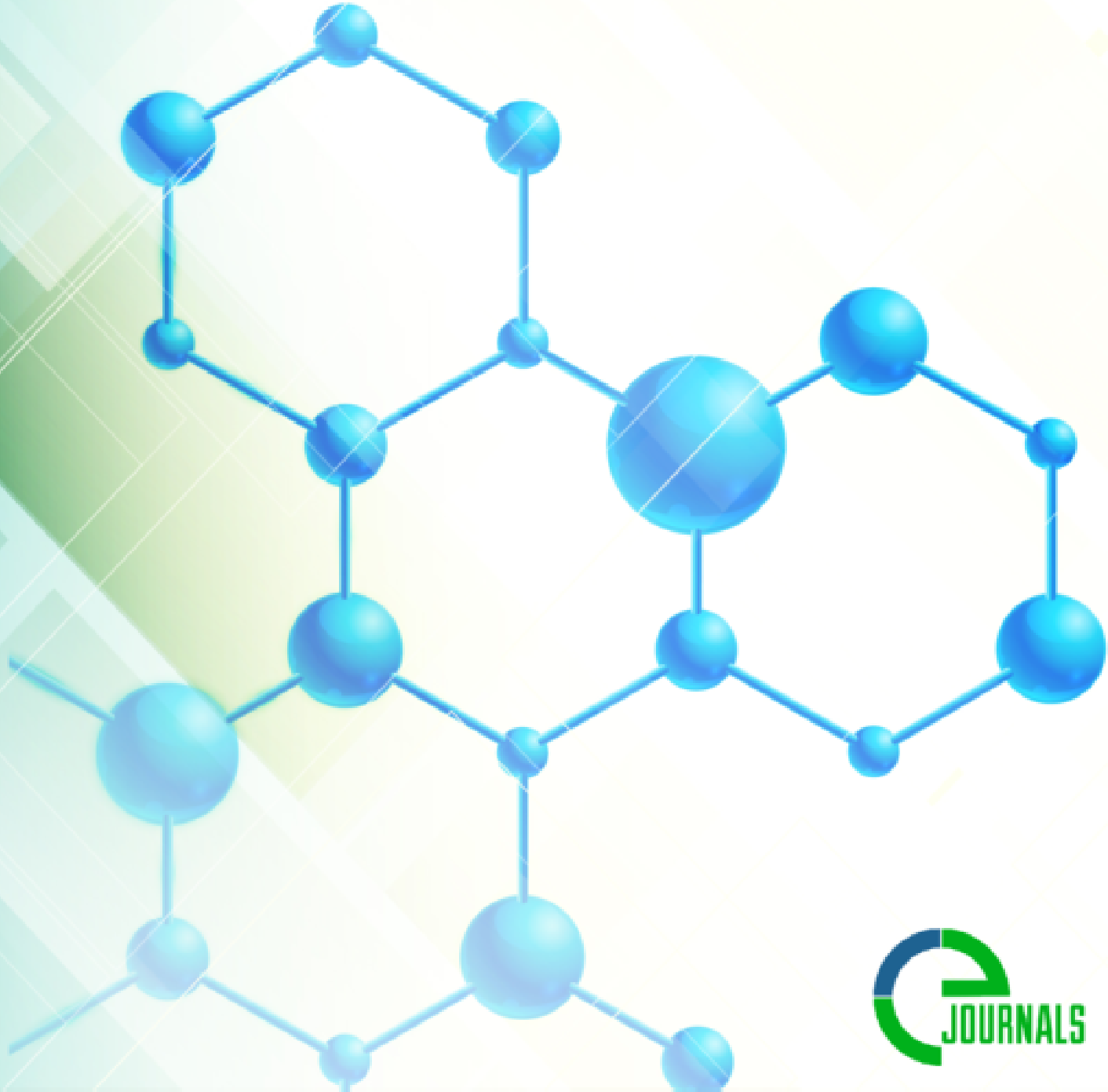
EUROPEAN JOURNAL OF

MOLECULAR MEDICINE



JOURNALS

European Journal of Molecular medicine

Volume 2, No.5, September 2022

Internet address: ttp://ejournals.id/index.php/EJMM/issue/archive
E-mail: info@ejournals.id
Published by ejournals PVT LTD
DOI prefix: 10.52325
Issued Bimonthly
Potsdamer Straße 170, 10784 Berlin, Germany

Requirements for the authors.

The manuscript authors must provide reliable results of the work done, as well as anobjective judgment on the significance of the study. The data underlying the work shouldbe presented accurately, without errors. The work should contain enough details andbibliographic references for possible reproduction. False or knowingly erroneous statementsare perceived as unethical behavior and unacceptable.

Authors should make sure that the original work is submitted and, if other authors'works or claims are used, provide appropriate bibliographic references or citations. Plagiarismcan exist in many forms - from representing someone else's work as copyright to copying orparaphrasing significant parts of another's work without attribution, as well as claimingone's rights to the results of another's research. Plagiarism in all forms constitutes unethicalacts and is unacceptable. Responsibility for plagiarism is entirely on the shoulders of theauthors.

Significant errors in published works. If the author detects significant errors or inaccuraciesin the publication, the author must inform the editor of the journal or the publisher aboutthis and interact with them in order to remove the publication as soon as possible or correcterrors. If the editor or publisher has received information from a third party that thepublication contains significant errors, the author must withdraw the work or correct theerrors as soon as possible.

CHIEF EDITOR

EDITORIAL BOARD

ASSOCIATION ANALYSIS OF TYROSIN RELATED PROTEIN (TRP) GENE POLYMORPHISM IN VITILIGO PATIENTS

Sobirov Ulugbek Yusuphanovich
Doctor of Medical Sciences, Professor Republican Specialized Scientific and Practical Medical Center for Dermatovenereology and Cosmetology of the Ministry of Health of the Republic of Uzbekistan
Mamadiev Asil Asqaralievich
Jizzakh branch of the Republican specialized scentific and practical medical center of dermatoveneorology and cosmetology.Dermatovenerologist.
Yuldashev Muzaffar Akramovich
First Deputy Director for Medical Work of the National Children's Medical Center. Professor of the Department of Dermatovenerology of the Tashkent Pediatric Medical Institute. Doctor of Medical Sciences, Professor

Abstract: The article presents the data of 108 patients aged 19 to 59 years old. The role of the rs752924961 polymorphic variant of the TRP-1 gene and the rs537718989 polymorphic variant in the TRP-2 gene was assessed. In a molecular genetic study of the tyrosinase - binding protein (TRP) gene, it was found that the second phase of the excretion of the TRP1 and TRP2 genes increases the number of carriers of the polymorphism of the TRP1(0/0) + TRP2(0/0) genes in the second phase of the isolation of the TRP1 and TRP2 genes compared with healthy donors, which may be considered a genetic component of susceptibility to vitiligo.

Vitiligo is a skin disease of unknown etiology, characterized by loss of pigmentation in some areas of the skin due to dysfunction of melanocytes [6, 7, 11] and this disease occurs in 0.5-1% of the population worldwide [10]. Vitiligo is observed equally in men and women, but women are much more likely to seek medical help from a doctor [12].

Over the past decades, in foreign literature, due to technological and methodological advances in clinical genetics, genetic conditioning has been increasingly important in the pathogenesis of autoimmune diseases in general and vitiligo in particular. Significant experience has been accumulated in the study of polygenically inherited multifactorial diseases, which has led to attempts to map specific genes responsible for the tendency to develop vitiligo and its pathogenesis [15]. Recently, significant progress has been made in identifying the genes responsible for the propensity to develop vitiligo, some of which may be new therapeutic and prophylactic targets for new approaches to the treatment of this disease.

Vitiligo is characterized by the appearance of foci of depigmentation on the skin, the histological examination of which reveals the absence or a sharp decrease in the content of melanin in melanocytes. The prevalence of this dermatosis is 1-2% among the European population, 3-4% of all known dermatoses in terms of visits to the clinic. In Central Asia, the incidence of vitiligo is the highest and reaches 10% in some areas [1, 2, 3].

Related cases of the disease indicate that the genes that cause depigmentation can be inherited. The etiology and pathogenesis of vitiligo is still not well understood. The disease is multifactorial, exogenous and endogenous factors play a role in its development. External stimuli include stress, mechanical irritation and injury (Koebner phenomenon), excessive ultraviolet exposure, and chemical agents. Of the endogenous diseases, somatic and infectious diseases (autoimmune thyroiditis, rheumatoid arthritis, lupus erythematosus, liver diseases of an infectious or toxic origin, helminthic invasions), the use of drugs

that affect the pigment-forming function of melanocytes are most often noted [5, 8, 15] .

Melanocytes of the skin originate from the neural tube of the fetus, after the closure of which a group of cells migrates in the dorsolateral direction, forming the neural crest. These cells are the precursors of many structural elements, including skin melanocytes. All melanocytes contain tyrosinase and produce melanin, but only skin melanocytes are able to transfer melanin to other cells, so they are considered as unicellular glands (secretory melanocytes) [4, 16].

The biosynthesis of melanin is a rather complex process. The main amino acid in the production of melanin is tyrosine or hydroxyphenylalanine. In melanosomes, tyrosine is converted to DOPA (dihydroxyphenylalanine) and then oxidized to DOPA-quinone. The copper-containing enzyme tyrosinase plays a regulatory role in the biosynthesis process. The levels of mRNA tyrosinase and enzymes are approximately the same in dark and white skin [9, 14].

Tyrosine related oxyl-2 (TRP-2) is considered one of the major melanocyte differentiation antigens . Functionally, TRP-2 is considered to be a dopachrome tautomerase (DXT) that shapes the structure and composition of melanin. Unlike tyrosinase , TRP-2 loading does not result in depigmentation, but rather in a hypopigmented state. Tyrosinase and its associated oxyl TRP 1 and TRP 2 play a key role in melanogenesis . Tyrosinase catalyzes the hydroxylation of L-tyrosine to L-3,4-dihydroxyphenylalanine, which is then oxidized to one step in the dopaquinone-pheomelanogen pathway (Hearing, 1999). It has been shown that additional mechanisms for the formation of L-DOPA are either the conversion of L -dopaquinone back to L-DOPA (Cooksey et al ., 1997), or direct hydroxylation of tyrosine to isoform I of tyrosine hydroxylase [13, 15]. In the production of L-DOPA, melanogenesis is triggered by spontaneous redox processes and molecules determined by local concentrations of hydrogen, metal cations, thiols , hydrogen peroxide, and oxygen ions. Regulation of the rate of eumelanogenic reactions is carried out with the help of TRPoxyls , the most important of which is tyrosinase itself , since it enhances the oxidation of dihydroxyindole . TRP2 also protects the human body from oxidative stress by increasing glutathione levels , reducing quinone toxicity, and repairing DNA damage [5, 15].

Thus, based on the above, it is relevant to study the role of the rs752924961 polymorphic variant of the TRP-1 gene and the rs537718989 polymorphic variant in the TRP-2 gene.

The purpose of the study: to study the role of TRP1 and TRP2 genes - tyrosine-dependent proteins in the development of vitiligo.

Materials and methods of research: 108 patients aged 19 to 59 years who were on outpatient and inpatient treatment at the Republican Scientific and Practical Medical Center of the Ministry of Health of the Republic of Uzbekistan and the regional department of the Jizzakh region were examined (head of the department, MD, prof. Yuldashev M.A.). Of these, 54 (50.0%) women and 54 (50.0%) men. The duration of the disease ranged from 6 months. up to 22 years, the majority of patients (58.3%) noted the duration of the disease from 1 to 10 years.

Among them, 24 patients had a segmental form of the disease and 84 patients had a non-segmental form of vitiligo . As a comparison group for genetic tests, a population control was used, where a DNA sample from the DNA bank of 101 conditionally healthy donors of the immunogenetic laboratory "Genotechnology" was used.

Genotyping of the rs2010963 polymorphism of the TRP-1, TRP-2, and VEGFA genes was carried out in programmable thermal cyclers SG-1-96 " Corbett Research " (Australia) and 2720" Applied Biosystems "(USA) using the test" MedLab "(Russia).

systems according to the manufacturer's instructions by polymerase chain reaction (PCR).

The results obtained during the study were performed by the method of variation statistics using the Microsoft package Office Excel-2010, which includes software support for statistical analysis.

Results of the study : the results of the study showed (Table 1) that the percentage of individuals with a negative allele when testing the polymorphism of the TRP1(0/0) gene in the main group of patients was 34.3% (? 2 =0.6; P=0.4 ; OR = 1.3; RR = 1.1; 95% CI = 0.6-2.3), while in the control group this figure was 28.7%.

Table 1

Distribution frequency of null alleles of TRP1 and TRP2 gene polymorphisms in patients with vitiligo and in controls

Forms of the disease	Frequency of distribution of genotypes							
	TRP1(+)		TRP1(0/0)		TRP2(+)		TRP2(0/0)	
	n	%	n	%	n	%	n	%
Main group n= 108	71	65.7	37	34.3	67	62.0	41	38.0
Segmental form, n=24	15	62.5	9	37.5	13	54.2	eleven	45.8
segmental form, n=84	48	57.1	34	42.9	39	46.4	45	53.6
Control group, n=101	72	71.3	29	28.7	77	76.2	24	23.7

Similar data were obtained in the study of TRP1(0/0) gene polymorphism in patients with segmental vitiligo - 37.5% (χ^2 =0.6; P=0.4; OR=1.4; RR=1.3; 95%CI=0.60-3.22). In the non - segmental form of vitiligo, when studying the polymorphism of the TRP1 (0/0) gene, it was found that the percentage of individuals with a negative allele was significantly increased, and compared with the control group was 42.9% (χ^2 =1.9; P=0, 2; OR=1.9; RR=1.6; 95%CI=0.76-4.53), however, the data were not statistically significant.

The results obtained showed that when studying the TRP1(0/0) gene, no significant differences were found in patients of the study group and subgroup (p>0.05).

When studying the polymorphism of the TRP2(0/0) gene in the main group of patients with vitiligo, it was found that the percentage of individuals with a negative allele was significantly increased and amounted to 38.0% (χ^2 =4.1; P=0.04; OR=1, 9; RR=1.7; 95% CI=1.01-3.58), in the control group - 23.7% (Table 2).

Table 2

Differences in the frequency of alleles and genotypes of the polymorphic marker TRP2 (0/0) in patients with different clinical forms of vitiligo and in controls

Forms of the disease	Genotype		OR	RR	χ2	R	95 %CI
	TRP2(+)	TRP2(0/0)	1.9	1.7	4.1	0.04	1.01-3.58
Main group n= 108	67	41	2.6	2.1	5.0	0.02	1.1-5.92
Segmental form, n=24	13	11	3.7	2.5	8.5	0.003	1.5-9.14
segmental form, n=84	39	45					
Control group, n=101	77	24					

A similar picture can be traced in the segmental form of vitiligo - 45.8% (χ^2 =5.0; P=0.02; OR=2.6; RR=2.1; 95% CI=1.1-5.92) and non- segmental forms e - 53.6% (χ^2 =8.5; P=0.003; OR=3.7; RR=2.5; 95% CI=1.5-9.14) . There is a tendency for the predominance of the detection rate of TRP2(0/0) among patients with a non -segmental form, but no statistical values have been obtained (P>0.05).

At a further stage, four haplotypes were evaluated: TRP1(0/0) + TRP2(0/0), TRP1(0/0) + TRP2(+), TRP1(+) + TRP2(0/0) and TRP1(+) + TRP2(+), the data obtained are presented in Table 3.

Table 3

Distribution frequency of null alleles of TRP1 and TRP2 gene polymorphisms in patients with vitiligo and in controls

genetic markers	Main group		Segmental form		segmental form		Control group	
	n	%	n	%	n	%	n	%
TRP1(+) + TRP2(+)	41	38.0	7	29.2	34	40.5	52	51.5
TRP1(0/0) + TRP2(+)	26	24.1	6	25.0	20	23.8	25	24.7
TRP1(+) + TRP2(0/0)	30	27.8	8	33.3	22	26.2	20	19.8
TRP1(0/0) + TRP2(0/0)	eleven	10.1	3	12.5	8	9.5	4	4.0
Total	108	100	24	100	84	100	101	100

Among patients with vitiligo, persons with the TRP1(0/0) + TRP2(0/0) genotype occurred in 10.1%, while in the control group only 4%. At the same time, the risk of developing vitiligo TRP1(0/0) + TRP2(0/0) (χ^2=2.4; P=0.1; OR= 2.7; RR= 2.3; 95% CI=0, 73-9.89) was more than 2 times higher, but the resulting difference did not reach the critical level of statistical significance.

The frequency of simultaneous distribution of TRP1(0/0) + TRP2(+) was the same in patients with vitiligo (24.1%) and in the control group (24.7%). In a pooled analysis of TRP1(+) + TRP2(0/0) genotypes, vitiligo patients and controls (27.8% and 19.8%, respectively; χ2=1.6? R=0.2; OR=1.5 ; RR=1.4; 95% CI=0.78-3.01) there was no statistically significant difference.

Analysis of the combined genotypes of the TRP1 and TRP2 genes in the group of patients with vitiligo, depending on the form of the disease, also revealed that the combination of TRP1(0/0) + TRP2(0/0) was more common in all subgroups of patients compared to the control group (4.0%), with a segmental form of vitiligo - in 12.5% (χ^2 = 2.4 ; P= 0.1 ; OR=3.2 ; RR=2.9 ; 95% CI= 0.67-15.1) and with a non-segmental form - 9.5% (χ^2 =1.2; P=0.3; OR= 2.2; RR= 2.0; 95% CI=0.51-9.8).

According to the calculated odds ratio, the risk of developing segmental vitiligo increases up to 2.7 times with the distribution TRP1(0/0) + TRP2(0/0). The TRP1(0/0) + TRP2(0/0) genotype is more common in patients with nonsegmental vitiligo. But all these differences were not statistically significant, i.e., the conjugation phenotype in the combined genotypes was not associated with the clinical form of the disease. This is probably due to the low frequency of TRP1(0/0) + TRP2(0/0) polymorphism in our population.

The frequency of occurrence of other TRP1 and TRP2 genotypes among patients of the main group did not differ from the frequency of occurrence in the control group (P>0.05). In a comparative analysis of the distribution frequency of the studied genotypes in patients with different forms of the disease with apparently healthy individuals, there were no differences between the groups (P>0.05). Analysis of the indicators of the course of the disease also showed their statistically insignificant deviation from the normal distribution (P>0.05).

Conclusion : there was no statistical difference in the frequency of "null" genotypes of the TRP1 and TRP2 genes between patients with vitiligo and the control group. However, in the group of patients with vitiligo, compared with conditionally healthy donors, a tendency to an increase in the frequency of TRP1(0/0) + TRP2(0/0) polymorphism carriers was shown, which can be considered a genetic component of predisposition to vitiligo. The statistical significance of such differences is probably due to the low frequency of TRP1(0/0) + TRP2(0/0) polymorphism combinations in our population.

Used literature.

1.Vaisov A.Sh., Mirodilova F.B. The role of nitric oxide and reactive oxygen species in the pathogenesis and clinic of patients with trichophytosis combined with a subclinical form of hypothyroidism // News of dermatovenereology and reproductive health. 2007. - № 4.S. 5-9.

2.Vasilchenko T.S., GabdrakipovaA.A., BelyanskayaI.A.Etiopathogenesis and diagnosis of vitiligo // Synergy of Sciences. - 2019. -№31. -S.1434-1437.

3.Dvoryankova E.V., Korsunskaya I.M. Modern classification and vitiligo nomenclature // Dermatology. Supplement to Consilium magazine Medicum . -2018. -#2. -FROM. 5-7.

4.Ismailov R.G. Regulation of melanogenesis in dyschromia leather // Bulletin Russian academy medical Sciences. - 2014. - No. 1. -2. - P.85-92.

5.Kayumova L.N., Khanbabyan A.B., Bruskin S.A. and others genetic and e pygenetic factors development some immunodependent dermatosis // Doktor.ru . -2013. -#4. - FROM. 40-46.

6.Lomonosov K.M., Gereykhanova L.G. Algorithm for the treatment of vitiligo // Russian journal of skin and venereal diseases. -2016. -T.19. -Number 3. -C.167-169.

7.Olisova O.Yu., Pinson I.Ya., Myzina K.A., Garanyan L.G. Combined method phototherapy vitiligo //Russian magazine skin and venereal diseases. -2017. -T.20. -#4. - C.238-242.

8.Proshutinskaya D.V. The state of melanogenesis and immune processes in the skin of patients with vitiligo, evaluation of the effectiveness of therapy with narrow -spectrum ultraviolet radiation in the range of 304-313nm: author . dis . Dr. honey. Sciences. - M., -2009. - 33 p.

9.Simonova N.I., Lomonosov K.M., Babeshko O.A. Genetic aspects of vitiligo (literature review) // Russian journal of skin and venereal diseases. - 2012. - No. 5. - P.56-59.

10.Cesar Silva de Castro C., Miot HA Prevalence of vitiligo in Brazil-A population survey // Pigment cell Melanoma Res. - 2018. - Vol.31(3). - P.448-450.

11.Edwards C. Measurement of vitiligo: human vs. Machine // Br. J. Dermatol. - 2019. - Vol.180(5). - P.991.

12.Onunu AN, Kubeyinje EP Vitiligo in the Nigerian African: a study of 351 patients in Benin city, Nigeria // Int. J. Dermatol . - 2003. - Vol. 42, No. 10.- _ P. 800-802.

13.Sardana K., Verma G. Overview of Medical Therapies and Phototherapy in Vitiligo Based on Their Pathogenetic Action and the Role of Platelet-Rich Plasma // J Cutan Aesthet Surg. - 2018. - Vol.11(4). - P.167-168.

14.Shen C., Gao J., Sheng Y. et al. Genetic Susceptibility to Vitiligo: GWAS Approaches for Identifying Vitiligo Susceptibility Genes and Loci // Front. Genet. - 2016. - Vol. 7. - P. 3.

15.Spritz RA The genetics of generalized vitiligo and associated autoimmune diseases. Pigment Cell Res. 2007; 20(4): 271-278.

16.Taieb A., Picardo M., Members V. The definition and assessment of vitiligo: a consensus report of the Vitiligo European Task Force // Pigment Cell Res. - 2007. - Vol. twenty, No. one. - P. 27-35.