisms (SNPs) is a useful approach to investigate the relationship between genes and vitiligo disease, and several studies have discovered over 50 vitiligo susceptibility loci [7]. The SNPs that occur in the miRNA gene may cause a change in the expression of the target genes by changing the tendency or specificity of miRNAs in binding to the target sequence [50, 51]. Therefore, by examining the SNPs in miRNAs, some of them can be introduced as special markers in determining the genetic susceptibility of people to the vitiligo disease. In addition, since the genetic composition is different in diverse populations, specific attention should also be paid to investigating the effect of polymorphisms on the phenotype of the disease in the studied population [52]. Therefore, in current study, our aim is to investigate the relationship of miR-202 rs12355840, mi-R211 rs8039189, and miR-1238 rs12973308 SNPs with vitiligo disease in the Iranian population.

Materials and methods

The number of 136 patients who referred to the Specialized Skin and Beauty Clinic in Zahedan were included as the case group and 129 healthy individuals who referred to the Khatam Al Anbia Hospital were included in the study as the control group. The ethics committee of Zahedan university of Medical science approved the investigation procedure (IR.ZAUMS.REC.1398.171). The present population in both groups were monitored through interviews for systemic diseases, autoimmune diseases, malignancy, high blood pressure, diabetes mellitus, and family history of autoimmune diseases. In this study, after obtaining informed consent, 2 cc of blood with EDTA anticoagulant was taken from all participants. DNA was extracted by salting out method. The PCR Primers (Sinacolon, Iran), and RFLP information for each site are given in Table 1. To perform the PCR reaction, the reaction mixture was prepared as follows: Taq DNA polymerase 2 × Master Mix Red Amplicon (10 µL), each primer (10 PM), genomic DNA (100 ng/µl), and distilled water (2 µL). The PCR condition was as follows: initial denaturation at 95 °C for 5 min, and then 35 cycles at 95 °C for 30 s, 57 °C for 30 s, and 72 °C for 30 s, and a final extension at 72 °C for 5 min. Afterward, the PCR products were digested with restriction enzymes (Thermo Fisher Scientific, USA) and subsequently loaded on 2.5% agarose gel with DNA safe stain. Finally, the fragments under UV light were visualized.

Statistical analysis

The SPSS V.23 software was used to analyze the obtained data. The Kolmogorov–Smirnov test was performed to assay the normality of the data. Analyzing the continuous variables was carried out using the independent *t* test or the Mann–Whitney *U* test whenever appropriate. The categorical data were analyzed by Chi-squared test. To determine the odds ratios (ORs) and 95% confidence intervals (95% CIs) in several genetic models, the SNPStats [53] (https://www.snpstats.net/start.htm) was used. The statistical significance level was *p* value less than 0.05.

Results

In present case–control investigation, we employed 136 individuals diagnosed with vitiligo and 129 healthy individuals as the control group. We collected information about the age and gender of both the cases and controls. In addition, the onset age of vitiligo, stage of disease, type and subtype, body surface, thyroid disease, and physiological trauma information in patients were recorded (Table 2). The mean age in patients was 23.83 ± 14.66 years, while in the healthy individuals was 41.03 ± 18.77 years, which was statistically significant ($p = 0.0001$).

Genotype and allele frequencies of miR-202 rs12355840 polymorphism in vitiligo patients and healthy individuals are shown in Table 3. The results demonstrated the significant association between miR-202 rs12355840 polymorphism and vitiligo under codominant CT and TT genotypes, dominant CT + TT vs CC, recessive TT vs CC + CT, and overdominant models. In addition, in terms of allelic model, the T allele was significantly higher in patients compared to control group which is associated with increased risk of vitiligo.

Genotype and allele frequencies of miR-211 rs8039189 polymorphism in case and control group are presented in Table 4. According to these results, there is a significant relationship between this polymorphism and vitiligo in the codominant GT and TT genotypes, dominant GT + TT vs GG, and overdominant models. Moreover, in allelic model, the T allele was significantly higher in control group compared to patients which is associated with decreased risk of vitiligo.

As indicated in Table 5, no significant relationship was observed between the miR-1238 rs12973308 polymorphism and risk of vitiligo.

Discussion

Our findings showed no significant association between miR-1238 rs12973308 polymorphism and vitiligo risk. However, we reported a protective effect of the codominant,

Table 1 The primer sequences, restriction enzymes, and fragment sizes for the PCR–RFLP method

	Primer 5′→3′	PCR product (bp)	Restriction enzyme	
Mir202 rs12355840	Forward: CGTTTTCCCATGCCCTATACCTC Reverse: TCGGCAGCAGCAGAACTC	363	TauI	C: 363 bp T: 281, 82
Mir211 rs8039189	Forward: GGATCCTCGTGTTGATGGAAAC Reverse: CAATGGCTGCTCACAGGTG	365	BSTEII	T: 365 G: 202, 163
Mir1238 rs12973308	Forward: AAGCTCCACCTCCTGGGTTCAT Reverse: ACCACGCCCAGCCAATTACAT	408	BSTUI	T: 408 G: 253,155

Table 2 The characteristics of vitiligo patients and control group

	Controls ($n=129$)	Cases ($n=136$)	p value
Age, mean ± sd (years)	41.03 ± 18.77	23.83 ± 14.66	0.0001
BMI (Kg/m^2)	22.6 ± 3.1	22 ± 3.9	0.08
Gender (%)			
Male	59 (45.8)	62 (45.6)	
Female	70 (54.2)	74 (54.4)	0.36
Onset age (%)			
≤ 20	–	84 (61.7)	
> 20	–	52 (38.3)	
Stage (%)			
Active		127 (93.5)	
Stable		9 (6.5)	
Type (%)			
Segmental		58 (42.4)	
Non-segmental		5 (3.8)	
Focal		73 (53.8)	
Subtype			
Universal		2 (1.3)	
Generalized		130 (96.1)	
Localized		4 (2.6)	
Body surface			
< %5		81 (59.4)	
5–20%		48 (35.4)	
> %20		7 (5.2)	
Thyroid disease			
Yes		18 (13.6)	
No		118 (86.4)	
Allergy			
Yes		20 (14.7)	
No		116 (85.3)	
Psychological trauma			
Yes		16 (11.6)	
No		120 (88.4)	

dominant, overdominant, and allelic models of miR-211 rs8039189 polymorphism on vitiligo development. Furthermore, CT and TT genotypes in codominant model and also dominant, recessive, overdominant, and allelic models of miR-202 rs12355840 polymorphism may act as a risk factor for vitiligo susceptibility.

To date, no investigation has been conducted regarding the possible role of miR-202, miR-211, and miR-1238 gene polymorphisms in vitiligo. However, the role of other miRNAs polymorphisms in vitiligo has been investigated. Huang et al. in Han Chinese population assessed the correlation of rs11614913 in miR-196a-2 with risk of vitiligo. Their results demonstrated a correlation between rs11614913 CC genotype in miR-196a-2 and decreased risk of vitiligo [54]. Cui et al. reported that miR-196a-2 rs11614913 variant is correlated with vitiligo through influencing tyrosinase and tyrosinase-related protein 1 complex [55].

The role of miR-1238 function in the development and progression of several cancer was reported [56–58]. KEGG analysis by Budak et al. reported effects of miR-1238 on several autoimmune-related pathways, including cytokine–cytokine receptor interaction, Jak-STAT signaling, Toll-like receptor signaling, and apoptosis [59].

The miR-211 is recognized to play a significant role in melanocyte homeostasis. It affects many cellular processes and actively regulates pigmentation, and loss of miR-211 is associated with stress and abnormal melanogenesis [60]. Brahmbhatt et al. observed a significant reduction in miR-211-5p expression in the lesional epidermis of patients with vitiligo, which was probably mediated by LncRNA MALAT1 in a reciprocal regulation, suggesting an important role of this microRNA in disease initiation and maintenance. Moreover, they found a protective manner of the MALAT1–miR-211–SIRT1 pathway in skin cancer development in the lesional vitiligo epidermis via UV-mediated DNA damage [61]. A study conducted by Sahoo and colleagues identified miR-211 as a key regulator of cellular metabolism in vitiligo cells. They discovered that miR-211 plays a role in controlling oxidative phosphorylation and mitochondrial energy metabolism specifically in vitiligo. The absence of miR-211 in melanocytes was found to have an impact on the expression of new target genes, including those responsible for managing melanocyte respiration. This research emphasizes the significance of miR-211 in understanding melanocyte biology and the development of vitiligo [46].

Among animal species, miR-202-3p is highly conserved and is a member of the let-7 family. The miR-202-3p has been described as acting as a new tumor suppressor, causing apoptosis and obstructing the proliferation and invasion of many tumor cells, including gastric cancer, neuroblastoma, lung cancer, and colorectal cancer. This is consistent with the action of let-7 family members [62]. As previously mentioned, peripheral blood cells from vitiligo patients showed lower miR-202 expression [49]. Evidence supports miR-202's involvement in the regulation and function of the immune system. Wang et al. showed a link between miR-202T-cell development and activity in allergic rhinitis [63]. Owen et al. analysis showed that miRs targeting the prototypical anti-inflammatory cytokine IL10 (miR-125a and miR-202) decrease after acute injury [64].

In conclusion, this is the first research to evaluate the relationship between miR-202 rs12355840, miR-211 rs8039189, and miR-1238 rs12973308 polymorphisms and susceptibility to vitiligo. Our findings revealed that miR-202 rs12355840 variant is associated with increased risk of vitiligo and miR-211 rs8039189 variant is associated with decreased risk of vitiligo. Our research has

Table 3 Association between miR-202 rs12355840 polymorphism and risk of vitiligo

Polymorphism	Case *n* (136)	Control *n* (129)	OR (95% CI)	*p* value
Codominant				
CC	57 (41.9%)	70 (54.3%)	1	
CT	59 (43.4%)	56 (43.4%)	1.29 (0.78–2.15)	< 0.0001
TT	20 (14.7%)	3 (2.3%)	8.19 (2.32–28.95)	< 0.0001
Dominant				
CC	57 (41.9%)	70 (54.3%)	1	
CT + TT	79 (58.1%)	59 (45.7%)	1.64 (1.01–2.67)	0.044
Recessive				
CC + CT	116 (85.3%)	126 (97.7%)	1	
TT	20 (14.7%)	3 (2.3%)	7.24 (2.10–25.01)	< 0.0001
Overdominant				
CC + TT	77 (56.6%)	73 (56.6%)	1	
CT	59 (43.4%)	56 (43.4%)	1.86 (1.25–2.76)	0.0016
Allele				
C	173 (63.6%)	196 (76%)	1	
T	99 (36.4%)	62 (24%)	1.8 (1.2–2.6)	0.002

Table 4 Association between miR-211 rs8039189 polymorphism and risk of vitiligo

Polymorphism	Case *n* (136)	Control *n* (129)	OR (95% CI)	*p* value
Codominant				
GG	113 (83.1%)	90 (69.8%)	1	
GT	23 (16.9%)	37 (28.7%)	0.50 (0.27–0.89)	0.014
TT	0 (0%)	2 (1.6%)	0.00 (0.00–NA)	0.014
Dominant				
GG	113 (83.1%)	90 (69.8%)	1	
GT + TT	23 (16.9%)	39 (30.2%)	0.47 (0.26–0.84)	0.01
Recessive				
GG + GT	136 (100%)	127 (98.5%)	1	
TT	0 (0%)	2 (1.6%)	0.00 (0.00–NA)	0.089
Overdominant				
GG + TT	113 (83.1%)	92 (71.3%)	1	
GT	23 (16.9%)	37 (28.7%)	0.51 (0.28–0.91)	0.022
Allele				
G	249 (92%)	217 (84%)	1	
T	23 (8%)	41 (16%)	0.5 (0.3–0.8)	0.01

Table 5 Association between miR-1238 rs12973308 polymorphism and risk of vitiligo

Polymorphism	Case n (136)	Control n (129)	OR (95% CI)	*p* value
Codominant				
TT	77 (56.6%)	77 (59.7%)	1	
TG	54 (39.7%)	47 (36.4%)	1.15 (0.70–1.90)	0.86
GG	5 (3.7%)	5 (3.9%)	1.00 (0.28–3.59)	0.86
Dominant				
TT	77 (56.6%)	77 (59.7%)	1	
TG + GG	59 (43.4%)	52 (40.3%)	1.13 (0.70–1.85)	0.61
Recessive				
TT + TG	131 (96.3%)	124 (96.1%)	1	
GG	5 (3.7%)	5 (3.9%)	0.95 (0.27–3.35)	0.93
Overdominant				
TT + GG	82 (60.3%)	82 (63.6%)	1	
TG	54 (39.7%)	47 (36.4%)	1.15 (0.70–1.89)	0.58
Allele				
T	208 (76%)	201 (78%)	1	
G	64 (24%)	57 (22%)	1.05 (0.7–1.6)	0.756

limitations that should be considered. First, the small sample size may influence our study's outcomes. Second, if we evaluated the expressions of miR-202, miR-211, and miR-1238 and subsequently assessed their association with these miRNAs polymorphisms, our results could become more valuable.

Ethical approval

The ethics committee of Zahedan university of Medical science approved the investigation procedure (IR. ZAUMS. REC.1398.171).

Author contributions M.JS, designed the project and literature search. M.R, and M.JS, prepared the material and performed the experimental sections. M.M, and S.A, contributed in sample processing. H.SG and M.S wrote the manuscript. M.S performed the statistical analysis. All the authors approved the final version of the paper.

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Data availability The datasets generated during and/or analyzed during the study are available upon reasonable request.

Declarations

Conflict of interests The authors declare that they have no competing interests.

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