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SIRT1 Gene Polymorphisms and the Risk of Vitiligo: Molecular Association and in Silico Approach

SIRT1 Gen Polimorfizmleri ve Vitiligo Riski İlişkisi: Moleküler ve "in Siliko" Yaklaşım

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ABSTRACT

Aim: The aim of our study is to analyze the SIRT1 gene rs2273773, rs7895833 and rs7069102 polymorphisms and the association of SIRT1 gene and interacting genes with vitiligo disease by molecular and in silico methods.

Material and Methods: The study group consisted of 78 vitiligo patients and 85 unrelated healthy controls. SIRT1 polymorphisms were determined using the Polymerase chain reaction confronting two-pair primers (PCR-CTPP) method. In addition, other genes with which the SIRT1 gene interacts and gene ontology (GO) were determined using the GeneMANIA and GeneCodis 4 tools, respectively.

Results: We have determined a significant difference in genotypes of rs7895833 in SIRT1 gene. Especially, the AG genotype was observed more in the group with vitiligo. It was determined that the rs7895833 G allele had a protective effect in terms of vitiligo (p=0.001). Intergene interaction analysis was also performed by in silico method, and it was shown that SIRT 1 is co-expressed with 16 genes and shares an area with only 12 genes physically interacting with 19 genes. We showed gene ontology and pathway analyzed with all relevant genes. It was determined that especially apoptosis and systemic sclerosis were associated with these genes.

Conclusion: The SIRT1 rs7895833 SNP genotype and allele frequencies of vitiligo patients are significantly different from healthy controls. Our study shows that the rs7895833 polymorphism of the SIRT1 gene may be associated with vitiligo susceptibility. Considering the role of sirtuin and related genes, especially in the apoptotic pathway, its effect on vitiligo can be further investigated to elucidate the molecular aspect of the disease.

Keywords: Gene polymorphism, In silico, SIRT1, Vitiligo

ÖZ

Amaç: Çalışmamızın amacı, SIRT1 geni rs2273773, rs7895833 ve rs7069102 polimorfizmlerinin ve SIRT1 geni ile etkileşimli genlerin vitiligo hastalığı ile ilişkilisinin moleküler ve in silico yöntemler ile analizini yapmaktır.

Gereç ve Yöntemler: Çalışma grubu 78 vitiligo hastası ve 85 sağlıklı kontrol katılımcısını kapsamaktadır. SIRT1 polimorfizmleri, iki çift primer (PCR-CTPP) yöntemiyle karşılıklı Polimeraz zincir reaksiyonu kullanılarak belirlendi. Ayrıca SIRT1 geninin etkileştiği diğer genler ve gen ontolojisi (GO) sırasıyla GeneMANIA ve GeneCodis 4 araçları kullanılarak belirlendi.

Bulgular: SIRT1 geninde rs7895833 genotipinin analiz edilen gruplar arasında anlamlı bir farklılık gösterdiğini belirledik. Özellikle AG genotipi vitiligolu grupta daha fazla gözlendi. rs7895833 G allelin vitiligo açısından koruyucu bir etki gösterdiği tespit edilmiştir (p=0.001). In silico yöntemle genler arası etkileşim analizi de yapılarak SIRT 1'in 16 gen ile birlikte eksprese edildiğini ve 19 gen ile sadece 12 gen fiziksel etkileşimi olan bir alanı paylaştığı gösterildi. İlgili tüm genlerle analiz edilen gen ontolojisini ve yolunu gösterdik. Özellikle apoptoz ve sistemik sklerozun bu genlerle ilişkili olduğunu belirlendi.

Sonuç: Vitiligo hastalarının SIRT1 rs7895833 SNP genotipi ve allel frekansları, sağlıklı kontrollerden önemli ölçüde farklıdır. Çalışmamız, SIRT1 geninin rs7895833 polimorfizmiyle vitiligo duyarlılığının ilişkili olabileceğini göstermektedir. Sirtuin ve ilgili genlerin özellikle apoptotik yolaktaki görevleri göz önüne alındığında vitiligoya etkisi, hastalığın moleküler yönünü aydınlatmak için daha fazla araştırılabilir.

Anahtar Sözcükler: Gen polimorfizmi, In silico, SIRT1, Vitiligo

INTRODUCTION

Vitiligo is an acquired dermatological disease with hard medical treatment, even though various healing interventions are applied. Milky white patches seen on the skin are areas with hypopigmentation or depigmentation, based on local loss of epidermal melanocytes (1). Worldwide occurrence frequency ranges between 0.1% and 2% (2). Several suggestions for the pathophysiological changes leading to vitiligo have been proposed and these diverse theories include genetic predisposition and other neural or autoimmune factors linked with apoptosis and oxidative stress (3, 4). However, the assumption for melanocyte damage is induced by autoimmune reasons prevails among neural and self-destruction hypotheses (5).

Sirtuins represent a deacetylase enzyme family, which is functionally NAD (nicotinamide adenine dinucleotide) dependent (6). They are involved in regulation of the metabolic processes in the cells by acting like sensors for the energy level (7). Human Sirtuins are represented in 7 types of enzymes (Silent Information Regulator T1-7, SIRT) with NAD^+- dependent activity (8). SIRT 1-3, and 5 were indicated to have powerful deacetylase effect toward histone proteins while remaining types have no such catalytic activity on the same substrates (9).

SIRT transcription status during oxidative stress and with their regulating role in chromatin dynamics, SIRT enzymes could be associated with cellular life span, glucose homeostasis, inflammation, apoptosis, autophagy and even cancer (10-14). Similarly, impaired normal cellular function beside those counted above, only a few studies investigated the relation of the SIRT 1 gene / enzyme with skin diseases (15). Its role and possible implication in dermatological diseases were also not studied in detail.

SIRT1 enzyme is mainly present in the nucleus and is partly localized in the cytoplasm as well (16). Different cellular compartments contain these enzymes which take on different deacetylation reactions like those of histones and several transcription factors in the nucleus and specific proteins in mitochondria (17-19).

The aim of our present study is to investigate the rs2273773, rs7895833 and rs7069102 polymorphisms of SIRT 1 gene in clinically diagnosed vitiligo patients, by focusing on evaluation of the frequency of the polymorphisms and a possible relation to the tendency for vitiligo occurrence. We also aimed to determine the possible interactions of SIRT 1 and related proteins by a web-based ontological analysis with *in silico* approach.

MATERIAL and METHODS

Study population

The whole procedure was carried out in accordance with the Declaration of Helsinki. Approval for the study was issued by the Committee for Clinical Research in Zonguldak Bülent Ecevit University - Faculty of Medicine, where the whole blood samples were obtained from. The participants in the present study group were recruited from the Department of Dermatology at Bülent Ecevit University Hospital and all declared their written informed consent. Questionnaire based data about clinical status and demographic information were obtained from all the subjects who were then evaluated for further analyses under two different groups as control (n=85) and vitiligo patients (n=78). Healthy control individuals were with no clinical evidence for family history of vitiligo or any other autoimmune disease or systemic disorders. Genomic DNA extraction was performed by using of separated venous blood samples, stored at -20 °C prior to extraction procedure. DNA extraction was performed by the spin column kit method in the Medical Biology laboratory (Invitrogen™ PureLink™ Genomic DNA Mini Kit, Catalog number: K182002).

DNA Extraction and Genotyping

Amplification procedure of the SIRT1 gene and the proper sequence site for the gene polymorphisms (rs7895833, rs7069102 and rs2273773) was performed by Polymerase

Chain Reaction (PCR) method with Confronting Two-pair Primers (CTPP). The PCR process was accomplished in a volume of 20μl distilled water containing 100ng DNA, 2mM dNTPs, 5 pmol of primers (for each F and R), 1.0 mM $MgCl_2$ and 0.5U Taq polymerase. Primers used for identification of rs7895833, rs2273773 and rs7069102 polymorphisms and band length specifications are presented in Table 1. Electrophoretic separation of PCR-CTTP products was performed on a 3% agarose gel and samples were visualized by using UV light.

Prediction of Gene-Gene Interactions and gene ontology with in silico analysis

SIRT 1 gene investigation of its association with other genes in order to predict the effect of SNPs on other related genes was used, GeneMANIA (https://genemania.org/) (accessed on 25 September 2022). The prediction of gene-gene interaction by GeneMANIA is that interaction is based on the basis of pathways, co-localization, co-expression protein domain similarity, and genetic and protein interaction (20). The ontological analysis for the list of the SIRT1-interacted genes was done by using the online GeneCodis 4 software (https://genecodis.genyo.es/). This tool is a web-based method for the ontological analysis of lists of proteins, genes and regulatory elements like miRNAs, transcription factors, and CpGs (21).

Statistical analysis

The analysis for all data obtained was completed by Statistical Package for the Social Sciences (SPSS) 20 program. Shapiro-Wilk test was applied for evaluation of conformity of quantitative data to the normal distribution. Two independent groups were compared by using the independent samples t-test. Categorical data comparison analysis was performed by Pearson's $\chi 2$ (exact) test. Results are presented as median (min-max) for non-continuous data. The categorical values are presented as number (n) and percentage (%). The confidence level chosen was 95% and the p value below 0.05 was accepted as significant. The association between the SIRT1 genotypes and the patients with vitiligo was estimated by computing the odds ratios (ORs) and 95% confidence intervals (CIs) using logistic regression analyses. Beside the above mentioned analyses, the effect of the genetic correlation between two polymorphic regions was determined by using a haplotype analysis.

RESULTS

Demographical information for vitiligo patients and control individuals is presented in Table 2. The mean age in the vitiligo group was 35.5 years and similarly, 34 years in the control group, with no statistical difference between 78 patients and 85 controls who participated in the study (p>0.05).

The SIRT1 gene allele distributions and genotypes of the vitiligo patients and the control group are shown in Tables 3 and 4. The distribution of the SIRT1 gene for the persons in the vitiligo and control groups was in Hardy-Weinberg equilibrium.

While TT, TC and CC genotype frequencies of rs2273773 were 29%, 21% and 28% respectively for the group with vitiligo, these were 29%, 36% and 20% for the control group (p = 0.083). While the frequencies of T and C alleles of the vitiligo group were 79% and 77%, these were 94% and 76% for the control subjects (p=0.558). While GG, AG and AA genotype frequencies of rs7895833 were 14%, 44% and 20% respectively for the vitiligo patients, these were 38%, 35% and 12% for the control group (p = 0.001). The frequencies of G and A alleles of the vitiligo group were 46% and 54% respectively, these results are significantly different from the control group allele frequency (p = 0.001. While CC,

Table 1: Primer sequences and annealing temperature values applied for detection of rs2273773, rs7895833 and rs7069102 polymorphisms of SIRT1 gene.

Polymorphism (SIRT1 gene)	Primers Sequence 5' - 3'	Annealing temperature (°C)	Fragment size (bp)
rs2273773	P1-P4	63	**CC:** 314, 228 **CT:** 314, 228, 135 **TT:** 314, 135
rs7895833	P5-P8	64	**AA:** 320, 241 **AG:** 320, 241,136 **GG:** 320, 136
rs7069102	P9-P12	64	**CC:** 391, 277 **CG:** 391, 277, 167 **GG:** 391, 167

P1:5'GTGTGTCGCATCCATCTAGATAC 3'; P2:5'CTCTCTGTCACAAATTCATAGCCT 3'
P3:5'GTAGTTTTCCTTCCTTATCTGACAG 3'; P4:5'CTGAAGTTTACTAACCATGACACTG 3'
P5:5'CCCAGGGTTCAACAAATCTATGTTG 3'; P6: 5'GGTGGTAAAAGGCCTACAGGAAA 3'
P7:5'GCTTCCTAATCTCCATTACGTTGAC 3'; P8: 5'CCTCCCAGTCAACGACTTTATC 3'
P9:5'GTAGCAGGAACTACAGGCCTG 3'; P10:5'GAGAAGAAAGAAAGGCATAATCTCTGC 3'
P11:5'CTATCTGCAGAAATAATGGCTTTTCTC 3'; P12:5' GATCGAGACCATCCTGGCTAAG 3'

CG and GG genotype frequencies of rs7069102 were 18%, 26% and 34% respectively for the vitiligo patients group, these were 17%, 39% and 29% for the control subjects group (p = 0.255). While the frequencies of C and G alleles of the vitiligo group were 62 % and 94%, these were 73% and 97% for the control group (p = 0.558) (Tables 3 and 4). GG, AG and AA genotypes of rs7895833 were found to be significantly different in between; especially the GG genotype of vitiligo group revealed a significant difference. Significantly lower percentages in the AG and AA genotypes were calculated by analysis. No significant difference was revealed in both groups for CC, CG and GG genotypes of

Table 2: Demographic characteristics of patients and controls

Clinical Characteristics		Vitiligo (n=78) Median (Min.-Max.)	Control (n=85) Median (Min.-Max.)	p-value
Age		35.50 (8-82)	34 (17-80)	0.950
Gender, n (%)	**Female**	36 (46)	46 (54)	
	Male	42 (54)	39 (46)	
Family history	**Yes**	60 (0.77)	–	
	No	18 (0.23)	–	
Vitiligo Types	**Generalized**	38 (0.49)		
	Segmental	2 (0.02)		
	Localized	22 (0.28)	–	
	Acrofacial	11 (0.15)	–	
	Vulgaris	2 (0.02)		
	Focal	3 (0.04)		
Stability	**Stable**	16 (0.21)	–	
	Active	62 (0.79)	–	

Table 3: Distribution of genotypes of patients and controls

SNP	Genotypes	Vitiligo, n (%)	Control, n (%)	p value*	OR (95% CI)	p value**
rs2273773	TT	29 (37)	29 (34)	0.083	**1 (Reference)**	
	TC	21 (27)	36 (42)		0.58 (0.27-1.22)	0.156
	CC	28 (36)	20 (24)		1.40 (0.64-3.02)	0.392
rs7895833	GG	14 (18)	38 (45)	**0.001**	**1 (Reference)**	
	AG	44 (56)	35 (41)		3.41 (1.60-7.27)	0.001
	AA	20 (26)	12 (14)		4.52 (1.76-11.60)	0.002
rs7069102	CC	18 (23)	17 (20)	0.255	**1 (Reference)**	
	CG	26 (33)	39 (46)		0.63 (0.27-1.44)	0.273
	GG	34 (44)	29 (34)		1.10 (0.48-2.53)	0.809

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk genotype and allele. * χ^2 analysis p-value, p< 0.05; ** Logistic regression analysis, p< 0.05

Table 4: Allele frequencies for vitiligo patients and control subjects

SNP	Allele frequency	Vitiligo, n (%)	Control, n (%)	p value*	OR (95% CI)	p value**
rs2273773	T	79 (51)	94 (55)	0.400	1 (Reference)	0.401
	C	77 (49)	76 (45)		1.20 (0.78-1.86)	
rs7895833	G	72 (46)	111 (65)	0.001	1 (Reference)	0.001
	A	84 (54)	59 (35)		2.19 (1.40-3.42)	
rs7069102	C	62 (40)	73 (43)	0.558	1 (Reference)	0.558
	G	94 (60)	97 (57)		1.14 (0.73-1.77)	

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk genotype and allele. * χ^2 analysis p-value, p< 0.05; ** Logistic regression analysis, p< 0.05

rs7069102 and TT, TC and CC genotypes of rs2273773. It shows that these polymorphisms of the SIRT1 gene could be associated with the vitiligo.

There was a significant difference between the two groups with regards to G and A alleles of rs7895833. While the percentage of the G allele, which was dominant in the control group, was decreasing in the group with vitiligo, the A allele, which was seen less often in the control group, was determined as more dominant in the group with vitiligo. While no difference was found in both groups with regards to G and C alleles of rs7069102, a high rate of G allele was determined in both groups. A difference was not found in both groups with regards to T and C alleles of rs2273773. A dominant rate of C allele was also found in this group.

Haplotype analysis of the rs2273773, rs7895833, and rs7069102 SIRT1 polymorphisms revealed that the AGT haplotype frequency was 23% in vitiligo patients and 12% in the controls, and the difference was significant (OR=2.99; 95% CI, 1.26–7.06) (Table 5). A further haplotype analysis among all three above mentioned polymorphisms has shown that the AGT haplotype could be a risk factor in etiology of vitiligo (p=0.013).

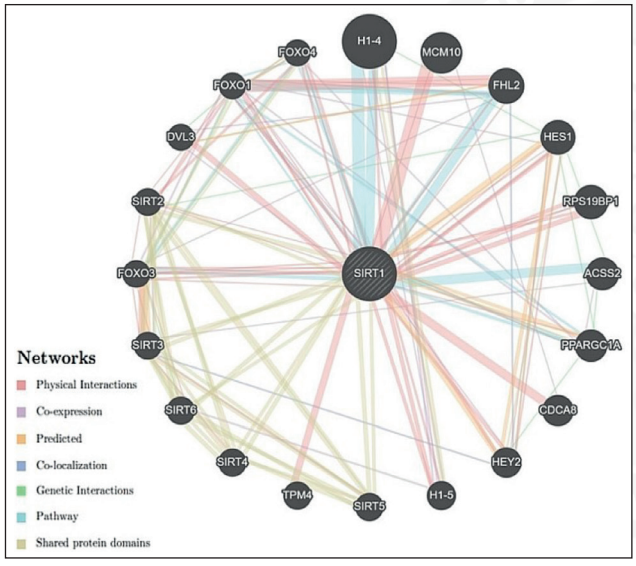

Figure 1: Gene-gene interaction network of SIRT1 using a GeneMANIA tool.

Prediction of Gene-Gene Interactions and gene ontology with in silico analysis

Our findings revealed that SIRT 1 is co-expressed with 16 genes (H1-4, MCM10, FHL2, HES1, ACSS2, PPAR6C1A, CDCA8, HEY2, H1-5, SIRT6 SIRT3, FOXO3, SIRT2, DVL3, FOXO1, FOXO4), shared a domain with only 12 genes (H1-4, HES1, HEY2, H1-5, SIRT5, SIRT4, SIRT3, FOXO3, SIRT2, FOXO1, FOXO4), physical interaction with 19 genes (all shown in figure 1 excepted ACSS2 gene) (Figure 1).

20 identified genes were found to be related to apoptosis, autoimmunity and oxidative stress genes and molecular events as revealed via a regulatory and functional analysis by GeneCodis 4 (Figure 2). The figures represent the visualizations generated for 10 top terms of associations with Gene Ontology (GO) and GO Annotations Biological Process (Figure 2A), GO Cellular Component (Figure 2B), GO Molecular Function (Figure 2C), annotation of Reactome Pathway Database (Figure 2D).

DISCUSSION

The present study investigated the possible interrelation between the SIRT1 gene and vitiligo disease, the first among other genetic research studies. Consequently, a significant linkage was detected for rs7895833 polymorphism of the SIRT1 gene which is known to be involved in the apoptotic process and histone modification. As demonstrated from the perspectives of biological process and molecular function (Figure 2A,C, respectively), the genes analyzed are responsible for cellular roles such as histone modifications, control of transcription, and chromatin-DNA interaction. The cellular activities determined as a result of

Table 5: Association between haplotypes of SIRT1 gene polymorphisms and risk of vitiligo

Haplotypes	Vitiligo, n (%)	Control, n (%)	OR (95% CI)	p-value
GCT	25 (16)	39 (23)	Reference	-
GGT	22 (14)	31 (18)	1.10 (0.52-2.32)	0.788
GGC	14 (9)	27 (16)	0.80 (0.35-1.83)	0.611
GCC	12 (7)	14 (8)	1.33 (0.53-3.35)	0.536
AGT	**23 (14)**	**12 (7)**	**2.99 (1.26-7.06)**	**0.013**
ACT	12 (7)	12 (7)	1.56 (0.60-4.01)	0.356
ACC	38 (24)	24 (16)	2.19 (1.08-4.43)	0.290
AGC	14 (9)	8 (5)	2.73 (1.00-7.44)	0.050

Results are given as n (%). **OR:** Odds ratio, **CI:** Confidence interval. The ORs were calculated with references to the risk haplotype. * Logistic regression analysis, p< 0.05

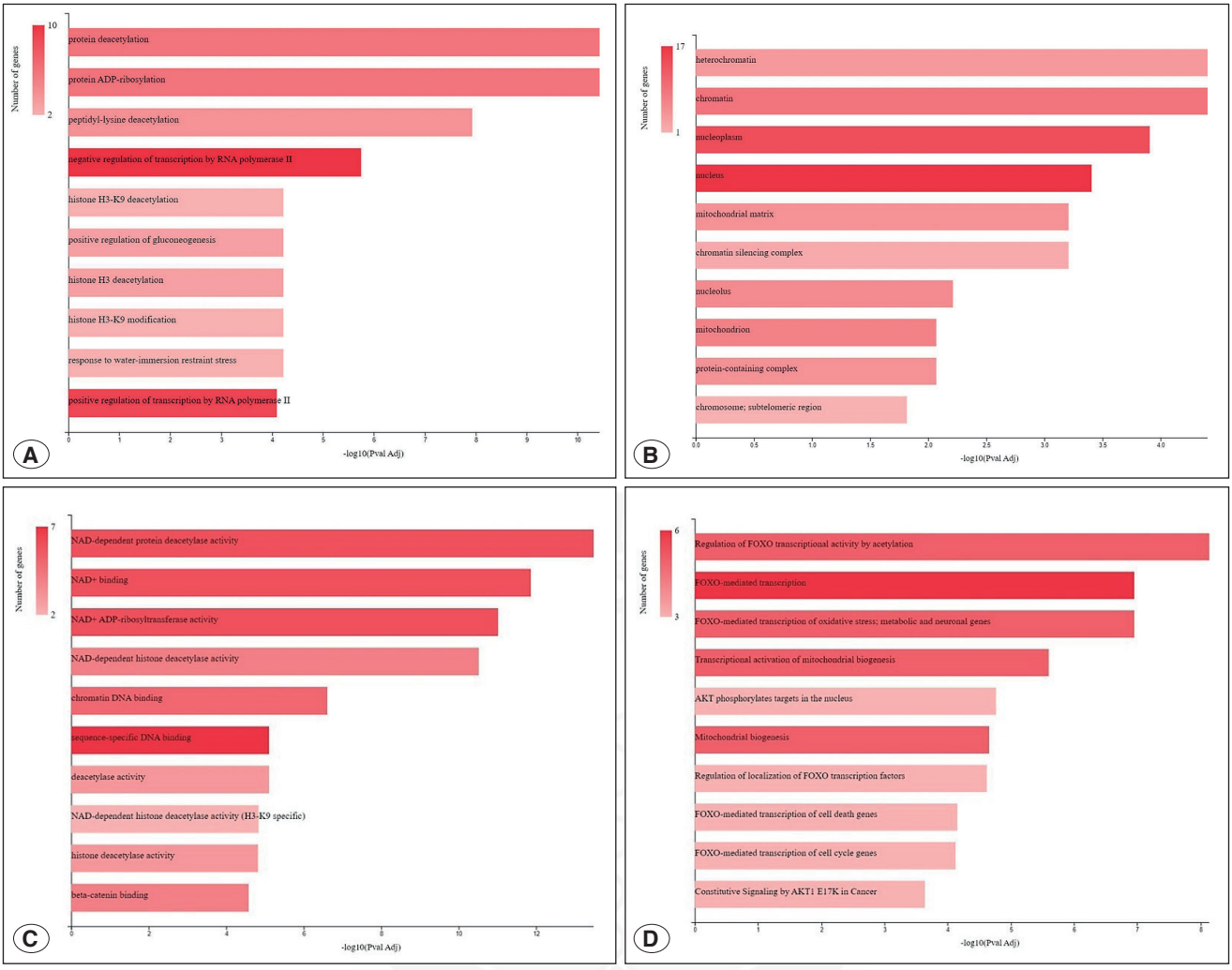

Figure 2: GeneCodis Ontological analysis. Visualizations generated for 10 top terms of related categories with our identified gene list are presented here for GO Biological Process **(A)**, GO Cellular Component **(B)**, GO Molecular Function **(C)**, Annotation of Reactome database **(D)**.

the analyzes control the genetic and epigenetic processes in the regulation of gene expression.

All seven sirtuins have been expressed in human epidermal and dermal cells (22). Sirtuins are involved in cellular pathways related to many skin diseases, including photoaging, inflammation, and cancer (23). SIRT1 expression was decreased in cultured skin keratinocytes damaged by UV and H_2O_2 (24). Upregulation of SIRT1, 3 and 7 are potential therapeutic targets for improving skin ageing and appearance (23).

It has been reported that the SIRT1 pathway is protective against skin damage as a result of H_2O_2-induced keratinocyte death (25). Becatti et al. showed decreased SIRT1 expression and activity in lesioned psoriatic fibroblasts (26).

Another study emphasized that SIRT1 has a critical role in maintaining the skin barrier and preventing atopic dermatitis (27). The rs7069102 polymorphism of the SIRT1 gene has been shown to be associated with early-onset psoriasis (28). SIRT1-related interaction and its possible contribution and involvement in dermatological diseases are not investigated enough as far.

Further investigation on cellular mRNA and the protein levels of SIRT1 and other genes involved in the apoptotic pathways may provide detailed data for their implication in vitiligo pathogenesis. Genes, cellular process and pathways that may be important in the pathogenesis of vitiligo have been demonstrated with in silico approaches. By in silico approaches, genes with which the SIRT1 gene interacts are determined, and target genes (FOXO3, SIRT2, DVL3, MCM10, etc.) that may be associated with apoptosis, oxidative stress and autoimmunity, which are the basis of vitiligo pathogenesis revealed. FOXO-mediated transcription, oxidative stress, mitochondrial biogenesis, and AKT signaling

pathway draw attention in the Reactome pathway analysis. Studies have revealed the relationship between FOXO genes, oxidative stress and apoptosis processes and vitiligo (23, 29-32). In a recent study, the AKT/MAPK pathway has been associated with apoptosis and oxidative stress of keratinocytes in vitiligo (23, 32). In this context, the importance of these pathways and related genes in the pathogenesis of vitiligo has been reported in some studies (33-36).

There is a limited number of studies investigating the linkage between the SIRT1 enzyme/gene and dermal fibroblasts or microvascular endothelial cells. SIRT1 related interaction and its possible contribution and involvement in dermatological diseases are not investigated enough as far.

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Author Contributions

Concept: **Oktay Kuru, Tuba Edgünlü, Ümmühani Özel Türkcü, Nilgün Solak,** Design: **Tuba Edgünlü, Nilgün Solak, Oktay Kuru, Sevim Karakaş Çelik,** Data Collection or Processing: **Nilgün Solak, Sevim Karakaş Çelik, Tuba Edgünlü, Oktay Kuru,** Analysis or Interpretation: **Ümmühani Özel Türkcü, Oktay Kuru, Tuba Edgünlü,** Literature search: **Oktay Kuru, Tuba Edgünlü, Writing: Oktay Kuru, Tuba Edgünlü,** Approval: **Sevim Karakaş Çelik, Oktay Kuru.**

Conflicts of Interest

No conflict of interest is reported by authors.

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Ethical Approval

Ethical approval for the current study was issued by the Institutional Review Board upon request (13-05-22/01-04). All procedures were performed in compliance with Declaration of Helsinki. Participants gave their written consent after being informed for contribution to study.

Review Process

Extremely peer-reviewed and accepted.

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