

Medical research has clearly demonstrated that a form of familial HS exists. This data supports the mission of the HSF by encouraging the development and funding of an International Patient Registry in order to adequately investigate the genetic relationships of Hidradenitis Suppurativa.

Worldwide clinical and scientific research participation, consolidation and collaboration are the methods by which the HSF seeks to hasten, expedite and coordinate the search for the genetic causes of HS. At the First International Hidradenitis Suppurativa Research Symposium, held March 30-April 2 2006 in Dessau, Germany, the world learned that there are at least three distinct HS genetic loci [gene locations] on chromosomes 1, 6 and 19. Genetic researchers at this HSF-sponsored symposium proposed that HS is most likely a polygenic disease with sporadic cases having defects in a number of critical genes involved in the pathogenesis of HS, and familial cases with a probable highly penetrant defect(s) in one of these genes. A "highly penetrant" defect refers to the likelihood of HS occurring when the gene mutation/defect is present.

Further genetic research and the development of a worldwide registry of affected people will lead to new and more effective therapies to relieve the pain and suffering of HS, and improve the quality of patients' lives. The data gathered from such a patient registry would be an invaluable resource for not only researchers studying the genetics of HS, but will also assist in the study of many issues related to this disease.

Chronology of HS Genetics Research

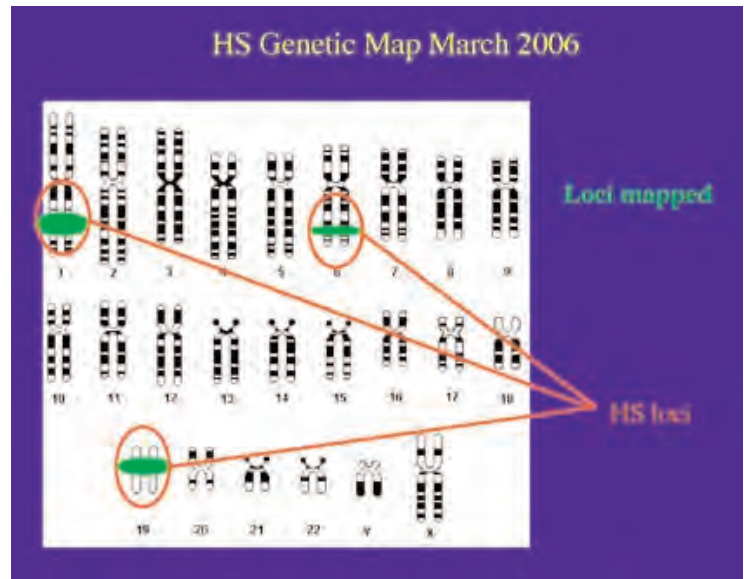
* Denotes full text provided on the HSF FTP HS Research Database
<http://www.hs-foundation.org/research/database.htm>

von der Werth, J., Wood P, Irvine A, McLean W. Genetics of Hidradenitis Suppurativa. In: Jemec G, Revuz J, Leyden J (eds). Hidradenitis Suppurativa. 1st ed. Heidelberg, Germany.: Springer, 2006 Sep: 70-85. "A study of the molecular genetics of HS has found linkage to two loci on chromosomes 6 and 19 in three families but no linkage to either of these loci in other families....Two regions on two different chromosomes co-segregated with the disease and the genes within these regions have been analysed. Although no mutation has been found some of the genes appeared to be good candidates due to their function or expression. In conclusion, the first two candidate genetic loci for HS have been identified, and this will form the basis of future genetic studies, using other families with clearly defined dominant inheritance, to narrow down these loci and identify the causative genetic lesions. Importantly, a number of other families do not link to either locus. These families were too small to perform genome-wide linkage analysis but it demonstrates that HS is indeed a genetically heterogenous disease with potentially three or more genes involved in its molecular pathogenesis. The eventual identification of these causative genes will undoubtedly be of benefit in understanding the pathomechanisms of HS and form the basis for a rational design of new therapeutic strategies."

* U. Radhakrishna 1, T.Y. Mehta 2, J.V. Solanki 3, U.C. Patel 3, U. Ratnamala 1, S.K. Nath 4 Autosomal dominant hidradenitis suppurativa is not linked to 1p21.1-1q25.3, in two large multigenerational Indian families. October 9-13, 2006 American Society of Human Genetics Annual Meeting, New Orleans, Louisiana, United States. 1504/C Poster presentation session (Mapping, Linkage and Linkage Disequilibrium). We have studied two large Indian hidradenitis suppurativa families with autosomal dominant mode of inheritance and full penetrance. There are 84 individuals in these pedigrees including 25 affected. Recently, a locus for autosomal dominant form of HS was (J Invest Dermatol. 2006 126:1302-6) reported on chromosome 1p21.1-1q25.3 in a large four generation Chinese pedigree, subsequently we genotyped two of our families using several polymorphic microsatellite markers closely linked to HS1 locus. Analyzing 45 individuals, all twenty markers yielded significant negative (<-2.0) at $q=0$. Thus the HS1 locus can be excluded as the

candidate locus responsible for HS in our Indian families. We suggest that genetic heterogeneity is present in the pathogenesis of HS and that the reported HS1 locus may be ethnic specific. We are planning to perform genome-wide linkage analysis in this family to identify the responsible locus. [AFFILIATIONS: 1) Green Cross Blood Bank & Genetics Research centre, Ahmedabad India; 2) Samarpan Medical & Research Organization, Modasa, India; 3) Department of Animal Genetics & Breeding, Veterinary College, Gujarat Agriculture University, Anand, India; 4) Arthritis and Immunology Research Program, Oklahoma Medical Research Foundation, Oklahoma City, USA.]

* Mapping of two genetic loci for autosomal dominant hidradenitis suppurativa. W. H. Irwin McLean (Presenter), Pam Wood, Alan D. Irvine and Jan von der Werth. Directions 2006-Developing a Global Roadmap for Hidradenitis Suppurativa Research, The First International Hidradenitis Suppurativa Research Symposium, March 30-April 2 2006, Dessau, Germany. (Abstract published online March 2006, presented March 31, 2006, published in *Experimental Dermatology* June 2006 - Vol. 15 Issue 6 p478-482). HS is a complex disease perhaps involving an initial genetic factor, plus environmental and hormonal effects. We identified several large kindreds from the United Kingdom and Ireland showing dominant transmission and carried out two genome-wide scans by genetic linkage analysis with 400 closely spaced microsatellite markers. This resulted in the identification of two separate genetic loci that show statistically significant linkage with HS. Marker D19S414 gave a significant log-of-the-odds (LOD) score of 3.66 in a single kindred and represents robust genetic linkage. Recombination with markers D19S911 and D19S1170 limited the interval to a 16.5-Mb region on chromosome 19, containing at least 35 known or strongly predicted genes. Many of these are transcription factors thought to be involved in modulation of the immune system, which may be consistent with HS. Two additional kindreds did not map to this locus but instead showed linkage to marker D6S290, giving a maximum combined 2-point LOD score of 4.0 with no recombination. Visible recombinants narrowed this disease interval to a 1.48-Mb region between D6S440 and D6S441 on chromosome 6q25.1-25.2 containing six genes. We have already screened a large number of exons in both loci for mutations without identifying any obvious mutations. The eventual identification of genes causing HS will shed



light on the pathomechanisms underlying inherited forms of the disease and, ultimately, will set the scene for rational design of therapies aimed at treating the root causes of this disorder.

Image from: WHI McLean, P Wood, AD Irvine, J von der Werth. Mapping of two genetic loci for autosomal dominant hidradenitis suppurativa.

* Genetic analysis of three large Indian pedigrees with autosomal dominant hidradenitis suppurativa. Uppala Radhakrishna (Presenter), Timir Y. Mehta, Jitendra V. Solanki and Swapan K. Nath. Directions 2006-Developing a Global Roadmap for Hidradenitis Suppurativa Research, The First International Hidradenitis Suppurativa Research Symposium, March 30-April 2 2006, Dessau, Germany. (Abstract published online March 2006, presented March 31, 2006, published in *Experimental Dermatology* June 2006 - Vol. 15 Issue 6 p478-482). We have studied three large Indian hidradenitis suppurativa families with an apparent autosomal dominant mode of inheritance and 100% penetrance. No skipping of generations was observed. Pedigrees consist of 149 individuals, including 48 affecteds (20 males/28 females). Cytogenetic analysis of two affecteds from each family did not show any abnormality. Genomewide linkage analysis is in progress to map the elusive locus and provide a target for positional cloning.

* Clinical characteristics and outcome measures in hidradenitis suppurativa research. Jean Revuz. Directions 2006-Developing a Global Roadmap for Hidradenitis Suppurativa Research, The First International Hidradenitis Suppurativa Research Symposium, March 30-April 2 2006, Dessau, Germany. (Abstract published online March 2006, presented March 31, 2006, published in *Experimental Dermatology* June 2006 - Vol. 15 Issue 6

p478-482). One hundred and sixty-four consecutive patients were prospectively evaluated. 30% had a family history of HS.

* Surgical treatment options for hidradenitis suppurativa and critical review of own experience. Wolfgang Christian Marsch. Directions 2006-Developing a Global Roadmap for Hidradenitis Suppurativa Research, The First International Hidradenitis Suppurativa Research Symposium, March 30-April 2 2006, Dessau, Germany. (Abstract published online March 2006, presented March 31, 2006, published in *Experimental Dermatology* June 2006 - Vol. 15 Issue 6 p478-482). Fifty-three patients have been treated surgically at our Dermatology Department. Familiarity 0.4%.

* Gao M, Wang P, Cui Y, et al. Inversa acne (hidradenitis suppurativa): A case report and identification of the locus at chromosome 1p21.1-1q25.3. *J Invest Dermatol.* 2006 Mar; Advance Online Publication (Mar 16) Volume 126, Issue 6 (June 2006) We performed a genome-wide scan in a four-generation Chinese family to map the chromosome location of the responsible gene. A four-generation family from Anhui province of China with the inversa acne features was recruited for this study. It showed an autosomal dominant inheritance pattern. We performed a genome-wide scan in this family and found that the two-point maximum LOD score obtained was 3.26 with markers D1S2624. We positioned the locus upper to D1S248 and lower boundaries to D1S2711. This 73Mb critical region chromosome (1p21.1-1q25.3) contained about 886 genes, including about 395 known genes, a large number of predicted genes, and numerous expressed sequence tags. This study firstly identified a novel locus for inversa acne on in a large Chinese family.

* Dixit R, George R, Jacob M, Sudarsanam T, Danda D. Dowling-Degos disease, hidradenitis suppurativa and arthritis in mother and daughter. *Clin Exp Dermatol.* 2006 Mar; Online Early.

* Xu W., Zhao J, Zhao H, Gu F, Huang X.. Follicular Occlusion Triad: Abstract of A Case Report and Pedigree Analysis Chinese Journal Of Dermatology 2005 Vol.38 No.3 P.157-159
<http://www.wanfangdata.com.cn/qikan/periodical/Articles/zhp/zhp2005/0503/050308.htm> (In Chinese and English transl. by Dr. Jihai Shi). A family of 13 affected individuals is reported.

* Valverde R, Sanchez MP, Rosales B, Sanchez-Largo E, Calzado L, Guerra-Tapia A. Two familiar cases of acne conglobata-hidradenitis suppurativa associated to pyoderma gangrenosum. P4386. Accessed 4/24/2004. EADV, EU, 2004. Report two cases (brother and sister).

* Loo WJ, Rytina E, Todd PM. Hidradenitis Suppurativa, Dowling-Degos and Multiple Epidermal Cysts: A New Follicular Occlusion Triad. *Clin Exp Dermatol.* 2004; 29(6):622-624. A 49-year-old woman presented with recurrent nodules and abscesses in her axillae and groins since the age of 11 years. Interestingly, eight relatives from her father's family have similar although milder skin lesions.

* Radhakrishna U, Mehta TY, Solanki JV, Rao UC. An autosomal dominant hidradenitis suppurativa in a large Indian family. 53rd Annual Meeting of The American Society of Human Genetics Los Angeles, California. <<http://genetics.faseb.org>. FASEB, USA, 2003. We have studied a large four generation Indian pedigree with autosomal dominant HS. The pedigree consists of 68 individuals including twenty affecteds (12 males/8 females). The age of onset was during puberty and the phenotype appeared to be 100% penetrant in this family. The expression of the phenotype was variable and ranged from very severe to moderate with typical features of HS. Detailed pathologic examinations were performed including histopathological studies in selected affecteds. The majority of the examined individuals were severely affected and their findings included cutaneous scars, folliculitis, GI polyps, familial gall stones, sinuses axillae, polymorph function defects, pilosebaceous abscesses and folliculitis. Hirsutism was observed in affected females. To our knowledge, this may be the biggest family with several affecteds. Blood DNA samples have been collected from selected individuals for future research.

* Lapins J, Sartorius K, Emtestam L. Scanner-assisted carbon dioxide laser surgery: A retrospective follow-up study of patients with hidradenitis suppurativa. *J Am Acad Dermatol.* 2002; 47(2):280-285. Family history of hidradenitis suppurativa in one or more first-degree relatives reported by the patient: Hereditary/nonhereditary variant 11/23

* Geh JLC, Niranjana NS. Perforator-based fasciocutaneous island flaps for the reconstruction of axillary defects following excision of hidradenitis suppurativa. *Br J Plast*

Surg. 2002; 55(2):124-128. A 25-year-old Indian woman with disfiguring scarring of both axillae was referred by the dermatology department. There was a family history of axillary hidradenitis suppurativa.

* Palmer RA, Keefe M. Early-onset hidradenitis suppurativa. *Clin Exp Dermatol.* 2001 Sep;26(6):501-3. A 9-year-old girl developed hidradenitis suppurativa 3 months after the first signs of adrenarche. Her mother and maternal grandmother gave a history consistent with hidradenitis suppurativa.

* Bohn J, Svensson H. Surgical treatment of hidradenitis suppurativa. *Scandinavian Journal of Plastic and Reconstructive Surgery and Hand Surgery.* 2001; 35(3):305-310. 138 patients with HS studied, including one pair of twins and 34 patients (29%) recording a family history of at least one first degree relative with HS.

* Von Der Werth JM, Williams HC, Raeburn JA. The Clinical Genetics of Hidradenitis Suppurativa Revisited. *Br J Dermatol.* 2000; 142(5):947-953. 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. 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. Molecular genetic studies to clarify whether one or more gene(s) are involved in HS are now necessary and have been commenced.

* Von der Werth JM, Williams HC. The natural history of hidradenitis suppurativa. *J Eur Acad Dermatol Venereol.* 2000 Sep;14(5):389-92. Thirty-seven of 97 patients (38%) stated that they knew of at least one affected family member with HS.

* Kurzen H, Schönfelder-Funcke S, Hartschuh W. Surgical treatment of acne inversa at the university of heidelberg. *Coloproctology.* 2000; 22:76-80. 66 patients 55% of patients had a positive family history of acne inversa.

* König A, Lehmann C, Happle R. Cigarette Smoking as a Triggering Factor of Hidradenitis Suppurativa. *Dermatology.* 1999; 198(3):261. 84 patients admitted between 1990 and 1997 for surgical treatment of moderate to severe HS in two dermatological centers (Marburg/Kassel, Germany) were asked to complete a mailed questionnaire. 73% of our patients had no family history of hidradenitis suppurativa whereas 27% reported at least one affected first-degree relative.

* Chaidemenos, G. Ch.; Karakatsanis, G.; Boutli, F.; Mourellou, O. Hidradenitis Suppurativa in Two Brothers. State Hospital of Skin and venereal Diseases, Thessaloniki, Greece. Abstract 99 Abstracts for the IV. International Dermatology Symposium Berlin "Sebaceous Gland, Acne and Related Disorders—Basic and Clinical Research, Clinical Entities and Treatment" *J Invest Dermatol* 1997 Mar;108(3):388. Our patients, 44 and 48-year-old brothers presented with a 25 year history of Hidradenitis Suppurativa involving the axillae, groins, scrotum, buttocks and thighs. HLA findings were A1, A26, B18, Cw3C, DR1, DR4, DQw7, DR53. The degree of severity differed between the two patients but their response to therapy was almost identical.

* Zisova L, Sakakushev B. Acne Tetrad in a Family. *Folia Med (Plovdiv).* 1994; 36(4):51-57. The authors report, for the first time in Bulgarian literature, a case of acne tetrad syndrome in a family. The patients were sisters who were found to have three of the four components of the syndrome: hidradenitis suppurativa, acne conglobata, and cysta pilaris.

* Gower-Rousseau C, Maunoury V, Colombel JF, et al. Hidradenitis suppurativa and crohn's disease in two families: A significant association? *Am J Gastroenterol.* 1992; 87(7):928. Two brothers with HS

* Kuster W, Rodder-Wehrmann O, Plewig G. Acne Inversa. Pathogenesis and Genetics. *Hautarzt.* 1991; 42(1):2-4. The familial presentations of acne inversa published in the literature and two observations of familial occurrence among the authors' own patients reveal an autosomal dominant inheritance with high penetrance.

* Mortimer P. Hidradenitis suppurativa – diagnostic criteria. In: Marks R, Plewig G (ed). Acne and Related Disorders. London: Dunitz, 1989:359-360. 16 of 74 female HS patients volunteered that one or more first-degree relatives suffered with recurrent blind boils in the armpits or groins.

* Jemec GB. The symptomatology of hidradenitis suppurativa in women. *Br J Dermatol.* 1988; 119(3):345-350. 18 out of 70 patients (26%) with HS had a positive family history, whereas of 96 control subjects matched for age and sex, who did not have HS, only two of their relatives suffered from HS.

* Camisa C, Sexton C, Friedman C. Treatment of Hidradenitis Suppurativa with Combination Hypothalamic-Pituitary-Ovarian and Adrenal Suppression. A Case Report. *J Reprod Med.* 1989; 34(8):543-546. A 33-year-old woman with severe familial hidradenitis suppurativa of the vulva and perineum is described.

* O'Loughlin S, Woods R, Kirke PN, Shanahan F, Byrne A, Drury MI. Hidradenitis suppurativa. glucose tolerance, clinical, microbiologic, and immunologic features and HLA frequencies in 27 patients. *Arch Dermatol.* 1988; 124(7):1043-1046. 14 male, 13 female subjects. 2/27 positive family history for HS.

* Norris JF, Cunliffe WJ. Failure of Treatment of Familial Widespread Hidradenitis Suppurativa with Isotretinoin. *Clin Exp Dermatol.* 1986; 11(6):579-583. We investigated a family of six subjects (2 sisters and their four children mentioned in Fitzsimmons 1984 family study).

* Fitzsimmons JS, Guilbert PR, Fitzsimmons EM. Evidence of Genetic Factors in Hidradenitis Suppurativa. *Br J Dermatol.* 1985; 113(1):1-8. Twenty-six probands suffering from hidradenitis suppurativa were identified from a busy general hospital providing specialist plastic surgical services for the East Midlands, City Hospital, Nottingham Hospital Activity Analysis (H.A.A.) records for the period 1980-83 and by direct referral from hospital specialists over a 6-month period in 1983-84. From the 26 probands investigation of their families eventually confirmed a total of 62 affected individuals from 23 families.

* Fitzsimmons JS, Fitzsimmons EM, Gilbert G. Familial Hidradenitis Suppurativa: Evidence in Favour of Single Gene Transmission. *J Med Genet.* 1984; 21(4):281-285. The three English families in this report have a total of 21 members (16 females and five males) suffering from chronic hidradenitis suppurativa. The familial aggregation and number of affected subjects suggests a single gene disorder and the pattern of transmission is consistent with autosomal dominant inheritance. Males and females are affected in successive generations and there is the anticipated variation in clinical severity in those suffering from the condition.

* Dvorak VC, Root RK, MacGregor RR. Host-defense mechanisms in hidradenitis suppurativa. *Arch Dermatol.* 1977; 113(4):450-453. Study includes 2 sisters with HS.

* Bell BA, Ellis H. Hydradenitis suppurativa. *J R Soc Med.* 1978; 71(7):511-515. Describes two sisters with HS.

* Gold SC, Delaney TJ. Familial acne conglobata, hidradenitis suppurativa, pili torti and cataracts. *Br J Dermatol.* 1974; 91(10):54-7. Male 35 year old, grandfather, mother and sister reported to have same condition.

* Knaysi GA, Jr, Cosman B, Crikelair GF. Hidradenitis suppurativa. *JAMA.* 1968; 203(1):19-22. A family history of hidradenitis was obtained in only 3 of 18 patients specifically questioned.