

The clinical genetics of hidradenitis suppurativa revisited

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Summary

A familial form of hidradenitis suppurativa (HS) with autosomal dominant inheritance was described in a study conducted 15 years ago in Nottingham but has not been systematically confirmed elsewhere. Prior to commencing molecular genetic studies, we wanted to test the validity of the previous study by assessing its reproducibility on the basis of a strict, newly devised disease definition for HS. We were also interested whether new cases of the disease had arisen meantime in the study group as should be expected for an autosomal dominant disease. We reviewed 14 surviving probands and their families. Seven of these probands had previously been noted to have a positive family history whereas the others had been classified as having a negative or possible family history. One hundred and thirty-two family members were assessed for their respective disease status. Participants were initially contacted by telephone or letter, and those who acknowledged a history of at least one previous boil were invited for a personal examination and interview. Only personally examined individuals were classified as a case. Twenty-eight relatives with HS were detected in total, and 27 of these were in the group previously labelled family history positive. Nine of these cases had not been detected in the previous study and in at least seven of these the disease had developed after the previous study had been conducted. Only twice did our criteria fail to confirm cases that had been labelled as HS in the previous study. Both times we classified the patients as 'possibly affected'. A further 16 relatives were judged to be possibly affected. In the group with positive family history we found 10 affected and nine possibly affected individuals among 37 surviving first-degree relatives of HS sufferers. Our findings support the concept of a familial form of HS with autosomal dominant inheritance. An insufficiently sensitive disease definition, a variable degree of gene penetrance and possibly a hormonal influence on gene expression may explain the reduced risk to first-degree relatives, which falls short of the expected 50% mark. Molecular genetic studies to clarify whether one or more gene(s) are involved in HS are now necessary and have been commenced.

Key words: autosomal dominant inheritance, clinical genetics, disease definition, familial, hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronically relapsing inflammatory skin disease characterized by recurrent boils, predominantly in skin folds that carry terminal hair and apocrine glands. The prevalence of HS in one part of the U.K. has been estimated at 1 : 600.¹ The disease has traditionally been considered a disorder of the apocrine glands, a concept based on a series of articles by Verneuil who described and named the condition and suggested its association with sweat glands.^{1–5} However, recent research has proved that

the key initiating event in the pathogenesis of HS is an occlusion of the follicular infundibulum, followed by rupture of the follicle and subsequent abscess formation.^{6–10} The resulting clinical lesion is either a non-suppurating, so-called 'blind boil' or a scantily or occasionally profusely suppurating abscess. Severe disease leads to the formation of burrowing sinus tracts. These are commonly foci of chronic and persistent inflammation and discomfort. Late sequelae of the condition are scars, dermal contractures and comedones. The latter are often double-ended. The particular distribution of the inflammatory lesions in HS is characteristic. Most commonly affected are

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axillae, groins, perineal and genital areas, buttocks and in women also the inframammary skin-folds.^{11,12} If the disease is severe, lesions may erupt elsewhere in areas such as the trunk, neck, limbs or head.¹³ This has been explained by the presence of heterotopic apocrine glands.¹⁴

The aetiology of HS is still largely obscure. Fifteen years ago a study by Fitzsimmons *et al.* postulated the existence of a familial form of HS with autosomal dominant inheritance.¹⁵ They analysed the family history of 26 consecutive probands with HS and found 11 families with evidence of a genetic aetiology and probable single gene transmission. Sixty-two HS patients were identified from the 26 families. The disease frequency among first-degree relatives of those with familial HS was 34%. This fell short of the 50% expected of an autosomal dominant condition. One of the reasons given was that over 40 first-degree relatives had been still under the age of 20 at the time of the study. It was suggested that a number of these could yet develop the condition in later years. Other explanations suggested were variable penetrance of the HS gene and incomplete ascertainment.

The findings of this study do not seem to have been widely accepted. None of the 10 U.K. Clinical Genetics Departments contacted by us knew of a case of familial HS, despite the fact that the condition is listed under MIM number 142690 in the 'Autosomal Dominant Catalog' of McKusick.¹⁶ The reason for this lack of acceptance is unclear, as it had been repeatedly recognized that a number of HS sufferers have affected family members.^{11,17-19}

We therefore reviewed the original study group to test the reproducibility of Fitzsimmons *et al.*'s findings based on a strict, dichotomous disease definition. A further interest was to analyse whether or not new HS cases had arisen, in particular in the group who were under the age of 20 at the time of the previous study.

Subjects and methods

A list of the previously studied probands was obtained from the files of the Department of Clinical Genetics. To allow comparison with the published data only the 23 families whose pedigrees were included in the previous publication were reviewed. Of these 23 probands four were deceased, three were no longer registered with general practitioners in our area and remained untraceable and one declined to participate in our study. Fifteen probands agreed to co-operate. One of these had lost all contact with his family, so that 14

families were available for a full review. These included seven of the 11 families who had been found to have a positive family history in the previous study, five of the nine families with negative family history and two of three thought to have a possible family history.

The nature of the study demanded a definition of HS that would allow classification of every family member into either 'affected' or 'unaffected'. We were forced to develop such a definition, as none yet existed in the published literature. For this we chose a consensus approach, combining information from the published literature and the views of leading experts in the field of HS research.

The consensus approach deemed that three key elements were required to make a diagnosis of HS: (i) typical lesions; (ii) a characteristic distribution; and (iii) the recurring nature over time. Based on these premises a set of typical lesions was compiled and termed 'primary lesions'. These were: (i) painful and/or tender erythematous papules (< 1 cm in diameter); (ii) painful and/or tender erythematous nodules (> 1 cm in diameter); (iii) painful and/or tender abscesses (i.e. inflamed, discharging papule or nodule); (iv) dermal contractures (i.e. a rope-like elevation of skin); (v) double-ended comedones. The characteristic sites were chosen in accordance with the two areas most frequently affected by HS, namely axillae and groins. These areas were defined by anatomical borders and termed 'designated sites'.

The definition used for the purpose of this study thus was that to be classified as a case of hidradenitis suppurativa a person must have either: (i) active disease: one or more primary lesion(s) in a designated site plus a history of three or more discharging or painful lumps (unspecified) in designated sites since the age of 10, or (ii) inactive disease: a history of five or more discharging or painful lumps (unspecified) in designated sites since the age of 10, in the absence of current primary lesions.

A complete family tree of each proband was then drawn up and attempts were made to contact all family members above the age of 20. Indirect inquiries were made about those under the age of 20 but this information was not used to classify individuals. Most individuals were contacted by phone. Those not on the phone were contacted by letter. Family members were asked a screening question: 'Have you ever had any boils under your arms or in the groins' and those answering 'No' were deemed not to have the disease. If probands were uncertain or answered 'Yes' they were asked to attend for a personal

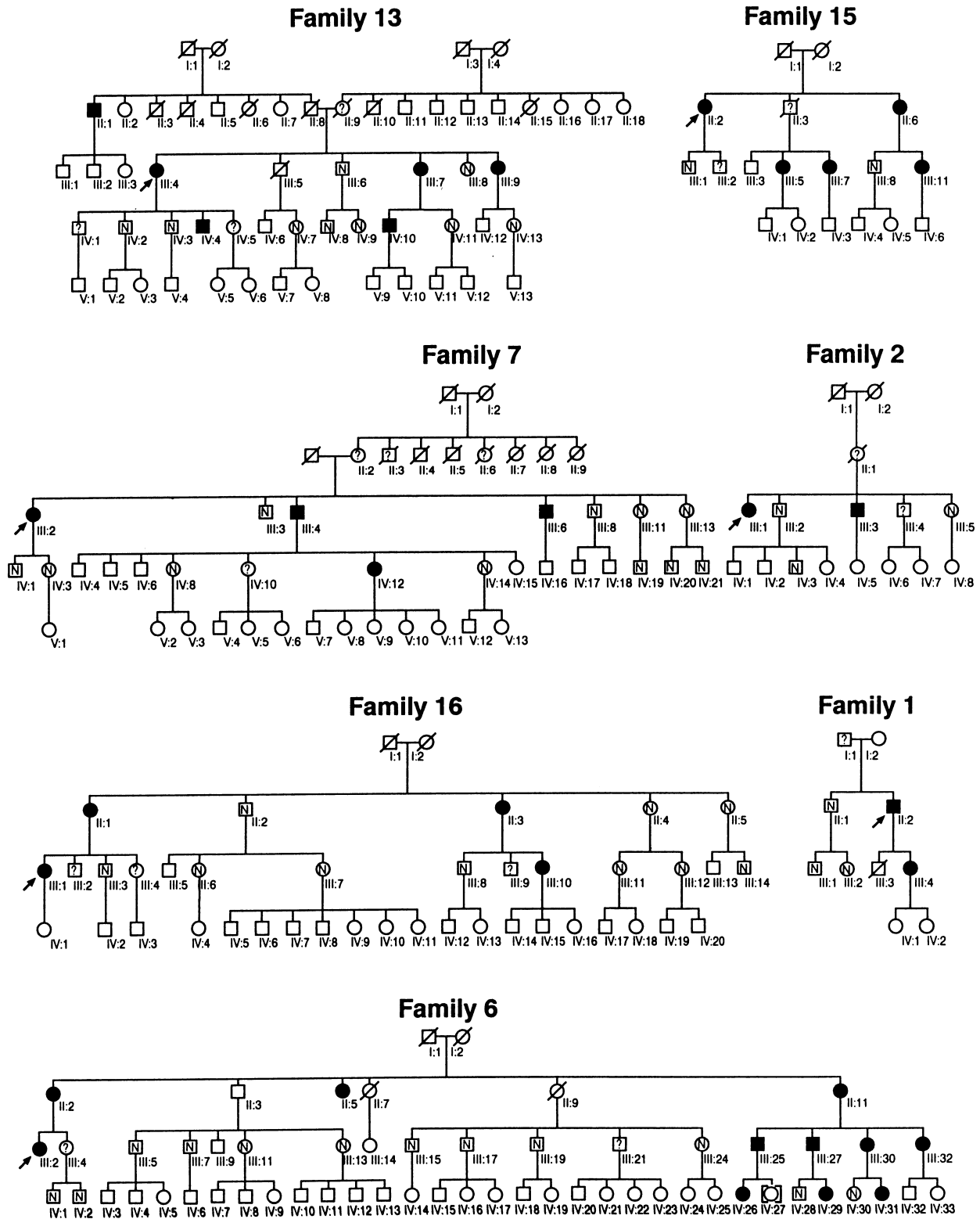


Figure 1. Group A: families with positive family history in a previous study.¹⁵ ▧ ▨, proband; ■ ●, affected; ▧ ▨, deceased; ▧ ⊙, possibly affected; ▨ ▨, unaffected; □ ○, not contacted.

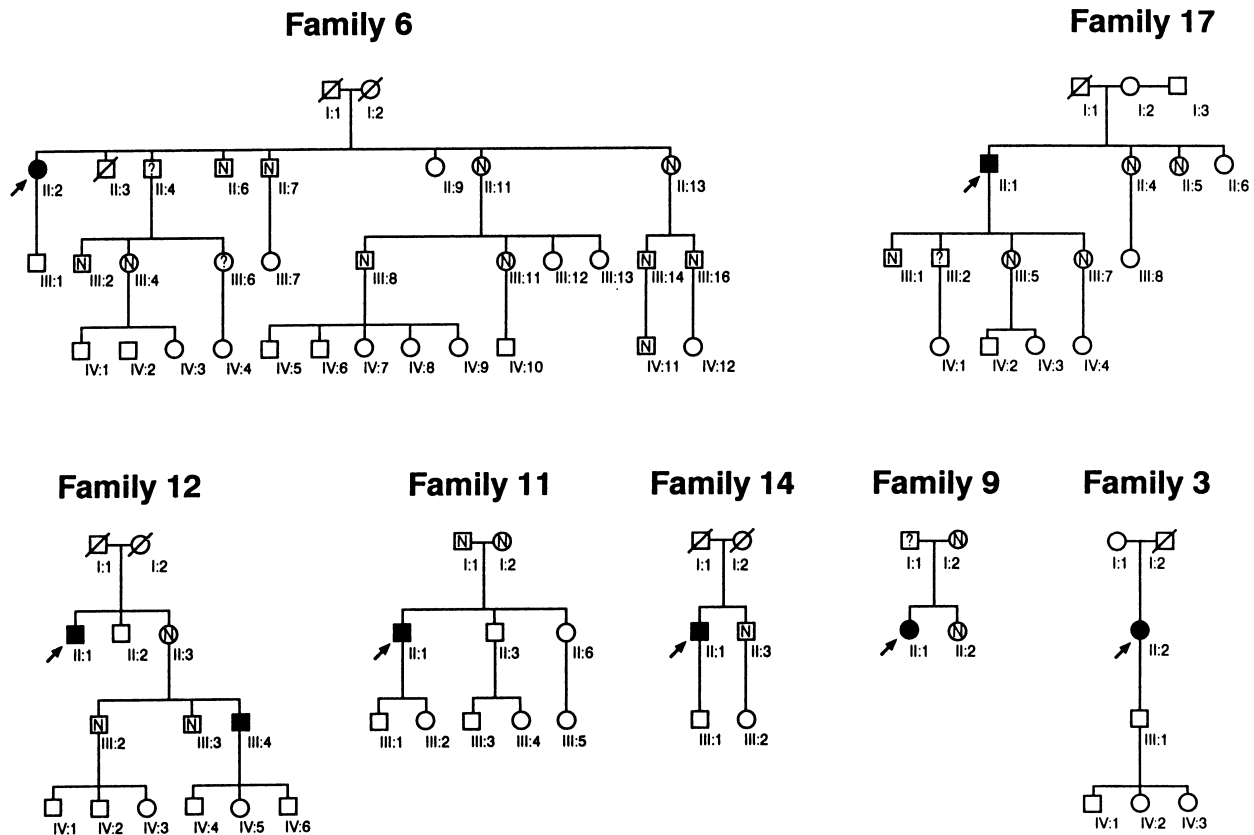


Figure 2. Group B: families with negative or uncertain family history in a previous study.¹⁵ ♂/♀, proband; ■/●, affected; ♂/♀, deceased; □/○, possibly affected; □/○, unaffected; □/○, not contacted.

interview and examination. They were then classified according to the specified criteria. To be classified as a case of HS individuals had to be personally examined. The study had received approval from the local ethics committee.

Results

The families of 14 probands were reviewed. In the previous study¹⁵ seven of these had been found to have a positive family history (group A) and the other seven had been classified as having a negative or possible

family history (group B). Our study recorded a total of 238 family members in group A (Fig. 1), of which 48 were first-degree relatives of the probands, 90 were second-degree relatives, 53 were third-degree relatives and 47 were fourth-degree relatives. This represented the complete set of first-degree relatives but recording of second, third and fourth-degree relatives was incomplete. Of the 48 first-degree relatives 11 were deceased at the time of our study. Three of the deceased had been recorded as HS sufferers in the previous study.¹⁵ Of the surviving 37 first-degree relatives 34 were personally interviewed and classified into cases or

Table 1. Group A (family history positive)

	No. of recorded relatives	Deceased	Seen and classified	Not seen (under 20 years old)	No. of hidradenitis suppurativa cases	Possibly affected
1st-degree relatives	48	11	34	3 (0)	10	9
2nd-degree relatives	90	24	30	36 (18)	9	1
3rd-degree relatives	53	–	21	32 (25)	5	2
4th-degree relatives	47	–	5	42 (32)	3	–
Total	238	35	90	113 (75)	27	12

Table 2. Group B (family history negative)

	No. of recorded relatives	Deceased	Seen and classified	Not seen (under 20 years old)	No. of hidradenitis suppurativa cases	Possibly affected
1st-degree relatives	40	9	18	13 (2)	–	5
2nd-degree relatives	25	–	10	15 (10)	1	1
3rd-degree relatives	18	–	–	18 (12)	–	–
4th-degree relatives	–	–	–	–	–	–
Total	83	9	28	46 (24)	1	6

non-cases by one of us (JDW). Three first-degree relatives were not personally seen, one of whom was a girl of 10 years who was thought to be too young for the disease. The other two failed to co-operate.

Ten first-degree relatives were found to have HS as defined by our criteria, two of whom (cases III.7 and IV.4 from family 13) had not been known to have HS at the time of the previous study. Patients were always only classified as HS sufferers if they had been personally examined. This led to problems with the classification of some patients (e.g. case IV.5 from family 13) who in a preliminary telephone interview gave a history fully fitting our case definition but who did not attend for a personal examination. She was rated as 'possibly affected' because it would have been misleading to call her 'not affected'. Seven further first-degree relatives who all gave a history of at least one boil in one of the designated sites but did not fit the criteria for HS laid out in our definition were also labelled 'possibly affected'. Altogether 27 affected relatives were found in group A, nine of whom were new cases. An additional 12 cases were classified as 'possibly affected' for reasons outlined above (Table 1). The previous study¹⁵ recorded for the same group of probands 47 first-degree relatives, 73 second-degree relatives and 69 third-degree relatives, with a total of 29 affected individuals, five of whom were already deceased at the time of the study.

In group B (Fig. 2) our study recorded 40 first-degree relatives, 25 second-degree relatives and 18 third-degree relatives. We detected one case of HS (case III.4 from family 12) in a second-degree relative and six 'possibly affected' cases, five of who were among first-degree relatives (Table 2). In the previous study¹⁵ this group contained 38 first-degree relatives, 63 second-degree relatives and 17 third-degree relatives. Two of those were listed as 'possibly affected'.

In our study we were able to determine the disease status in 132 of a total of 335 recorded family members. Ascertainment of the disease status among

first-degree relatives of probands was achieved in 52 of 68 living first-degree relatives (76%), but to a lesser extent in more distant relatives, where recording of the pedigree had been incomplete to begin with. Of the 203 cases where the disease was not assessed, 44 were deceased, 99 were under the age of 20, and disease ascertainment was attempted only in exceptional cases in teenagers or children, and the remaining 60 cases could either not be contacted or refused to co-operate. All together we detected 42 cases of HS and an additional 18 'possibly affected' cases. In one instance an HS patient with unaffected parents was found, otherwise all cases were either first-degree relatives of another affected individual or had no affected family member at all.

Discussion

This study set out to test the reproducibility of an autosomal dominant inheritance for HS in the original study group under conditions of an explicit and strict disease definition. For this purpose we carried out a follow-up examination of the original group and of the original probands' previously 'unaffected' family members. Our case ascertainment was based on a clear, dichotomous disease definition, which was designed to allow easy and reproducible classification of participants into cases and non-cases.

Our results show overall the same autosomal dominant inheritance as was demonstrated in the previous study. This inheritance was only detectable in the group where a positive family history had been noted previously (group A). Here 27% of surviving first-degree relatives were definitely affected by the disease. This is obviously lower than the 50% expected of an autosomal dominant disease. It may be partially explained by our rigid disease definition, which excluded anyone who was unable to remember a minimum of three painful lesions under the axillae or in the groins. Some patients may have found it rather

difficult to recollect distinctly three let alone five such episodes, particularly where these might have occurred some years back. Furthermore, it seems conceivable that less severe variants of HS lead to fewer than five inflammatory lesions and our definition might thus have excluded patients at the mildest end of the disease spectrum. Perhaps this is reflected in the 12 participants who were classified 'possibly affected'. Every one of them reported a history of at least one painful boil in a 'designated site' and several reported two or three such lesions. These could easily represent mild cases of HS, as the recurrence of boils in sites such as the axillae is a very strong indication for the presence of this disease. Leach *et al.* found in a study of axillary abscesses that all patients who developed such lesions recurrently were HS sufferers.²⁰ If all those participants classified as 'possibly affected' were assumed to be genuine cases and were added to those with definite disease the percentage of affected first-degree relatives would rise to 51% in our study group A.

Another reason for the relatively low degree of observed 'true cases' in our study was the stipulation that participants needed to be personally examined to be classified as a case. This excluded for example case I.1 from family 1 who had been labelled as a HS sufferer in the previous study¹⁵ and who indeed had a convincing history according to hospital case notes, but was unwilling to be examined again. He was classified as 'possibly affected'. In addition younger patients particularly were sometimes felt to be reluctant to talk about boils in their intimate areas. This could have led to further underreporting of the disease. Some uncertainty about our results may be caused by the significant number of family members who could not be contacted or were unwilling to co-operate. However, by personally assessing 132 individuals from 14 families we feel that we have achieved a reasonable degree of case ascertainment. This is particularly true as the majority of those not seen by us were juveniles under the age of 20. In these the disease might not yet have erupted even if a genetic predisposition was present. The average age of onset of HS in several published studies is about 23 years.^{11,21,22}

The concept of autosomal dominant inheritance in families from group A is further strengthened by the detection of nine new HS cases, in seven of whom the disease developed after the previous study¹⁵ within the past 14 years. It is striking that all new cases in this group descended from affected parents, whereas none of the offspring of unaffected family

members developed HS. In this study we placed particular emphasis on contacting the children of unaffected relatives.

Our study not only supports the concept and the main findings of the previous study¹⁵ but is also able to verify its case classification. In 28 of 30 individuals who had been found to have HS in the previous study¹⁵ our definition-based assessment matched that of the previous study. Only twice (case III.4 from family 6 and case II.2 from family 7) were we unable to confirm the diagnosis made in the previous study.¹⁵ In two cases (II.1 and III.7 from family 13) we diagnosed HS in individuals who might already have had the condition at the time of the earlier study. This allows two conclusions: the first is that the findings of the previous study¹⁵ were based on sound clinical grounds, which seem to have stood the test of time and that of a formalized review. This should lend further strength to its key statements. The second is that our disease definition is able to detect most cases that would be judged clinically to represent HS. A possible lack of sensitivity of the definition has already been acknowledged, and a formal validation would be necessary before its use in epidemiological or other studies could be recommended. Further modifications of the definition require more knowledge of the natural history of HS, in particular how it presents in its milder form.

Some other points that have emerged from this study deserve further consideration. In particular the occurrence of HS in a member of a family from group B seems interesting (case III.3 from family 12). The parents of this patient do not display any evidence of the disease and his case therefore might suggest either a multigenic form of inheritance in this family or incomplete penetrance of the putative HS gene. Such incomplete penetrance could be an additional explanation for the lower than expected disease frequency in our group A.

More difficult to reconcile with a proposed autosomal dominant inheritance is the observed female predominance in our study and in others before. The female/male ratio in most published series is 2–5 : 1^{15,22,23} and in our study was 2 : 1. The reasons for this are unclear. Several hormonal abnormalities have been postulated for HS patients in the past but all of these have been detected in exclusively female groups^{21,23,24} and have failed to provide an explanation why men should be affected. If HS were a largely genetically determined disease, as suggested by our study, then one would have to consider the possibility of hormonal

influences on gene expression or even the possibility of an X-chromosomal disease.

As stated before the aim of this study has been to test the concept of autosomal dominant inheritance in familial HS. Our findings support this notion, although we are aware that there is still no conclusive proof. To achieve this a much larger study would be necessary. However, such a study would again be restricted by the difficulties with disease definition and ascertainment that we encountered. It seems a more efficient use of resources to embark on a search for the molecular genetic abnormality underlying the disease, and to establish the pattern of inheritance once the involved gene(s) is found. We have now begun this search in the hope to elucidate further the genetic basis of HS.

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References

- Harrison BJ, Mudge M, Hughes LE. The prevalence of hidradenitis suppurativa in South Wales. In: *Acne and Related Disorders* (Marks R, Plewig G, eds). London: Martin Dunitz, 1991: 365–6.
- Verneuil A. Etudes sur les tumeurs de la peau et quelques maladies des glandes sudoripores. *Arch Gén Méd* 1854; **4** (447): 693.
- Verneuil A. Hypertrophie d'une glande sudipare axillaire survenu à la suite d'un abcès tubéforme de laisselle. *Gaz Hebd Méd* 1857; **4**: 555.
- Verneuil A. De l'hydrosadénite phlegmoneuse et des abcès sudoripares. *Arch Gén Méd* 1864; **4**: 537.
- Verneuil A. De l'hydrosadénite phlegmoneuse et des abcès sudoripares. *Arch Gén Méd* 1865; **5**: 327.
- Attanoos RL, Appleton MAC, Douglas-Jones AG. The pathogenesis of hidradenitis suppurativa: a closer look at apocrine and apoeccrine glands. *Br J Dermatol* 1995; **133**: 254–8.
- Jemec GBE, Thomsen BM, Hansen U. The homogeneity of hidradenitis suppurativa lesions. *APMIS* 1997; **105**: 378–83.
- Jemec GBE, Hansen U. Histology of hidradenitis suppurativa. *J Am Acad Dermatol* 1996; **34**: 994–9.
- Layton AM, Pace D, Cunliffe WJ, Barth J. A prospective histological study of acute hidradenitis suppurativa. *Br J Dermatol* 1995; **131** (Suppl. 44): 38–9.
- Yu CC-W, Cook MG. Hidradenitis suppurativa: a disease of follicular epithelium, rather than apocrine glands. *Br J Dermatol* 1990; **122**: 763–9.
- Jemec GBE. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol* 1988; **119**: 345–50.
- Hurley HJ. Hidradenitis suppurativa. In: *Dermatology in General Medicine* (Fitzpatrick TB, Eisen AZ, Wolff K, Freedberg IM, Austen KE, eds), 4th edn. New York: McGraw-Hill, 1993: 761–6.
- Hight AS. Suppurative hidradenitis. In: *Textbook of Dermatology* (Champion RH, Burton JL, Burns DA, Breathnach SM, eds), 6th edn. Oxford: Blackwell Science, 1998: 1176–9.
- Morgan WP, Hughes LE. The distribution, size and density of the apocrine glands in hidradenitis suppurativa. *Br J Surg* 1979; **66**: 853–6.
- Fitzsimmons JS, Guilbert PR, Fitzsimmons EM. Evidence of genetic factors in hidradenitis suppurativa. *Br J Dermatol* 1985; **113**: 1–8.
- McKusick VA. In: *Mendelian Inheritance in Man*. Baltimore: Johns Hopkins University Press, 1997.
- Mortimer PS. Hidradenitis suppurativa—diagnostic criteria. In: *Acne and Related Disorders* (Marks R, Plewig G, eds). London: Martin Dunitz, 1991: 359–60.
- Knaysi GA, Cosman B, Crikelair GF. Hidradenitis suppurativa. *JAMA* 1986; **203**: 73–6.
- Küster W, Rödder-Wehrmann O, Plewig G. Acne inversa. *Hautarzt* 1991; **42**: 2–4.
- Leach RD, Eykyn SJ, Phillips I *et al*. Anaerobic axillary abscesses. *Br Med J* 1979; **2**: 5–7.
- Mortimer PS, Dawber RPR, Gales MA, Moore RA. Mediation of hidradenitis suppurativa by androgens. *Br Med J* 1986; **292**: 245–8.
- Harrison BJ, G Hughes LE. Characterization of the endocrine 'lesion' in hidradenitis suppurativa. In: *Acne and Related Disorders* (Marks R, Plewig G, eds). London: Martin Dunitz, 1991: 361–3.
- Jemec GBE, Heidenheim M, Nielsen NH. Hidradenitis suppurativa—characteristics and consequences. *Clin Exp Derm* 1996; **21**: 419–23.
- Barth JH, Layton AM, Cunliffe WJ. Endocrine factors in pre- and postmenopausal women with hidradenitis suppurativa. *Br J Dermatol* 1996; **134**: 1057–9.