Inversa Acne (Hidradenitis Suppurativa): A Case Report and Identification of the Locus at Chromosome 1p21.1–1q25.3

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Acne inversa (hidradenitis suppurativa) is a chronic relapsing inflammatory skin disease characterized by recurrent draining sinuses and abscesses, predominantly in skin folds that carry terminal hairs and apocrine glands. The genetic basis for this disease is unknown. In this study, we performed a genome-wide scan in a four-generation Chinese family to map the chromosome location of the responsible gene. We first identified a locus at chromosome 1p21.1–1q25.3 with the maximum logarithm of odds (LOD) score of 3.26 at the marker D1S2624 (at recombination fraction = 0.00). The other two-point LOD scores $\geqslant 3$ were observed at markers D1S2695, D1S2726, D1S252, and D1S2777. Haplotype analysis localized this locus to a 76 Mb region flanked by D1S248 and D1S2711. This is the first locus for the inversa acne and will be a starting point towards understanding the molecular mechanisms of this disease.

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INTRODUCTION

The inversa acne (OMIM: %142690, hidradenitis suppurativa) is a chronic relapsing inflammatory skin disease characterized by recurrent draining sinuses and abscesses, predominantly in skin folds that carry terminal hairs and apocrine glands. Healing occurs with substantial scarring. It could be associated with acne conglobata and dissecting cellulitis of the scalp to form the follicular occlusion triad. The pattern of transmission is consistent with autosomal dominant inheritance (Von der Werth *et al.*, 2000). The prevalence of acne inversa has been estimated at one in 100 to one in 600 (Jansen *et al.*, 2001). It is more frequent in black people, but the incidence in China is unknown. To date, a few cases of it have been reported in different countries (Olafsson and Khan, 1992; Meyers *et al.*, 2003; Scheinfeld, 2003; Loo *et al.*, 2004; Montgomery *et al.*, 2004). The histopathological studies have identified acne inversa as a disorder of follicular rather than apocrine occlusion (Yu and Cook, 1990; Attanoos *et al.*, 1995). It often has been reported to coexist with other skin diseases that show poral occlusion. The squamous cell carcinoma that could arise in the follicular occlusion triad has been reported in nearly 30 cases (Camisa, 1984; Dufresne *et al.*, 1996). The peripheral arthritis is associated with follicular occlusion triad, and the rheumatoid factor and HLA-B27 were absent in these patients (Ellis *et al.*, 1987; Thein *et al.*, 2004).

Although the inversa acne has been reported in some literatures, the molecular basis of it is unknown and the disease gene locus has not been genetically mapped. In this study, we collected available family members' information and performed a genome-wide scan in a large inversa acne Chinese family. The results firstly showed that the disease gene of the inversa acne is located on chromosome 1p21.1–1q25.3.

RESULTS

Linkage analysis

We performed the whole gene scan and firstly found the significant logarithm of odds (LOD) score from the marker D1S252 ($Z_{max} = 3.16$, $\theta = 0.00$). For fine mapping, the other 20 polymorphic microsatellite markers at chromosome 1 were further typed. Table 1 summarizes the two-point linkage analyses for the markers at chromosome 1. Maximum two-point LOD score were obtained for the marker D1S2624 ($Z_{max} = 3.26$, $\theta = 0.00$). The other LOD scores > 3 were also obtained for the markers D1S2695, D1S2726, D1S252, and D1S2777.

Haplotype analysis

To determine the smallest interval containing the inversa acne locus, recombination events among the family members

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Abbreviation: LOD, logarithm of odds

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Table 1. Two-point linkage analysis between the inversa acne and the markers at chromosome 1

		LOD score at θ=						
Markers	**Location (cM)**	**0.00**	**0.10**	**0.20**	**0.30**	**0.40**	Z_{max}	θ_{max}
D1S495	140.80	–	0.74	0.64	0.39	0.13	0.74	0.10
D1S248	143.30	–	−0.11	0.11	0.10	0.03	0.11	0.20
D1S2695	147.90	3.21	2.62	1.98	1.27	0.54	3.21	0.00
D1S2726	149.00	3.25	2.66	2.01	1.29	0.55	3.25	0.00
D1S2746	152.20	2.10	1.65	1.15	0.62	0.17	2.10	0.00
D1S2881	153.30	1.80	1.48	1.13	0.75	0.37	1.80	0.00
D1S252	155.10	3.16	2.57	1.91	1.19	0.45	3.16	0.00
D1S2696	158.50	2.77	2.29	1.76	1.17	0.53	2.77	0.00
D1S2715	164.10	1.54	1.20	0.83	0.45	0.13	1.54	0.00
D1S2777	165.70	3.21	2.63	1.98	1.27	0.54	3.21	0.00
D1S2624	167.30	3.26	2.67	2.01	1.30	0.56	3.26	0.00
D1S484	173.90	1.34	1.02	0.69	0.36	0.10	1.34	0.00
D1S2705	175.10	2.25	1.79	1.29	0.75	0.23	2.25	0.00
D1S2844	179.20	2.78	2.30	1.77	1.18	0.53	2.78	0.00
D1S2799	188.50	2.76	2.26	1.73	1.14	0.52	2.76	0.00
D1S218	196.50	1.68	1.54	1.21	0.77	0.30	1.68	0.00
D1S2691	197.00	2.57	2.16	1.68	1.13	0.52	2.57	0.00
D1S2640	199.70	2.10	1.69	1.24	0.75	0.26	2.10	0.00
D1S2623	203.00	1.44	1.17	0.88	0.59	0.29	1.44	0.00
D1S2701	203.70	0.20	0.19	0.12	0.09	0.06	0.20	0.00
D1S2711	205.10	–	0.26	0.32	0.22	0.08	0.32	0.20

Note: LOD scores were calculated under an autosomal dominant mode of inheritance, a penetrance of 100% at various recombination fractions. Genetic coordinates in centiMorgans according to the final Genethon human linkage map (Dib *et al.*, 1996).

were analyzed by haplotype reconstruction (Figure 1). The recombination events in unaffected member III:7 and patient IV:3 place this locus upper to D1S248 and individual III:7 place the lower boundaries to D1S2711. These results suggest that the gene responsible for the inversa acne in this family lies in the 61.8 cM (about 76 Mb) interval between D1S248 and D1S2711. Haplotype indicated that individuals IV:7 and IV:8 are carrying the disease-associated haplotype but, because of their young ages, disease symptoms are not present. Additionally, the recombination event in the IV:7 defined the proximal border to the marker D1S2623.

DISCUSSION

In this study, we collected a large inversa acne pedigree and performed a genome-wide scan. The proband and his brother (III:10) were affected by acne conglobata, inversa acne and dissecting cellulitis of the scalp, but other affected members mainly have mild acne inversa. Acne conglobata is a severe type of acne vulgaris and characterized by abscess and cyst. It may occur as an independent trait associated with other disease. Acne inversa is a recurrent, suppurative disease manifested by abscesses, fistulas, and scarring, predominantly in skin folds that carry terminal hairs and apocrine glands (Jansen and Plewig, 1998). It is a different from acne vulgaris. Acne inversa is localized in non-facial regions, where there are terminal, pigmented, coarse hairs, as in the axillae, groins, anal fold, mons pubis, and scalp (Jemec and Gniadecka, 1997). A relationship has been suggested between this disease and the development of non-melanoma skin cancer. A study found that the risk of developing any cancer in the cohort with hidradenitis suppurativa increased 50% (Lapins *et al.*, 2001). The squamous cell carcinomas and arthritis could be associated with follicular occlusion triad, but in this family no individual associated with them except the proband had low fever and joints pain for about 1 year.

The loci of the diseases have not been genetically mapped. 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 73 Mb critical region contained about 886 genes, including about 395 known genes, a large number of predicted genes, and numerous expressed sequence tags. There are many possible candidates in this region. This study firstly identified a novel

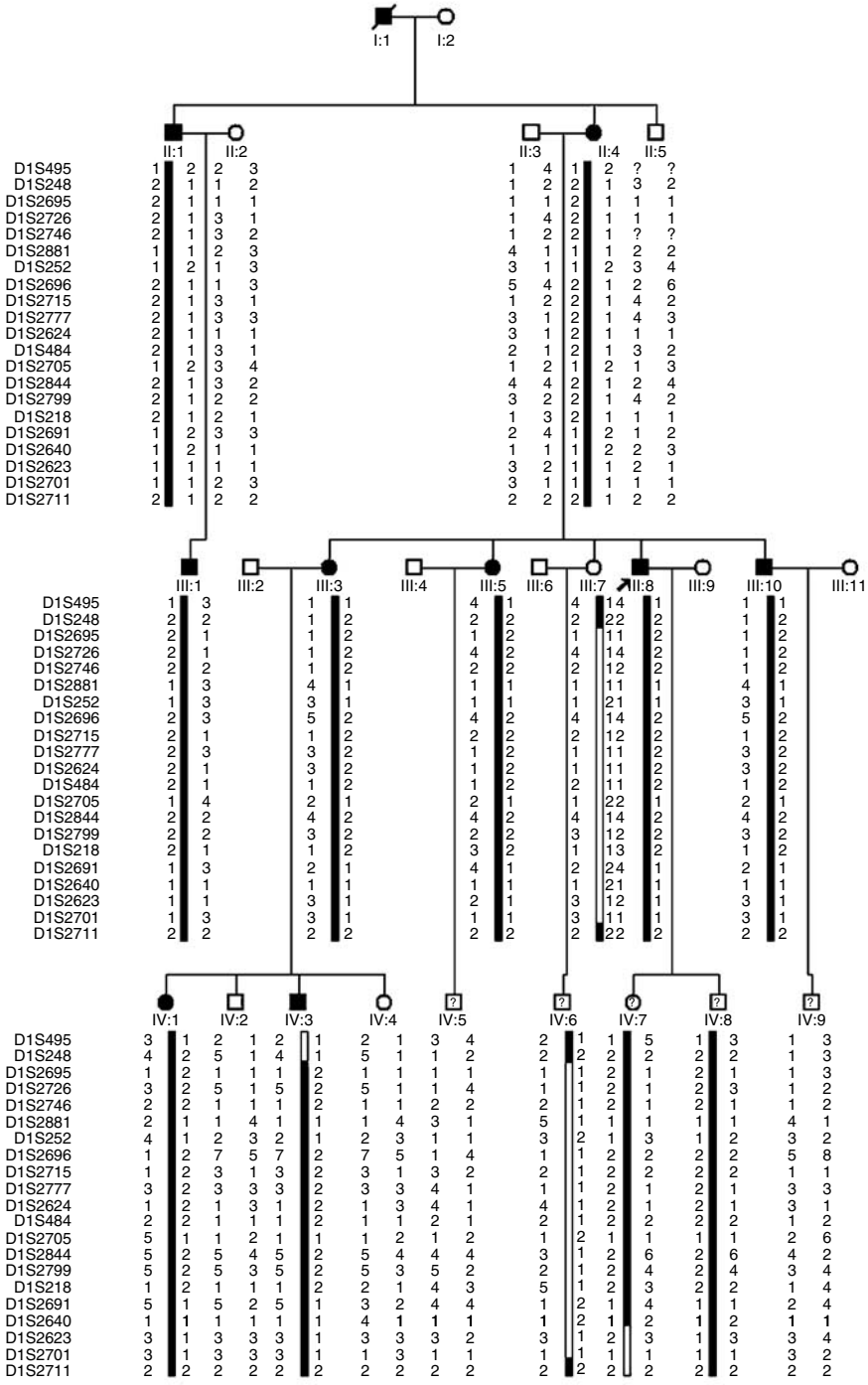

Figure 1. Haplotype analysis of this family. Black symbols denote affected individuals, whereas white symbols denote unaffected individuals. Haplotypes are shown for all available members with marker names at the left of each generation. Black bars represent disease-carrying haplotypes, and the gray bar denotes non-informative regions adjacent to critical recombination events. The black arrow indicates the proband of this family. The question marks indicate that the phenotypes of the individuals (IV:5–IV:9) are unknown.

locus for inversa acne on chromosome 1p21.1–1q25.3 in a large Chinese family. Because this region is still too wide to find the disease gene, the further studies are continuing to collect new families to confirm and fine mapping this locus. It will be a starting point towards understanding the molecular mechanisms of this disease.

MATERIALS AND METHODS

Study participants

A four-generation family (Figure 1) from Anhui province of China with the inversa acne features was recruited for this study. It showed an autosomal dominant inheritance pattern. The proband, individual III:8, is a 34-year-old male, and at the age of 12 years, he presented

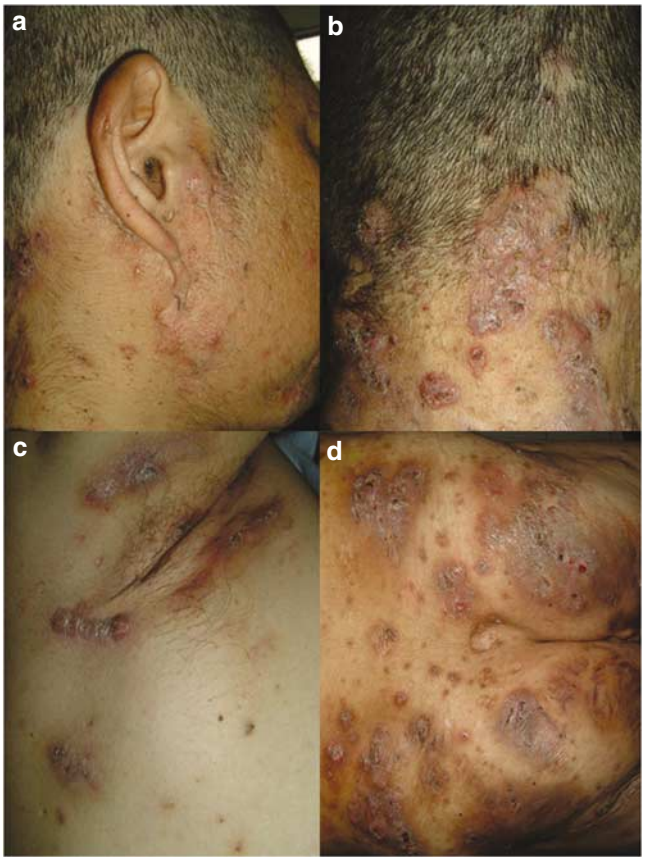

Figure 2. The clinical findings of the proband in this family. (**a**–**d**) The nodules, pustules, sinuses, and abscesses on the face, neck, scalp, axillae, and buttocks.

the red papules on his face and neck. In the recent 2 years, the disease had gradually become prominent on his face, neck, limbs, truck, groin, especially on the scalp, axillae, and buttocks, and the lesions developed inflammatory papules, painful nodules, pustules, sinuses, and abscesses (Figure 2a–d). The eruptions were remarkable after alcohol intake. The ages of onset in this family are between 10 and 20 years. After obtaining informed consent from all the participants, blood samples were collected from available family members and genomic DNAs were extracted from peripheral blood by use of a blood kit (Qiagen Inc., Hilden, Germany). This study was approved by Anhui Medical Institutional Review Board and conducted according to the Declaration of Helsinki Principles.

Genotyping

We performed a genome-wide scan using 382 fluorescent microsatellite markers from the autosomers (ABI Prism Linkage Mapping Set Version 2). The average distance between markers for the genome scan is about 10 cM. Twenty-one additional microsatellite markers were selected from Genethon linkage maps (Dib *et al.*, 1996). Polymerase chain reactions were performed with a touchdown program in a 5 μl solution that contained 10 ng of genomic DNA, 10 mM Tris-hydrochloride (pH 8.3), 50 mM magnesium chloride, 0.2 mM each dinucleoside triphosphate, 0.04 μM of each primer, and 0.2 U AmpliTaq Gold™ (Applied Biosystems, Foster City, CA). The polymerase chain reaction conditions were: *Taq* activation at 94°C for 12 minutes, followed by 40 cycles, each having denaturation at 94°C for 30 seconds, annealing at 56°C for 60 seconds and extension at 72°C for 90 seconds, except that in the first 15 cycles, the annealing temperature decreased from 63 to 56°C by 0.5°C per cycle, and the final extension was 10 minutes. Products were separated on an ABI PRISM® 3730 automated sequencer (Applied Biosystems, Foster City, CA). Gene Mapper software (Applied Biosystems, Foster City, CA) was used for size calculation of all the alleles.

Linkage and haplotype analyses

Because the ages of the individuals from IV:5 to IV:9 are less than 10 years, we assumed their phenotypes are unknown and therefore did not include the linkage analysis. Autosomal dominant inheritance with 99.9% penetrance was assumed. The affected allele frequency was taken as 0.0001. Marker allele frequencies were obtained from all individuals' genotyping data. The recombination frequency was assumed to be equal for both sexes. Two-point linkage analysis was performed using Linkage programs version 5.10 (Lathrop and Lalouel, 1984). Haplotypes were constructed with Cyrillic Version 2.02 software (Sobel and Lange, 1996).

CONFLICT OF INTEREST

The authors state no conflict of interest.

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ELECTRONIC DATABASE INFORMATION

Accession numbers and URLs for data in this paper are as follows:
Mapview, http://www. ncbi.nlm.nih.gov/mapview/
Online Mendelian Inheritance in Man (OMIM), http://www.ncbi.nlm.nih.gov/OMIM.

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