BENHA MEDICAL JOURNAL bmj

Print ISSN 1110-208X.

Online ISSN 2357-0016

Nicastrin in Focus: Illuminating a New Path in Vitiligo Research

Shymaa M. Rezk [a], Asmaa M. El-Refai[a], Hamasat A. Abdel-Khalik[b], Huda A. Abdel-Maksoud[a], Eman M. Hassan[a]

[a] Dermatology and Andrology Department, Faculty of Medicine Benha University, Egypt.

[b] Clinical and Chemical Pathology Department, Faculty of Medicine Benha University, Egypt.

Corresponding to:
Dr. Shymaa M. Rezk. Dermatology and Andrology Department, Faculty of Medicine Benha University, Egypt.

Email:
Shimaa.rezk@fmed.bu.edu.eg

Received: 8 July 2025

Accepted: 28 August 2025

Abstract:

Background: Multiple factors, including metabolic problems, oxidative stress, production of inflammatory mediators, cell detachment, and immunological responses- could play a role in vitiligo by causing melanocytes to cease functioning. Nicastrin is a type 1 membrane glycoprotein, which has one transmembrane portion at its C-terminus and a big extracellular domain (ECD). Nicastrin- including 709 amino acids and glycosylation ranging from 30 to 70 kDa- is a major part of the whole human γ-secretase, making up around two-thirds of its 230 kDa apparent molecular mass. It is believed that the Nicastrin ECD is pivotal in γ-secretase recruitment. Purpose: The objective was to compare vitiligo patients' serum nicastrin levels to those of healthy controls and to explore whether there was a correlation between vitiligo extent and nicastrin levels. **Subjects and Methods:** A case-control study was carried out on 50 patients with vitiligo and 30 healthy controls. The Vitiligo Area Scoring Index (VASI) was used. The serum level of nicastrin was measured using enzyme-linked immunosorbent assay (ELISA). **Results:** Nicastrin levels were significantly lower among patients with vitiligo than the control subjects, and lower serum nicastrin levels were considered a predictor of higher VASI. **Conclusions:** It is well known that vitiligo greatly impacts quality of life. Decreased plasma nicastrin levels in patients with vitiligo correlate with severity. It is believed that nicastrin is a crucial component in vitiligo's patho-physiology and might be a useful clinical indicator of the severity of the illness.

Keywords: Vitiligo; Nicastrin; γ-secretase

Introduction

Vitiligo is an acquired condition characterised by chronic skin depigmentation. While the exact origin is still a mystery, we do know that it manifests as a selective loss of melanocytes, which in turn causes pigment dilution in the affected skin and mucosa. Melanocyte precursors can be identified in the hair follicle bulge, while developed, pigment-producing melanocytes can be located in the epidermis' basal layers and the hair matrix **(1)**.

Several processes, including immunological attack or cell degeneration and detachment, may be implicated in the increasing loss of melanocytes. The differences in clinical patterns led to the assumption that the pathogenetic mechanisms causing non-segmental and segmental vitiligo were unique. Somatic mosaicism or a neural hypothesis has therefore been proposed for the segmental type **(2)**.

Nicastrin- a component of the γ-secretase complex- is a transmembrane type I glycoprotein essential for the complex's assembly and function. It acts as a substrate receptor, recruiting specific proteins, like beta-amyloid precursor protein and Notch receptors, for cleavage by the γ-secretase complex. This process, known as proteolysis, is crucial for various cellular functions, including development and signaling (3). Hermasch et al. (4) found that nicastrin mutations encoding null alleles cause pigment homeostasis loss in zebrafish. In comparison, the missense mutation was less destructive, retaining enough nicastrin function to keep zebrafish coloration. Their findings indicated that one of the roles of nicastrin in humans is to decrease inflammatory responses in the skin, which may alter skin pigmentation.

The objective of the current study was to compare vitiligo patients' serum nicastrin levels to those of healthy controls and to explore whether there was a correlation between vitiligo extent and nicastrin levels.

Subjects and methods

This is prospective case-control research. Participants were chosen from the Dermatology, Venereology, and Andrology outpatient clinic at Benha University Hospitals. The study was conducted from December 2021 till January 2023. All necessary ethical considerations for human subjects' research were met, and the study was approved prior to the study, by the Research Ethics Committee of Benha Faculty of Medicine, Benha University **(approval code: Ms.22.11.2020)**. All patients were asked to sign a written informed consent form before they could be enrolled in the clinical investigation. Fifty vitiligo patients and thirty healthy controls participated in this study. Patients with non-segmental vitiligo- were eligible for the research. This study excluded individuals who were currently pregnant or lactating, had chronic liver disease or autoimmune diseases, patients with debilitating diseases, and patients receiving any topical treatment [for at least one month] or systemic therapy [for at least 3 months] before the study.

All patients underwent comprehensive history taking, general examination, and assessment of other systems to exclude any signs of chronic illness. The patients were thoroughly evaluated clinically, and the spread of vitiligo was determined by the Vitiligo Area Scoring Index (VASI) **(5)**.

Blood sampling

Five milliliters of blood were taken under strict aseptic conditions, left to clot, and subsequently spun at 3000 rotations per minute for ten minutes to extract serum. The serum was then transferred to a sterile Eppendorf tube and preserved at -20°C until it was tested.

Laboratory investigations

Serum nicastrin level was measured using the Fine Test Human (Nicastrin) ELISA Kit, Catalogue No.: EH15003. It relied on the technique of sandwich enzyme-linked immunosorbent assay. Plates with 96 wells were pre-coated with capture antibody.

The detecting antibody was the biotin-conjugated antibody. Wash buffer was used to wash the wells after adding the standards, test samples, and biotin-conjugated detection antibody.

Statistical analysis

The Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 25.0, Armonk, NY: IBM Corp., 2017) was used to edit, code, and tabulate the gathered data [(6)]. Data were displayed and analyzed appropriately based on each parameter's data type. Numerical data was described using the following terms: the median, mean, range, standard deviation (±SD), and standard error (±SE). For non-numerical data, percentages and frequencies- were utilized for description.

Comparisons between the different study groups were conducted using the Mann-Whitney test (U test), the chi-square test, the receiver operating characteristic (ROC) curve, correlation analysis, regression analysis, and logistic regression analysis to measure the degree of association between two numerical variables.

The strength of an association between two variables can be expressed as an odds ratio (OR). If the p-value is less than or equal to 0.05 with a 95% confidence interval, it is regarded as significant.

Results

The study was conducted on 50 patients with vitiligo, of whom 54.0% were males and 46.0% were females. The mean age was 29.30 +/- 2.07 years. In addition, 30 healthy individuals were included as a control group, of whom 40% were males and 60% were females, and a mean age of 29.20 ± 2.68 years. The mean disease duration was 9.44 ± 1.02 years. Lower limbs were affected in all cases studied (100%).

The mean VASI was 15.18 ± 0.94 and ranged from 10 to 35. Depending on VASI, cases were stratified into moderate (10-19) to severe (above 20).

The median serum Nicastrin level was statistically significantly lower in the vitiligo group (242.15 ng/ml) than in the control group (355.85 ng/ml) ($p < 0.001$) **(Figure 1).**

Table-1 shows that among vitiligo patients, serum nicastrin level showed a significant negative correlation with duration, VASI score, and BSA, while no significant correlations were found regarding age.

Table 1: Correlation between serum Nicastrin level and different parameters among studied vitiligo patients.

	Serum Nicastrin level (ng/mL)	
	Spearman	**P**
Age	-0.233	0.104
Duration	-0.699	<0.001*
VASI Score	-0.992	<0.001*
BSA	-0.992	<0.001*

*: Significant when p-value ≤ 0.05.

Abbreviations: BSA: body surface area; ng/mL: nanogram per millilitre; VASI: the vitiligo area scoring index.

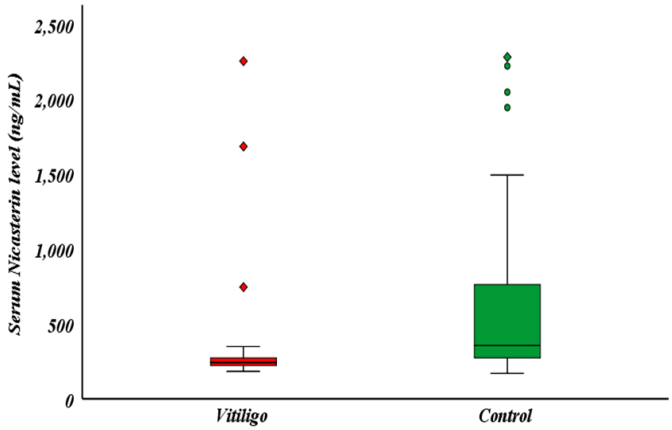

Figure 1. Boxplot compares serum nicastrin levels among vitiligo patients and the control group.

Discussion

In the current study, serum levels of nicastrin were investigated in patients with vitiligo and a group of healthy control participants. Results of the current work showed a significant decrease in serum nicastrin levels in the patients' group, in contrast to the control group ($p < 0.001$).

In the current study, lower limbs were affected in all cases (100%), and upper limbs were affected in 70%. In line with the present study, Phulari et al. [7] found that 48% of cases occurred on the leg, followed by 42% occurring on the forearms, 38% on the hands, 36% on the abdomen, and 28% on the face, in that order.

The present study reported that the median serum nicastrin level was significantly lower in the vitiligo group than in the control group. After reviewing the current literature, serum levels of nicastrin have not been previously evaluated in vitiligo. However, in the study of Hsu et al. [8], a zebrafish insertional mutant with a substantial decrease in nicastrin mRNA was shown to have a deficiency in melanosome maturation, enlargement of the mitochondria depending on tyrosinase, and death of the melanophore cells. The depigmentation abnormalities are proven to be caused by the inactivation of γ-secretase.

Wang et al. [9] also found that when nicastrin transcript levels dropped significantly, it caused serious harm to the melanophores, which then attracted macrophages that started to engulf the damaged cells. These results demonstrate that the inflammatory reaction begins close to the necrotic-like melanophore. In a clinical experiment [10], no conclusive pathological research has been documented; however, γ-secretase inhibitor medication did cause differences in hair color and pigment loss in animal models.

To assess the mRNA expression of genes involved in melanin production and Notch signaling pathways, Li and colleagues [11] conducted research and created a sequence that targets nicastrin mRNA in the zebrafish. The nicastrin gene controls melanin formation in zebrafish, which the researchers found to be an effect of melanocyte biological processes.

According to our present investigation, there was a strong inverse relationship between VASI and serum nicastrin levels. Low serum nicastrin levels may be linked to an increased risk of vitiligo susceptibility and severity.

Conclusions

Based on current results, serum nicastrin could be a promising marker for objectively evaluating vitiligo severity and occurrence.

Conflicts of Interest:

The authors have no conflict of interest to declare.

References

1. Okoro U, Usatine RP, Heath CR. DX across the Skin Color Spectrum. Quadrant Healthcom Inc.: Parsippany, NJ, USA. 2023 Feb 1; 111:106-7.
2. Bergqvist C, Ezzedine K. Vitiligo: a review. Dermatology. 2020 Nov 13;236(6):571-92.
3. Choi JH, Han J, Theodoropoulos PC, Zhong X, Wang J, Medler D, et al. Essential requirement for nicastrin in marginal zone and B-1 B cell development. Proceedings of the National Academy of Sciences. 2020 Mar 3;117(9):4894-901.
4. Hermasch MA, Janning H, Perera RP, Schnabel V, Rostam N, Ramos-Gomes F, et al. Evolutionary distinct roles of γ-secretase subunit nicastrin in zebrafish and humans. Journal of Dermatological Science. 2022 Feb 1;105(2):80-7.
5. Hamzavi I, Jain H, McLean D, Shapiro J, Zeng H, Lui H. Parametric modeling of narrowband UV-B phototherapy for vitiligo using a novel quantitative tool: the Vitiligo Area Scoring Index. Archives of dermatology. 2004 Jun 1;140(6):677-83.
6. Peacock JL, Peacock PJ. Oxford handbook of medical statistics. Oxford University Press; 2020 Jun 11.
7. Phulari YJ, Kukreja R, Hiremath RN, Patil CC, Patel P. Vitiligo: Prevalence, Clinical Patterns, and Efficacy of Narrow Band Ultraviolet B Phototherapy. Clinical Dermatology Review. 2023 Apr 1;7(2):153-7.
8. Hsu CH, Liou GG, Jiang YJ. Nicastrin deficiency induces tyrosinase-dependent depigmentation and skin inflammation. Journal of Investigative Dermatology. 2020 Feb 1;140(2):404-14.
9. Wang B, Yang W, Wen W, Sun J, Su B, Liu B, et al. γ-Secretase gene mutations in familial acne inversa. Science. 2010 Nov 19;330(6007):1065.
10. Hamada H, Watanabe M, Lau HE, Nishida T, Hasegawa T, Parichy DM, et al. Involvement of Delta/Notch signaling in zebrafish adult pigment stripe patterning. Development. 2014 Jan 15;141(2):318-24.
11. Li W, Jia W, Zhang Y, Lin L, Li C. Construction of a nicastrin gene-silenced zebrafish model and a primary study on the mechanism of abnormal pigmentation. Chinese Journal of Dermatology. 2021:402-7.

To cite this article: Shymaa M. Rezk, Asmaa M. El-Refai, Hamasat A. Abdel-Khalik, Huda A. Abdel-Maksoud, Eman M. Hassan. Nicastrin in Focus: Illuminating a New Path in Vitiligo Research. BMFJ XXX, DOI: 10.21608/bmfj.2026.401392.2520.