OPEN ACCESS Freely available online

Hair Therapy & Transplantation

ISSN: 2167-0951

Short Communication

Nonsynonymous Variant in *CCHCR1* as a Susceptibility Gene for Alopecia Areata

Nagisa Yoshihara, Shigaku Ikeda*

Department of Dermatology and Allergology, Juntendo University, Tokyo, Japan

DESCRIPTION

Alopecia Areata (AA) affects 1-2% of the population and is especially common in young women [1]. In severe cases, hair loss occurs over a wide area of the head, and sometimes the symptoms spread systemically, substantially reducing the patient's Quality of Life (QoL) due to their appearance. The condition is considered an autoimmune disease of the Hair Follicle (HF) during the growth phase. Although the cause is not clear, it is suspected that triggers such as viral infection and mental stress may cause the collapse of HF immune privileges, and autoreactive cytotoxic CD8+ NKG2D+ T cells may trigger an autoimmune response targeting HF autoantigens [2,3]. AA is recognized as a type 1 inflammatory disease, but the details of its cause and pathophysiology are still unknown. Oral Janus Kinase (JAK) inhibitors have become a treatment option in recent years [4], but there is no radical treatment, and symptomatic treatment is the convention. AA is an intractable chronic skin disease that is more resistant to treatment and recurs in many cases.

In our recent study, we identified the *CCHCR1* gene as a susceptibility gene for Alopecia Areata by association analysis using microsatellite markers and next-generation sequencing analysis [5]. A nonsynonymous single-nucleotide polymorphism risk variant (rs142986308; p. Arg to Trp) was detected in the *CCHCR1* gene at the MHC region in 15% of AA patients participating in genomic analysis. In 16.1% of heterogeneous mice and 27.1% of homogeneous mice genome-edited using *CRISPR/Cas9*, non-symptomatic patchy alopecia lesions similar to human AA, including black dots and tapering hair, were observed. The incidence of hair loss was significantly higher in *CCHCR1* genome-edited mice than in C3H/HeJ mice, which have been recognized and used as AA animal models [6].

In addition, when the hair morphology of these genome-edited mice was examined with electron microscopy, abnormal cuticle formation was observed, suggesting that *CCHCR1* genome-edited mice had abnormal keratinization. Subsequently, gene expression microarray analysis of dorsal and ventral skin biopsies of homogeneously edited mice showed upregulation of hair-related protein genes, such as hair keratin and *Keratin-Related Peptide* (*KRTAP*) genes, which are major components of the hair shaft, compared to control mice.

To verify whether similar results could be obtained in humans carrying the *CCHCR1* non-synonymous variant, the hair around the hair loss area of AA patients with the variant was evaluated by electron microscopy and gene expression microarray analysis. Under the electron microscope, abnormal cuticle formation was observed, and in microarray analysis, AA patients with the variant had abnormalities in the keratin gene compared to AA patients without the variant [5].

Next, a stress test was performed on *CCHCR1* gene knockout (KO) mice created by the Cre/LoxP system to confirm whether AA-like symptoms appeared. Briefly, we used a water avoidance stress test in which a narrow platform large enough to accommodate one mouse was placed in a water tank, and the mouse was placed on the stand for 2 hours for a total of 10 days. At the eighth week after the stress test, 25% of *CCHCR1* gene knockout mice developed AA-like symptoms [7]. Pathological findings at the hair loss site showed mild lymphocyte infiltration around the hair follicle. The infiltrating lymphocytes were CD4- and CD8-positive lymphocytes. To investigate the biological functions that may underlie hair loss, gene expression microarray analysis using the dorsal skin of *CCHCR1* KO mice showed upregulation of the keratin and *KRTAP* genes compared to control mice. These results were similar to those obtained by microarray analysis on *CCHCR1* genome-edited mice and AA patients with the variant, as shown above [7].

These findings strongly indicate that even in a mouse model, AA is believed to develop due to overlapping factors in addition to the genetic background. Furthermore, the fact that this variant was detectable in 5% of normal control individuals also strongly suggests that other factors in addition to the genetic background are necessary to cause AA [5].

Next, we evaluated the clinical characteristics of AA patients with and without the variant. We examined 1) sex distribution, 2) age of onset, 3) clinical type, 4) family history of AA, 5) history of atopic dermatitis, 6) response to steroid therapy, and 7) recurrence rate for AA in patients with the variant (n=12) and

Correspondence to: Shigaku Ikeda, Department of Dermatology and Allergology, Juntendo University, Tokyo, Japan, E-mail: ikeda@juntendo.ac.jp

Received: 26-Jul-2023, Manuscript No. HTT-23-25825; **Editor assigned:** 28-Jul-2023, PreQC No: HTT-23-25825 (PQ); **Reviewed:** 14-Aug-2023, QC No. HTT-23-25825; **Revised:** 21-Aug-2023, Manuscript No: HTT-23-25825 (R); **Published:** 28-Aug-2023; DOI: 10.35248/2167-0951.23.13.221

Citation: Yoshihara N, Ikeda S (2023) Nonsynonymous Variant in *CCHCR1* as a Susceptibility Gene for Alopecia Areata. Hair Ther Trasplant. 13:221.

patients without the variant (n=142). Multivariate logistic regression analysis and Fisher tests were used for statistics. The results indicated that the patients with the variant tended to respond better to steroid treatment and had significantly higher recurrence rates than patients without the variant. There was no difference between the two groups for other characteristics [8].

The hair of patients in both groups was examined by electron microscopy. When the hair cross-section and hair shaft structure were observed with electron microscopy, the hair of AA patients with the variant exhibited abnormal cuticle formation, especially at sites close to the scalp and sites between the hair slightly away from the scalp. In addition, the hair of patients without the variant had a circular hair cross-section similar to that of healthy individuals, while the cross-section of the hair of patients with the variant was oval, suggesting that there is an abnormality in the hair shaft morphology in addition to cuticle abnormality in patients with the variant [8].

CONCLUSION

The treatment of AA has entered a new era, and not only steroids but also JAK inhibitors have been added to the treatment options. We expect that the variant in *CCHCR1* may be a prognostic marker for short-term steroids when determining treatment options, and further research is needed to investigate the effect of steroids and JAK inhibitors in patients with or without the variant. In the future, we will attempt to introduce personalized medical care, such as choosing whether to perform steroid systemic therapy according to the presence or absence of this variant.

CONFLICT OF INTEREST

None.

REFERENCES

1. Safavi KH, Muller SA, Suman VJ, Moshell AN, Melton LJ, Incidence of alopecia areata in Olmsted County, Minnesota, 1975 through 1989. Mayo Clin Proc. 1995;70(7):628-633.
2. Xing L, Dai Z, Jabbari A, Cerise JE, Higgins CA, Gong W, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043-1049.
3. Ito T, Ito N, Saatoff M, Hashizume H, Fukamizu H, Nickoloff BJ, et al. Maintenance of hair follicle immune privilege is linked to prevention of NK cell attack. J Invest Dermatol. 2008;128(5): 1196-1206.
4. King B, Ohyama M, Kwon O, Zlotogorski A, Ko J, Mesinkovska NA, et al. Two phase 3 trials of baricitinib for alopecia areata . N Engl J Med. 2022;5(18):1687-1699.
5. Oka A, Takagi A, Komiyama E, Yoshihara N, Mano S, Hosomichi K, et al. Alopecia areata susceptibility variant in MHC region impacts expressions of genes contributing to hair keratinization and is involved in hair loss. EBioMedicine. 2020;57:102810.
6. Sundberg JP, Cordy WR, King LE. Alopecia areata in aging C3H/HeJ mice. J Investig. Dermatol. 1994;102:847-856.
7. Zhao Q, Koyama S, Yoshihara N, Takagi A, Komiyama E, Wada A, et al. The alopecia areata phenotype is induced by the water avoidance stress test in *CCHCR1*-deficient mice. Biomedicines. 2021;9:840.
8. Koyama S, Yoshihara N, Takagi A, Komiyama E, Oka A, Ikeda S. Clinical findings, response to steroid treatment, and recurrence rate in alopecia areata patients with or without a nonsynonymous variant of coiled-coil alpha-helical rod protein 1. Ann Dermatol. In press.