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Letter to Editor

## There is no proven association between sensitization to benzyl salicylate and frontal fibrosing alopecia

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To the Editor,

Pastor-Nieto *et al.* report a case series of 36 patients with frontal fibrosing alopecia (FFA) who have undergone patch testing.<sup>1</sup> Based on their observations, they hypothesize that contact sensitization to benzyl salicylate may occur as a cause or consequence of the pathogenic mechanisms underlying this disorder. We wish to comment on the possible relationship between FFA and contact sensitization to benzyl salicylate described in this study.

FFA is a sub-variant of lichen planopilaris characterized by scarring hair loss affecting the frontotemporal scalp, but also involvement of the occipital scalp, eyelashes, eyebrows, beard area and body.<sup>2</sup> It occurs primarily in postmenopausal women, although cases in younger women and men have also been reported.<sup>3</sup> Histologically, there is distinctive perifollicular lichenoid inflammation with fibrosis and follicular dropout in advanced disease.<sup>4</sup> In accordance with its histology, FFA pathogenesis is postulated to be driven by collapse of hair follicle immune privilege, which subsequently facilitates T helper 1 cell-mediated destruction of follicular stem cells and irreversible hair loss.<sup>5</sup> A genome-wide association study in 1016 female FFA patients has also established a robust association between FFA and causal genetic variation (*HLA-B\*07:02*, *CYP1B1*, *SEMA4B* and *ST3GAL1*), indicating that FFA is underpinned by a significant genetic predisposition.<sup>6</sup> Nonetheless, a dramatic worldwide rise in FFA incidence since its first description in 1994 has also led to speculation regarding potential environmental triggers, e.g., sunscreens, although causal associations have not yet been demonstrated.<sup>7,8</sup>

Pastor-Nieto *et al.* observed positive patch test reactions to benzyl salicylate in 8 of 36 patients with FFA (22%). Consequently, the authors have reported an association between FFA and sensitization to benzyl salicylate. Although the reported patch test positivity to benzyl salicylate in FFA patients (22%) is higher than that of a comparable regional patch tested population (1.1%),<sup>1</sup> there remain significant doubts regarding this relationship. First, the selection procedure for inclusion in this study is unclear. Given that 20 of 36 (69.4%) FFA participants had a current or preceding history of dermatitis, it is reasonable to assume that

only FFA patients in which there was a genuine clinical suspicion of contact allergy were tested. If true, this represents a genuine selection bias, and the study results may not be generalizable to the FFA population at large. Furthermore, if there was a genuine clinical suspicion of contact allergy in these FFA patients, this study may over-estimate the prevalence of benzyl salicylate sensitivity in the wider FFA population. Secondly, the study's small sample size and absent control group raise concerns that the specific association reported may be the result of chance. Lastly, 7 of 8 reported reactions to benzyl salicylate were weak positive (+, n=4) or equivocal (?+, n=3) and it is unclear for how many FFA patients benzyl salicylate sensitivity relevance was established or what criteria were used. Thus, the strength of any existing association remains uncertain.

Subsequently, Pastor-Nieto *et al.* propose several hypotheses to account for their observed association between benzyl salicylate sensitivity and FFA, notably suggesting that benzyl salicylate could be a sole or significant factor in FFA pathogenesis. However, benzyl salicylate is a weak sensitizer and poses a low risk as a contact allergen.<sup>9</sup> It is, therefore, doubtful whether cutaneous sensitization to benzyl salicylate alone could induce the profound lichenoid inflammatory reaction observed in FFA. Moreover, it is suggested that benzyl salicylate could contribute to FFA through endocrine disruption, a mechanism that lacks supporting evidence in the wider literature. Although hypothesis generation remains a central aspect of the scientific process that necessitates speculation, we suggest that these hypotheses lack robust evidential backing.

In conclusion, in our opinion an association between contact allergy to benzyl salicylate and FFA is not clearly established by this study and it remains unlikely that cutaneous sensitization to benzyl salicylate alone significantly drives FFA pathogenesis, the epicenter of which is autoimmunity, T cell homeostasis and xenobiotic clearance, as unequivocally identified previously.<sup>6</sup> Since FFA is a complex or multifactorial disorder with evidence of a higher disease risk in genetically predisposed individuals, the role of environmental triggers in the pathobiology of FFA will require careful investigation via a gene-environment interaction study.

## References

1. Pastor-Nieto MA, Gatica-Ortega ME, Sánchez-Herreros C, Vergara-Sánchez A, Martínez-Mariscal J, De Eusebio-Murillo E. Sensitization to benzyl salicylate and other allergens in patients with frontal fibrosing alopecia. *Contact Dermatitis*. 2021; 84(6):423-30.
2. Kossard S, Lee M-S, Wilkinson B. Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. *J Am Acad Dermatol*. 1997;36(1):59–66.
3. Kanti V, Constantinou A, Reygagne P, Vogt A, Kottner J, Blume-Peytavi U. Frontal fibrosing alopecia: demographic and clinical characteristics of 490 cases. *J Eur Acad Dermatology Venereol*. 2019;33(10):1976–83.
4. Stefanato CM. Histopathology of alopecia: a clinicopathological approach to diagnosis. *Histopathology*. 2010;56(1):24–38.
5. Harries MJ, Paus R. The pathogenesis of primary cicatricial alopecias. *Am J Pathol*. 2010 Nov 1;177(5):2152–62.
6. Tziotzios C, Petridis C, Dand N, et al. Genome-wide association study in frontal fibrosing alopecia identifies four susceptibility loci including HLA-B\*07:02. *Nat Commun*. 2019;10(1):1150.
7. Kossard S. Postmenopausal frontal fibrosing alopecia: scarring alopecia in a pattern distribution. *Arch Dermatol*. 1994;130(6):770–4.
8. Tavakolpour S, Mahmoudi H, Abedini R, Kamyab Hesari K, Kiani A, Daneshpazhooh M. Frontal fibrosing alopecia: an update on the hypothesis of pathogenesis and treatment. *Int J Women's Dermatology*. 2019;5(2):116–23
9. Fernández-Canga P, Ruíz-González I, Varas-Meis E, Valladares-Narganes LM, Rodríguez-Prieto MA. Contact allergy to benzyl salicylate. *Contact Dermatitis*. 2017;76(5):315–6.