Assessment of familial risk in patients with hidradenitis suppurativa

DEAR EDITOR, Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder resulting in recurrent, painful nodules, abscesses and sinuses, with predilection for intertriginous sites.[1] In previous cohorts relying primarily on chart review, 30–40% of patients reported family history of disease,[2] but familial risk has not been formally assessed with more meticulous and focused data collection. A cohort of 676 patients with HS at the University of North Carolina Chapel Hill was enrolled in our clinical registry from August 2018 to December 2019, which collected detailed family history data using questionnaires and skilled interviewers. In total 57·5% of patients reported HS in either first- or second-degree relatives, including 49·5% with an affected first-degree relative. This suggests a possible genetic contribution to HS. This study's aim was to quantify familial risk in patients with HS. This study was approved by the University of North Carolina School of Medicine Institutional Review Board, approval #18-1209.

Sibling recurrence risk ratio (λs) is a metric of familial aggregation defined as the risk ratio of disease in the affected patient's siblings compared with prevalence in the general population.[3] λs is calculated using all available pedigree data from a set of probands and serves as a widely used metric of familial risk calculated based on pedigree data. Larger λs indicates high risk of disease among individuals with an affected sibling. Although environmental factors may also influence disease risk, λs quantifies potential genetic contributions of a disease. Parent–offspring recurrence risk (λo) is calculated similarly and also approximates familial risk, although in some instances offspring knowledge of parental disease is less complete than for siblings.

Pedigrees from 281 consecutively recruited patients from our registry were constructed and analysed. The registry contains data on affected and unaffected parents, grandparents, siblings, half-siblings and children with HS. Affected aunts, uncles, cousins and grandchildren were included when available. λs was determined using the formula outlined by Cordell and Olson.[4]

In total 80% of probands were female, while 53·4% were black, 42·6% white and 6·0% of other races. The median age was 35 years. Of 371 identified siblings, 74 are affected. Based on an overall estimated population risk of 1%, analysis of 280 pedigrees found a λs of 19·9, without significant difference by race. To avoid underestimating risk by including family members who may have been too young to develop disease, we evaluated a range of age thresholds (Figure 1a). Although we expected λs to increase as we excluded younger relatives who might not yet have developed disease, it decreased instead. This may indicate that patients are more aware of disease in younger relatives such as their children or siblings than in older, more distant relatives. Thus, excluding younger relatives may underestimate overall risk. λo was similarly found to be 18·6, although age data for offspring were often missing and limited meaningful calculations with age cutoffs. In comparison with λs from diseases with known genetic contributions (Figure 1b), the λs of 19·9 observed in HS is relatively high, consistently with a strong genetic contribution to the aetiology of HS. These findings are in concordance with a recent study of 58 twin pairs with HS. Dizygotic and monozygotic concordances were 0·08 and 0·31, respectively, with calculated heritability of 77%.[5] This is similar to the heritability of Crohn disease, which is consistent with our data.

In clinical practice, patients often inquire about disease risk for family members. Recent estimates suggest HS may affect 0·7–1% of the general population.[1] Assuming 0·7–1% prevalence, the λs of 19·9 indicates that 13·9–19·9% of siblings and offspring of patients may be affected. While it is possible that environmental effects such as shared microbiome characteristics, smoking and obesity among related individuals could explain familial clustering, there is a notable lack of reports suggesting concordance or spread between unrelated household contacts, spouses or sexual partners who share environments and close physical contact. The environment may influence susceptibility, but the more conspicuous clustering among related individuals suggests that genetic susceptibility plays a prominent role.

Our data are limited by lack of confirmed clinical diagnosis in relatives, but patients' reporting of typical and recurrent HS lesions in family members is likely highly predictive.[6] Only a single patient was adopted, and lacked knowledge about
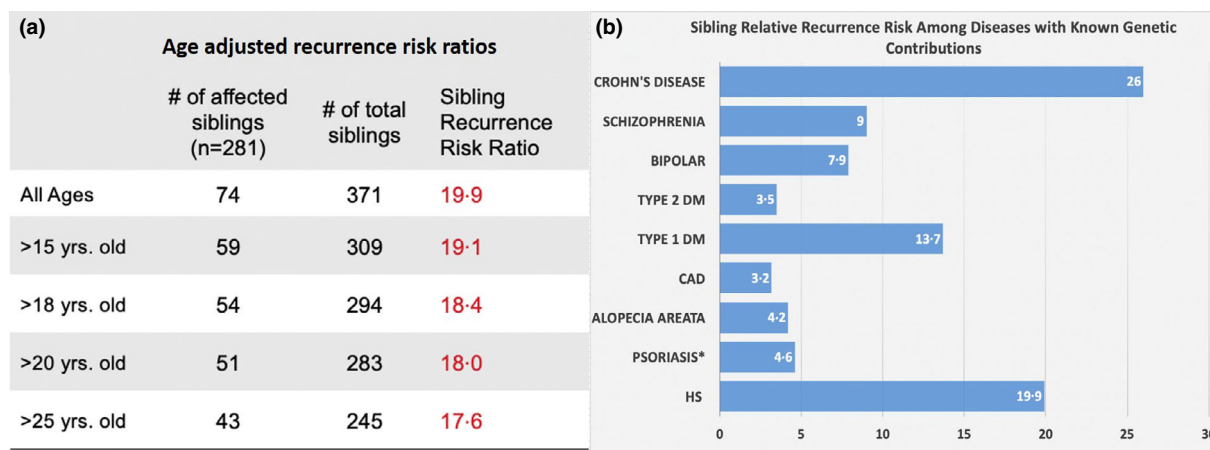
Figure 1 (a) Age-adjusted recurrence risk ratios of hidradenitis suppurativa (HS). (b) Sibling relative recurrence risk for HS compared with diseases with known genetic contributions.[7–9] *λs in psoriasis of 1·6–4·6 was calculated based on a reported estimate of 8–23% of first-degree relatives of patients with psoriasis being affected and an assumed population prevalence of 5%.[8] CAD, coronary artery disease; DM, diabetes mellitus.

family history, which did not significantly influence the λs estimation. We may also underestimate familial risk if patients are unaware of their family members' symptoms. In addition, we also did not analyse specific phenotypic or genetic factors that might influence familial risk due to the limited sample size, which prevents reasonably powered analyses of subcategories. Despite these limitations, an estimate of general familial risk for this population is highly valuable for clinicians counselling patients on the risk of disease development for children and other relatives, particularly as robust genetic data are currently unavailable.

Future research including genome-wide association studies is essential to characterize further the genetic, environmental and clinical factors that influence familial risk, and to understand better the genetic architecture of HS.

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References

1 Alikhan A, Sayed C, Alavi A *et al.* North American clinical management guidelines for hidradenitis suppurativa: a publication from the United States and Canadian Hidradenitis Suppurativa Foundations. Part I: diagnosis, evaluation, and the use of

complementary and procedural management. *J Am Acad Dermatol* 2019; **81**:76–90.

2 Schrader AM, Deckers IE, van der Zee HH *et al.* Hidradenitis suppurativa: a retrospective study of 846 Dutch patients to identify factors associated with disease severity. *J Am Acad Dermatol* 2014; **71**:460–7.

3 Wray NR, Yang J, Goddard ME, Visscher PM. The genetic interpretation of area under the ROC curve in genomic profiling. *PLOS Genet* 2010; **6**:e1000864.

4 Cordell HJ, Olson JM. Correcting for ascertainment bias of relative-risk estimates obtained using affected-sib-pair linkage data. *Genet Epidemiol* 2000; **18**:307–21.

5 van Straalen KR, Prens EP, Willemsen G *et al.* Contribution of genetics to the susceptibility to hidradenitis suppurativa in a large, cross-sectional Dutch twin cohort. *JAMA Dermatol* 2020; https://doi.org/10.1001/jamadermatol.2020.3630.

6 Esmann S, Dufour DN, Jemec GB. Questionnaire-based diagnosis of hidradenitis suppurativa: specificity, sensitivity and positive predictive value of specific diagnostic questions. *Br J Dermatol* 2010; **163**:102–6.

7 Risch N. Linkage strategies for genetically complex traits. I. Multilocus models. *Am J Hum Genet* 1990; **46**:222–8.

8 Gupta R, Debbaneh MG, Liao W. Genetic epidemiology of psoriasis. *Curr Dermatol Rep* 2014; **3**:61–78.

9 Petukhova L, Duvic M, Hordinsky M *et al.* Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. *Nature* 2010; **466**:113–7.