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Contribution of Genetics to the Susceptibility to Hidradenitis Suppurativa in a Large, Cross-sectional Dutch Twin Cohort

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IMPORTANCE Hidradenitis suppurativa is a chronic, inflammatory skin disease in which genetic factors are considered to play a role, with up to 38% of patients reporting a family history. Variations in the γ-secretase genes are found mainly in familial cases with an autosomal dominant pattern of inheritance. These variations are rare in the general population with hidradenitis suppurativa, even in patients who report a family history of the disease.

OBJECTIVE To assess the heritability of hidradenitis suppurativa in a nationwide Dutch twin cohort.

DESIGN, SETTING, AND PARTICIPANTS In this cross-sectional study on self-reported hidradenitis suppurativa conducted from 2011 to 2016, data were collected from twins participating in the surveys of the nationwide Netherlands Twin Register. All complete twin pairs answering the question on hidradenitis suppurativa in the survey were included: 978 female monozygotic twin pairs and 344 male monozygotic twin pairs and 426 female dizygotic twin pairs, 167 male dizygotic twin pairs, and 428 dizygotic twin pairs of the opposite sex. Statistical analysis was performed from July to November 2019.

MAIN OUTCOMES AND MEASURES The main outcome is the proportion of susceptibility to hidradenitis suppurativa due to additive genetic factors (narrow-sense heritability), dominant genetic factors, common or shared environmental factors, or unshared or unique environmental factors. The main outcome was evaluated prior to data collection.

RESULTS The prevalence of hidradenitis suppurativa among twin pairs was 1.2% (58 of 4686); the mean (SD) age was 32.7 (15.4) years. The narrow-sense heritability of hidradenitis suppurativa was 77% (95% CI, 54%-90%), with the remainder of the variance due to unshared or unique environmental factors based on an age-adjusted model combining additive genetic factors and unshared or unique environmental factors.

CONCLUSIONS AND RELEVANCE The high heritability found in this study suggests a stronger than previously assumed genetic basis of hidradenitis suppurativa. Environmental factors were also shown to contribute to the susceptibility to hidradenitis suppurativa, supporting a multifactorial cause of the disease. Moreover, the results of this study strongly support the need for a global genome-wide association study in the general population of patients with hidradenitis suppurativa.

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Supplemental content

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Hidradenitis suppurativa (HS) is a chronic, inflammatory skin disease in which genetic factors are thought to play a role.[1] Up to 38% of patients with HS report a family history of the disease, and several variations have been identified in the γ-secretase genes in familial cases.[2] However, these families often present with an autosomal dominant inheritance pattern and an atypical phenotype.[3] Moreover, γ-secretase variations could not be replicated in the general population with HS, even in patients with a family history of the disease.[4] This outcome signifies that the autosomal dominant inheritance pattern of HS may be limited to the familial forms with an atypical phenotype and that the γ-secretase variations may underlie only a limited number of HS cases.[4,5] In the general population, HS might arise from a different and more complex genetic origin than familial HS, or it might be more dependent on the presence of well-known environmental risk factors, such as smoking and obesity.[1]

Twin studies provide a unique and powerful approach to elucidate the contribution of genetic and environmental factors to the development of disease, but they are currently lacking in individuals with HS, to our knowledge.[6] Therefore, the aim of this study was to assess the proportion of susceptibility to HS that was due to genetic factors (heritability) in a nationwide Dutch twin cohort.

Key Points

Question What is the heritability of hidradenitis suppurativa in a nationwide Dutch twin cohort?

Findings In this cross-sectional study, the narrow-sense heritability of hidradenitis suppurativa was 77% (95% CI, 54%-90%), with the remainder of the variance due to unique environmental factors based on an age-adjusted model combining additive genetic factors and unshared or unique environmental factors.

Meaning The high heritability found in this study suggests a stronger genetic basis of hidradenitis suppurativa than previously assumed; the environmental factors were also shown to contribute to the susceptibility to hidradenitis suppurativa support a multifactorial cause of the disease.

Methods

Participants

In this cross-sectional study conducted from 2011 to 2016, the question "Has a medical doctor diagnosed the presence of recurrent, painful, and inflammatory lesions in the axillae or groin?" with the answer options "no," "yes, in the past," and "yes, present at the moment" was added to the eighth survey sent to adult participants of the Netherlands Twin Register.[7] The option "yes, in the past" was included as self-reported HS in the analysis. Patient characteristics were collected from the same survey. Zygosity of the twin pairs was previously assessed.[7]

Statistical Analysis

Statistical analysis was performed from July to November 2019. Probandwise concordance rates and tetrachoric correlations were calculated. Structural equation modeling using a liability threshold model was performed to assess the proportion of susceptibility to HS due to additive genetic factors (A), dominant genetic factors (D), common or shared environmental factors (C), or unshared or unique environmental factors (E) (eFigure in the Supplement). This main outcome was evaluated prior to data collection. Approval of this study was obtained from the of the Erasmus Medical Centre institutional review board, who considered filling out the study survey as providing informed consent.

A saturated model was fitted, and changes in the model fit were evaluated when constraining the thresholds across twin order and/or zygosity. Equating thresholds across twin order resulted in the best model fit based on the Akaike information criterion. Subsequently age-adjusted ACE models and ADE models were fitted, and nested submodels (ACE>AE>CE>E, ADE>AE>E) were tested for deterioration of the model fit based on the Akaike information criterion. To test the robustness of the obtained results, a sensitivity analysis was performed using a worst-case scenario in which the answer "yes, in the past" was included as no HS (eTable in the Supplement).

Statistical analyses were performed in R, version 3.6.1 (R Project for Statistical Computing), and structural equation modeling was performed using the package OpenMx.[8,9] All *P* values were from 2-sided tests, and results were deemed statistically significant at $P \leq .05$. Missing data were not imputed.

Results

A total of 2343 complete twin pairs (mean [SD] age, 32.7 [15.4] years) who answered the survey question about HS were included: 978 female monozygotic (MZ) pairs, 344 male MZ pairs, 426 female dizygotic (DZ) twin pairs, 167 male DZ pairs, and 428 DZ pairs of opposite sex. The prevalence of HS among these twin pairs was 1.2% (58 of 4686).

Probandwise concordance rates were higher for the MZ twins compared with the DZ twin pairs (0.31 vs 0.08; **Table 1**). All concordant MZ pairs were female, and the concordant DZ pair was an opposite-sex pair. No significant differences were found between the affected and unaffected siblings of the discordant pairs regarding median body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) or the percentage of current smokers (DZ twins: BMI, 21.9 [interquartile range, 20.9-25.0] and 59.1% [13 of 22] vs BMI, 23.6 [interquartile range, 21.0-25.8] and 57.1% [12 of 21]; and MZ twins: BMI, 22.1 [interquartile range, 20.6-24.6] and 70.0% [14 of 20] vs BMI, 22.2 [interquartile range, 20.3-24.2] and 59.1% [13 of 22]). Tetrachoric correlations in MZ twins (0.76 [95% CI, 0.74-0.78]) were more than twice that of DZ twin pairs (0.36 [95% CI, 0.31-0.41]), suggesting a genetic contribution to the susceptibility to HS (Table 1).

Fitting the genetic structural equation models showed that the ADE and ACE models were essentially equivalent based on

Table 1. Probandwise Concordance Rates and Tetrachoric Correlations

Twin pair	Concordant HS negative	Discordant	Concordant HS positive	Prevalence of HS, %	Probandwise concordance	Tetrachoric correlation (95% CI)
MZ pairs	1295	22	5	1.2	0.31	0.76 (0.74-0.78)
Female pairs	954	19	5	1.5	0.34	0.77 (0.74-0.79)
Male pairs	341	3	0	0.4	NA	0.67 (0.61-0.72)[a]
DZ pairs	996	24	1	1.3	0.08	0.36 (0.31-0.41)
Female pairs	410	16	0	1.9	NA	0.24 (0.15-0.33)[a]
Male pairs	165	2	0	0.6	NA	0.66 (0.56-0.74)[a]
Opposite-sex pairs	421	6	1	1.9	0.25	0.70 (0.65-0.75)

Abbreviations: DZ, dizygotic; HS, hidradenitis suppurativa; MZ, monozygotic; NA, not applicable.

[a] To correct for continuity, cells with a count of 0 were replaced with 1/30th of the discordant cell count to calculate tetrachoric correlations.

Table 2. Standardized Variance Components and Goodness-of-Fit Statistics

Model	Standardized variance components[a]			Fit statistics						Heritability, h^2 (95% CI)
	A	C/D	E	AIC	ΔAIC	−2LL	Δ−2LL	ep	*P* value	
Threshold model fitting										
Saturated	NA	NA	NA	−9349.64	NA	658.36	NA	8	NA	NA
Covariate age	NA	NA	NA	−9353.14	−3.50	658.86	0.50	6	.80	NA
Threshold T1 = T2	NA	NA	NA	−9350.68	−1.04	665.32	6.96	4	.14	NA
Threshold MZ = DZ[b]	NA	NA	NA	−9356.64	−7.00	659.36	1.00	4	.91	NA
Thresholds T1 = T2 and MZ = DZ	NA	NA	NA	−9352.25	−2.61	665.75	7.39	3	.19	NA
Genetic model fitting										
ACE	0.77	0.00	0.23	−9356.63	0.01[c]	659.37	0.01	5	NA	NC
ADE	0.70	0.07	0.23	−9356.64	0.00[c]	659.36	0.00	5	NA	NC
AE[b]	0.77	0.00[d]	0.23	−9358.63	−2.01	659.37	0.00	4	>.99	77% (54%-90%)
CE	0.00[d]	0.64	0.36	−9355.10	1.52	662.90	3.53	4	.06	NC
E	0.00[d]	0.00[d]	1.00	−9330.68	25.94	689.32	29.95	3	<.01	NC

Abbreviations: −2LL, −2 log likelihood; Δ−2LL, the difference in −2LL between the submodel and the main model; ep, estimated parameters; AIC, Akaike information criterion; ΔAIC, the difference in AIC between the submodel and the main model; DZ, dizygotic; h^2, narrow-sense heritability, defined as the proportion of genetic variance to total phenotypic variance; MZ, monozygotic; NA, not applicable; NC, not calculated; T1, twin 1; T2, twin 2.

[a] A represents the proportion of the variance explained by additive genetic effects, C represents the proportion of the variance explained by common or shared environmental effects, D represents the proportion of the variance explained by dominant genetic effects, and E represents the proportion of the variance explained by unique environmental effects.

[b] Indicates the best fitting model.

[c] Compared with best threshold model.

[d] Indicates fixed values.

the Akaike information criterion. Assessment of the nested submodels revealed the AE model as the most parsimonious model. From this model, the narrow-sense heritability of HS was calculated at 77% (95% CI, 54%-90%), with the remainder of the variance due to unshared or unique environmental factors (**Table 2**). Analysis of the worst-case scenario yielded similar results (heritability, 75% [95% CI, 37%-93%]; eTable in the Supplement).

Discussion

The results of this unique nationwide twin study suggest a genetic contribution to the susceptibility to common HS. The calculated heritability of HS of 77% (95% CI, 54%-90%) seems higher than the estimates published for other diseases with a well-known genetic component, such as psoriasis (68% [95% CI, 60%-75%]) and rheumatoid arthritis (65% [95% CI, 50%-77%]).[10,11] The heritability of HS is more in line with that of Crohn disease (0.75 [95% CI, unknown]).[12]

The affected twins had a relatively low median BMI compared with individuals in the current HS literature.[1] One explanation could be inherent to this specific population, as twins are known to have a lower birth weight and continue to have lower weight throughout their lives compared with singletons.[14] In addition, smoking status, a well-established risk factor for HS, was not different between discordant twin siblings.[1] The discordant twin pair design is a strong design to explore causality vs genetic correlations, and our results might indicate the absence of a causal association.[15]

The high heritability of HS found in our study is promising for future genome-wide association studies. Nonetheless, genome-wide association studies are known to account for less than the heritability found in twin studies, as some of the effect sizes for many common single-nucleotide variations are hidden below the genome-wide association study threshold.[16]

Limitations

This study has some limitations, including the use of a nonvalidated question. After sending out the study surveys, 3 questions were validated for the survey-based diagnosis of HS, with positive predictive values ranging from 0.85 to 0.89.[13] The question used in our study is similar to these validated questions with the exception of the answer option "yes, in the past." This option was based on the format of the preexisting questionnaire but could introduce recall bias. However, recall bias would not be different between MZ and DZ twins or between the co-twins, making it unlikely to have a significant influence on our results. Nonetheless, we performed a sensitivity analysis to address this potential issue and found similar outcomes, supporting the results from our primary analysis.

Another limitation of this study is that, owing to the low prevalence of HS and the female to male ratio of 3:1, the number of affected males in our population is limited. Therefore, the results of this study are almost exclusively driven by female patients, and no analysis could be performed regarding the existence of sex differences in the susceptibility to HS. Future twin studies would need to assess the potential influence of qualitative or quantitative sex differences on the heritability of HS.

Conclusions

The results of this nationwide twin study suggest a stronger than previously assumed contribution of genetic factors to the susceptibility to HS in the general population. Our results further support a multifactorial cause of the disease and support the need for a global genome-wide association study of patients with HS.

ARTICLE INFORMATION

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Author Contributions: Dr van Straalen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Prens, Boomsma, van der Zee.
Acquisition, analysis, or interpretation of data: van Straalen, Willemsen, van der Zee.
Drafting of the manuscript: van Straalen, Boomsma, van der Zee.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: van Straalen.
Obtained funding: Prens, Boomsma.
Administrative, technical, or material support: Prens, Willemsen, van der Zee.
Supervision: Prens, Boomsma, van der Zee.

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