Benha Journal of Applied Sciences (BJAS) **print: ISSN 2356–9751**
Vol. (8) Issue (6) (2023), (75-78) **online: ISSN 2356–976x**
http://bjas.journals.ekb.eg

Uncoupling Protein 2 and Dynamin-related Protein1mRNA Expression as Genetic Markers for Vitiligo

Karim.R.Karim[1], Fatma.M.El Esswey[1], Amany I.Mustafa[1] and Maha.M.Othman[2]
[1]Dermatology, Venereology and Andrology Dept., Faculty of Medicine, Benha University
[2]Clinical and Chemical Pathology Dept., Faculty of Medicine, Benha University
E-mail: karimreda89@gmail.com

Abstract

Background: Vitiligo is a depigmenting skin condition characterized by specific melanocyte depletion, resulting in the attenuation of melanin within the affected skin regions. Mitochondrial dysfunction and oxidative stress have been implicated in the pathogenesis of vitiligo. This study aimed to investigate the gene expression levels of Uncoupling Protein 2 (UCP2) and Dynamin-related Protein 1 (Drp1) in vitiligo patients and their potential association with disease severity and activity. Methods: This case- control study was conducted, including 40 vitiligo patients and 40 age and sex-matched healthy controls. Gene expression levels of UCP2 and Drp1 were measured in plasma samples using an enzyme-linked immunosorbent assay (ELISA). Results: The study included 40 patients with vitiligo. Their mean age was 28.9 years. They were 77.5% males and 22.5% females. In addition to 40 healthy control subjects od matched age and gender ($p \geq 0.05$). The study revealed significant downregulation of UCP2 gene expression and upregulation of Drp1 gene expression in vitiligo patients compared to healthy controls. Conclusions: The findings suggest that dysregulation of UCP2 and Drp1 gene expression may play a role in the pathogenesis of vitiligo.

Keywords: Vitiligo, Uncoupling Protein 2, UCP2, Dynamin-related Protein 1, Drp1; Gene Expression, Disease Severity, Disease Activity.

1. Introduction

Vitiligo is a chronic, autoimmune skin condition characterized by the selective death of melanocytes and the formation of depigmented skin areas. Approximately 1-2 percent of the world population is affected, regardless of age, color, or gender [1]. Despite the fact that vitiligo is not life-threatening, its psychological and social effects can be severe, resulting in diminished quality of life and self-esteem problems. The specific cause of vitiligo is currently unknown, however it is believed to entail a complex interaction between genetic, environmental, and immune factors [2].

Numerous studies have highlighted the importance of certain genes and pathways in disease susceptibility and pathogenesis in the development of vitiligo, which has long been linked to genetic factors [3]. The discovery of valid genetic markers for vitiligo might facilitate early diagnosis, risk assessment, and the development of focused treatment strategies. In recent years, there has been an increasing interest in studying the mRNA expression levels of certain genes as possible genetic markers for vitiligo [4, 5].

Uncoupling Protein 2 (UCP2) is an essential mitochondrial protein that regulates cellular energy metabolism. It participates in the decoupling of oxidative phosphorylation, which might enhance the formation of reactiveoxygen species (ROS) [68-].

Dynamin-Related Protein 1 (DRP1) is a crucial regulator of mitochondrial fission, a process vital in maintaining the dynamics and function of mitochondria. Mitochondrial fission mediated by DRP1 is essential for cellular functions including apoptosis, mitophagy, and energy consumption [9,10]. Emerging data shows that DRP1 dysregulation may be linked to a variety of autoimmune conditions, including vitiligo. Observations of dysfunctional mitochondrial dynamics and shape in melanocytes from vitiligo patients, as well as DRP1 expression variations in lesional skin, imply a possible role for DRP1 in the etiology of vitiligo.

The aim of this study is to investigate the mRNA expression levels of UCP2 and DRP1 as potential geneticmarkers for vitiligo.

2. Methods

The study comprised 40 vitiligo patients and 40 healthy controls of the same age and gender. The patients were randomly selected from the outpatient clinic of the Department of Dermatology and Venereology at Benha University Hospital in Benha, Egypt. The control group consisted of persons of comparable age and gender who were in good health. Patients of varied genders and ages with variable degrees of vitiligo severity were included in the research. The diagnosis of vitiligo was verified by wood's inspection using a light.

All patients were subjected to a comprehensive clinical evaluation, which included a general medical examination to detect any underlying medical disorders besides vitiligo.

Blood samples were collected from all subjects. A volume of 5 ml of venous blood was collected in sterile disposable vacuum blood-collecting vessel tubes (red tubes). Serum was separated by centrifugation, and the samples were stored at <-20°C. The levels of UCP2 and DRP1 in the serum were determined using enzyme-linked immunosorbent assay (ELISA) kits specific to each protein. The ELISA kits used were Human Uncoupling Protein 2 ELISA Kit and Human Dynamin 1 (DNM1) ELISA Kit. The ELISA kits

employed a double-antibody sandwich technique to detect the respective proteins in the serum samples.

Statistical analysis:

The normality of data distribution was examined using the Shapiro-Wilks test and histograms. Quantitative parametric data were presented as mean and standard deviation (SD) and analyzed using the unpaired Student's t-test. Non-parametric quantitative data were reported and analyzed as median and interquartile range (IQR) using the Mann-Whitney U test.

3.Results

The current study included 40 patients with vitiligo with a mean age of 28.9 years. 77.5% were males and 22.5% were females. In addition to 40 healthy control subjects od matched ageand gender ($p \geq 0.05$). **Table 1**

Table (1) Demographic data in vitiligo patients and control groups.

	Vitiligo patientsn = 40		Controln = 40		Test (p)
	N.	%	N.	%	
Sex					
Male	31	77.5	26	65.0	X^2=1.526p=0.217
Female	9	22.5	14	35.0	
Age (years)					
Mean ± SD.	28.98 ± 10.53		29.58 ± 10.89		t=0.251p=0.803
Median (Range)	23.0 (19.0 – 55.0)		24.50 (19.0 – 50.0)		

SD. Standard deviation, Range: Min. – Max; X2, Chi-Square; t, t student test.

The study showed 32.5% of patients with vitiligo had a family history of vitiligo. The course of vitiligowas of progressive course in 25 (62.5%)patients while 9 (22.5%) patients were complaining of stationary course.

The study showed the activity ofvitiligo was divided into 25 (62.5%) active and15 (37.5%) stable. **Figure**

Sites of disease and types of disease among vitiligo patients were illustrated in **Figure 1 and 2**.

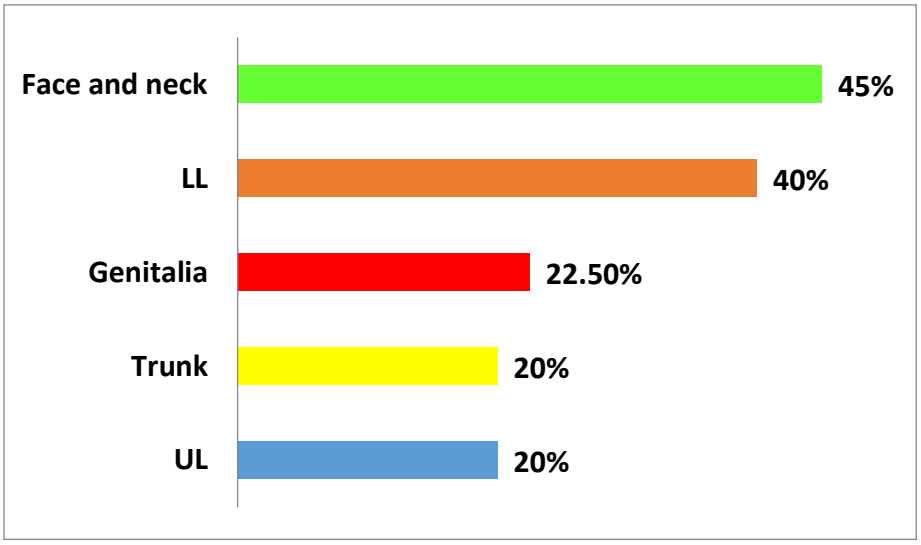

Fig. (1**)** Bar chart for sites of disease among vitiligo patients.

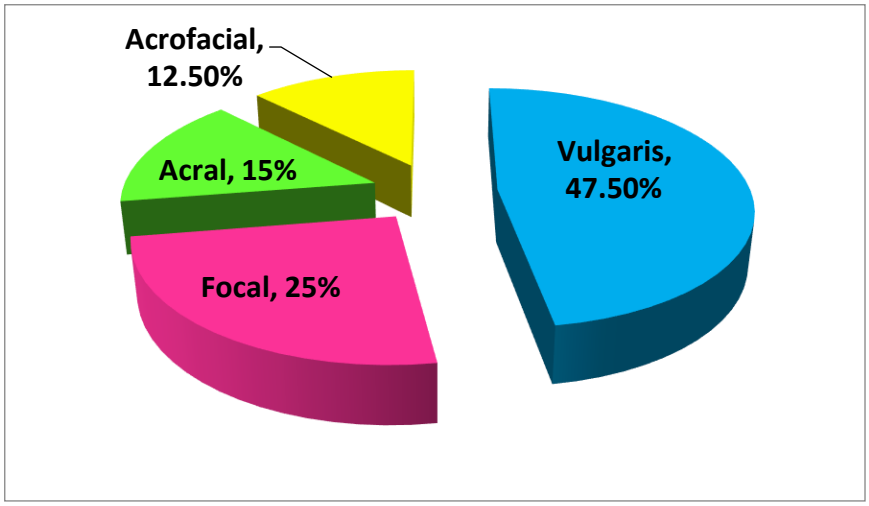

Fig. (2) Pie chart for types of disease among vitiligo patients.

3. Discussion

Vitiligo is a skin disorder defined by the loss of skin pigmentation, primarily owing to the depletion of melanocytes, resulting in the obvious bleaching of afflicted regions. A distinguishing feature of vitiligo is the appearance of pigment- free, nonscaly, chalky-white maculeswith distinct borders [11].

Our understanding of vitiligo's causes has significantly advanced. It is now widely accepted as an autoimmune disorder linked to various factors such as metabolism, oxidative stress, cellular detachment, genetic predisposition, and environmental influences. The psychological impact of vitiligo can be distressing and significantly affect a person's daily life [7, 12].

UCP2 is a mitochondrial inner membrane protein that is a member of the uncoupling protein family. Its principal role is to control mitochondrial membrane potential and discharge metabolic energy, hence limiting oxidative stress buildup [13, 14].

The continual fission and fusion processes of mitochondria are governed by dynamin-related proteins, a group of large GTPases (Drps). Drp1 is the principal mediator of mitochondrial fission; it is situated inthe cytoplasm and is drawn to specific sites on the mitochondrial surface for division. [15, 16].

Considering the importance of mitochondrial regulatory proteins in autoimmunity, the expression of these proteins, such as UCP2 and Drp1, may be related with autoimmune illnesses such as vitiligo. Therefore, the objective of this case-control study was to investigate the levels of UCP2 and Drp1 gene expression in the plasma of forty vitiligo patients selected from the Dermatology and Venereology Department at Benha University Hospitals. The research also included 40 age- and gender-matched healthy controls. The goal was to uncover any alterations in gene expression levels and investigate their link with the degree and activity of vitiligo.

Gene expression levels of UCP2 and Drp1 in vitiligo patients were significantly different from those of healthy controls, according to the findings of this study.. As an inner mitochondrial membrane protein, UCP2 is essential for maintaining mitochondrial membrane potential and limiting oxidative stress buildup. Therefore, decreased UCP2 expression may contribute to increased oxidative stress inside the melanocytes, resulting in their depletion and eventual depigmentation in vitiligo [8, 17].

In addition, the elevation of Drp1 gene expression in vitiligo patients suggests an accelerated mitochondrial fission process. [18, 19].

This study's correlation analysis found a strong relationship between the levels of gene expression for UCP2 and Drp1 and the degree and activity of vitiligo. The correlation between decreased UCP2 expression and increasing disease severity suggests a relationship between mitochondrial malfunction and the development of vitiligo. In addition, the correlation between the overexpression of Drp1 and disease activity suggests that enhanced mitochondrial fission may belinked to the active stages of vitiligo.

4. Conclusion

In conclusion, this case-control study provides evidence of altered geneexpression levels of UCP2 and Drp1 in vitiligo patients. The downregulation of UCP2 and upregulation of Drp1 suggest mitochondrial dysfunction and dysregulated mitochondrial dynamics in vitiligo pathogenesis.

markers for vitiligo. Further research inthis area could contribute to the development of targeted therapeutic approaches and personalized medicine for vitiligo patients.

References

[1] K. AL-smadi, M. Imran, V.R. Leite-Silva, Y. Mohammed. Vitiligo: A Review of Aetiology, Pathogenesis, Treatment, and Psychosocial Impact. Cosmetics;10:84. 2023

[2] W.L. Chang, W.R. Lee, Y.C. Kuo, Y.H. Huang. Vitiligo: An Autoimmune Skin Disease and its Immunomodulatory

Therapeutic Intervention. Front Cell Dev Biol;9:797026. 2021
[3] J. Chen, S. Li, C. Li. Mechanisms of melanocyte death in vitiligo. Medicinal Research Reviews;41:1138-66. 2021
[4] R.A. Spritz, G.H. Andersen. Genetics of Vitiligo. Dermatol Clin;35:245-55. 2017
[5] E.L. Katz, J.E. Harris. Translational Research in Vitiligo. Front Immunol;12:624517. 2021
[6] S.A. Sinenko, T.Y. Starkova, A.A. Kuzmin, A.N. Tomilin. Physiological Signaling Functions of Reactive Oxygen Species in Stem Cells: From Flies to Man. Front Cell Dev Biol;9:714370. 2021
[7] W.L. Chang, C.H. Ko. The Role of Oxidative Stress in Vitiligo: An Update on Its Pathogenesis and Therapeutic Implications. Cells;12. 2023
[8] F. Papaccio, B. Bellei, M. Ottaviani, A. D'Arino, M. Truglio, S. Caputo, et al. A Possible Modulator of Vitiligo Metabolic Impairment: Rethinking a PPARγ Agonist. Cells;11. 2022
[9] M.T. Breitzig, M.D. Alleyn, R.F. Lockey, N. Kolliputi. A mitochondrial delicacy: dynamin-related protein 1 and mitochondrial dynamics. Am J Physiol Cell Physiol;315:C80-c90. 2018
[10] J.Y. Jin, X.X. Wei, X.L. Zhi, X.H. Wang, D. Meng. Drp1-dependent mitochondrial fission in cardiovascular disease. Acta Pharmacol Sin;42:655- 64. 2021
[11] M.L. Frisoli, K. Essien, J.E. Harris. Vitiligo: Mechanisms of Pathogenesis and Treatment. Annu RevImmunol;38:621-48. 2020
[12] Y. Xuan, Y. Yang, L. Xiang, C. Zhang. The Role of Oxidative Stress in the Pathogenesis of Vitiligo: A Culprit for Melanocyte Death. Oxid Med Cell Longev;2022:8498472. 2022
[13] G. Pierelli, R. Stanzione, M. Forte, S. Migliarino, M. Perelli, M. Volpe, et al. Uncoupling Protein 2: A Key Player and a Potential Therapeutic Target in Vascular Diseases. Oxid Med Cell Longev;2017:7348372. 2017
[14] M. Čater, L. Križančić Bombek. Protective Role of Mitochondrial Uncoupling Proteins against Age- Related Oxidative Stress in Type 2 Diabetes Mellitus. Antioxidants (Basel);11. 2022
[15] L. Tilokani, S. Nagashima, V. Paupe, J. Prudent. Mitochondrial dynamics: overview of molecular mechanisms. Essays Biochem;62:341- 60. 2018
[16] A. Green, T. Hossain, D.M. Eckmann. Mitochondrial dynamics involves molecular and mechanical events in motility, fusion and fission. Front Cell Dev Biol;10:1010232. 2022
[17] Z. Lei, S. Yu, Y. Ding, J. Liang, Y. Halifu, F. Xiang, et al. Identification of key genes and pathways involved in vitiligo development based on integrated analysis. Medicine (Baltimore);99:e21297. 2020
[18] L. Ren, X. Chen, X. Chen, J. Li, B. Cheng, J. Xia. Mitochondrial Dynamics: Fission and Fusion in Fate Determination of Mesenchymal Stem Cells. Front Cell Dev Biol;8:580070. 2020
[19] M. Zerihun, S. Sukumaran, N. Qvit. The Drp1-Mediated Mitochondrial Fission Protein Interactome as an Emerging Core Player in Mitochondrial Dynamics and Cardiovascular Disease Therapy. Int J Mol Sci;24. 2023