SUSCEPTIBILITY TO PSORIASIS VULGARIS IS CONTROLLED IN PART BY TWO UNLINKED GENES IN A DOUBLE RECESSIVE MANNER

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Summary   The mode of inheritance of the susceptibility to psoriasis vulgaris (PV) was investigated by segregation analysis.   Because our main aim was to search a possibility of the double recessive hypothesis for the disease susceptibility, we examined 83 families of normal × normal mating by single selection out of 93 probands, a number sufficient to be analyzed genetically.   Nine of the 83 couples had two or more affected children, including probands.   As to the 83 families, the hypothesis of the single recessive model for PV was ruled out, but the double recessive model allowing for 62 to 80% of sporadic cases was fitted to the family data. Penetrance value of the disease trait ranged from 33 to 43%.   It is thus likely that about 20 to 38% of patients with psoriasis are homozygous for two unlinked autosomal recessive genes.

Key Words   psoriasis vulgaris, double recessive model, genetic heterogeneity

INTRODUCTION

It is well established that genetic factors are involved in the development of psoriasis vulgaris (PV) (Lomholt, 1976).   However, the mode of inheritance of the susceptibility genes influencing PV has not been established.   For Caucasians, monogenic, oligogenic and multifactorial inheritances have been reported (Steinberg

et al., 1952; Abele et al., 1963; Watson et al., 1972).   A genetic analysis of Japanese patients with the disease has rarely been reported.

   Yasuda and Sasazuki (1984) developed a new genetic method, complex segregation analysis for a two-locus model.   This approach implements the analyses of segregation frequency, ascertainment probability and proportion of sporadic cases for two major loci.

   We used this method to analyze the inheritance of susceptibility to PV in a Japanese population.

PATIENTS AND METHODS

   Patients.   Ninety-three families with psoriasis were collected through 93 probands in the Dermatology Clinic of the Medical Institute of Bioregulation Hospital, Kyushu University.   PV was diagnosed on clinical features by observing typical erythematous plaques with silvery scales distributed symmetrically and/or associated nail changes.   Out of these 93, 83 families of normal × normal mating and seven families of normal × affected mating were ascertained through children (single selection) and three families of normal × affected mating were collected through parents (complete selection).   Out of the 83 couples of normal × normal mating, nine had two or more affected children, including probands.   The 83 psoriatic families were the subjects of the following study.   The 83 probands had 353 siblings, including themselves.   The overall numbers of psoriatic patients were 93 of 353 (26.2%). Out of the 83 probands, 62 (74.7%) were males.   However, we found no significant sex difference in frequency (male : female=1 : 0.9) of PV among the first-degree relatives of the 83 probands.   On the basis of these observations, we assumed that a greater frequency of males among the psoriatic probands was probably due to an ascertainment bias.

   Data analyses.   Testing of the double recessive model was performed by complex segregation analysis, as described by Yasuda and Sasazuki (1984).   This approach allows for possibility of the genetic heterogeneity of the disease.   Gene frequencies of the two recessive genes in the double recessive model were estimated to be 0.197, respectively, from the observed frequency of parents phenotypes.

RESULTS

Mode of inheritance for the susceptibility to PV
   From the findings in affected children segregated from 83 couples of normal × normal mating, there is the possibility that susceptibility to PV is a single recessive event.   However, the data did not fit a single recessive model with full penetrance $(\chi_{14}^2=127.39; \ p<1\times10^{-5})$, under single ascertainment (Table 1).   If one calculates the penetrance value under the single recessive model, then one can obtain only the low figure of 15% (0.037/0.25=0.15) since the expected and observed segregation

Table 1. Tests of goodness-of-fit to a single recessive hypothesis for the susceptibility to PV.

Sibship size	Numbers of affected sibs [a]	Observed	Expected	χ^2
1	1	2	2.00	0.00
2	1	13	9.75	1.08
2	2	0	3.25	3.25
3	1	20	11.81	5.68
3	2	1	7.88	6.01
3	3	0	1.31	1.31
4	1	12	7.17	3.25
4	2	4	7.17	1.40
4	3	1	2.39	0.81
4	4	0	0.27	0.27
5	1	9	3.16	10.79
5	2	1	0.42	0.80
5	3–5	0	6.42	6.42
6	1	4	1.19	6.64
6	2	1	1.98	0.49
6	3–6	0	1.83	1.83
7	1	7	1.42	21.93
7	2	1	2.85	1.20
7	3–7	0	3.73	3.73
8	1	6	0.80	33.80
8	2–8	0	5.20	5.20
10	1	1	0.08	10.58
10	2–10	0	0.92	0.92
Total		83	83.00	127.39* (df = 14)

*$p < 1 \times 10^{-5}$. [a] Probands are included.

frequencies are 0.25 and 0.037 (10/270=0.037), respectively. Thus, the susceptibility to PV in these families cannot be explained by a single locus.

We then examined a goodness-of-fit to a double recessive model in this disease, since Steinberg *et al.* (1952) suggested that the susceptibility to PV might be a double recessive trait. The results of the segregation analysis are given in Table 2. The null hypothesis of a double recessive model (segregation frequency=0.0625, probability of ascertainment=0, and no sporadic cases) was rejected (χ_{14}^2=91.68; $p < 1 \times 10^{-5}$). However, there was no statistical significance (χ_{12}^2=11.52; $p > 0.40$) under the hypothesis (maximum likelihood estimate of segregation frequency=0.0270, probability of ascertainment=0, and maximum estimate of proportion of sporadic

Table 2. Complex segregation analysis of the susceptibility to PV under a double recessive mode of inheritance.[a]

Mating type	p	x	π	χ^2(df)		Penetrance
Normal × normal						
Simplex and multiplex	0. 0625	0	0	91. 68 (14)	$p < 1 \times 10^{-5}$	100%
families (n=83)	0. 0270[b]	0. 62[b]	0	11. 52 (12)	$p > 0.40$	43%
	0. 0625	0. 80[b]	0	11. 44 (13)	$p > 0.40$	100%
Normal × normal						
Multiplex families	0. 0625	—	0	3. 02 (6)	$p > 0.70$	100%
alone (n=9)	0. 0210[b]	—	0	1. 59 (5)	$p > 0.80$	33%

p, segregation frequency; x, proportion of sporadic cases; π, probability of ascertainment; χ^2, goodness-of-fit of segregation distribution to the expectation.   [a] Gene frequencies of the two recessive genes were estimated to be 0.197, respectively.   [b] Maximum likelihood estimate under each condition.

cases=0.62).   There was also no significance (χ_{13}^2=11.44; p>0.40) under the hypothesis (segregation frequency=0.0625, probability of ascertainment=0, and maximum likelihood estimate of proportion of sporadic cases=0.80).   These observations suggest that the susceptibility to PV is highly heterogeneous (62–80%) and that about 20–38% of patients with PV are homozygous for two unlinked autosomal recessive genes.   On the other hand, with nine psoriatic multiplex families, there was no statistical difference between the expectation and the observation in the distribution of the psoriatics (χ_6^2=3.02; p>0.70) under the null hypothesis of a double recessive model (segregation frequency=0.0625, probability of ascertainment=0).   The estimated segregation frequency (0.0210) in the nine psoriatic multiplex families differed little from that (0.0270) in the 83 psoriatic families.   Thus, the penetrance of the disease trait was estimated to be 33–43%.

DISCUSSION

Among a sample of 93 psoriatic families through 93 probands, we examined 83 families of normal × normal mating for segregation analysis.   Our main aim in this work was to search for possible evidence of a double recessive model for this susceptibility to PV.   If we use 7 families of normal × affected mating collected through children, we can obtain the data (χ_1^2=0.44; p>0.70) fitted to the double recessive model (segregation frequency=0.25, maximum likelihood estimate of sporadic cases=0.75, and ascertainment of probability=0).   In addition, if we use 3 normal × affected mating families collected through parents, we get a similar result (χ_2^2=3.51; p>0.10) under the double recessive model (segregation frequency=0.25, proportion of nonsegregating family=0, and ascertainment of probability=1).

These results enable a discussion on the mode of inheritance to PV in 83 families of normal × normal mating, a number sufficient to be analyzed genetically. In our sample of 83 psoriatic families, about 20 to 38% of the susceptibility to PV might be homozygous on two unlinked autosomal recessive genes. However, a much larger proportion (62 to 80%) is due to an apparent genetic heterogeneity on the susceptibility to PV. Some investigators favored a genetic heterogeneity in PV (Farber and Nall, 1974; Pietrzyk *et al.*, 1982; Iselius and Williams, 1984; Henseler and Christophers, 1985). For this reason, several hypotheses have been proposed (Steinberg *et al.*, 1952; Abele *et al.*, 1963; Watson *et al.*, 1972).

Our results are based on the assumption that gene frequencies of the two unlinked autosomal recessive genes are even, as is the case with PV analyzed by Steinberg *et al.* (1952). The accuracy of this assumption has not been established. One way to resolve this problem would be to carry out a population survey with use of genetic markers. Out of various genetic markers, the HLA system shows a significant association with PV. Ozawa *et al.* (1986) reported that there are strong associations between HLA (HLA-Cw6, Cw7, and DR7) antigens and PV in a Japanese population. These associations suggest that the PV susceptibility genes might be in linkage disequilibrium with these *HLA* alleles. At present, there is no clear evidence of linkage between *HLA* and the hypothesized PV susceptibility genes. For confirmation, the linkage may be verified by data on various markers such as HLA and complements (Dewald *et al.*, 1983). If we made use of the nine multiplex families with PV in the current study and performed linkage analyses with the above genetic markers, we would be able to estimate gene frequencies of the hypothesized PV susceptibility genes.

Penetrance value ranged from 33 to 43% in the double recessive mode of inheritance. The finding of the reduced penetrance value was not surprising since environmental factors such as streptococcal infection appear to play a role in the etiology of PV (Asboe-Hansen, 1971).

In conclusion, some (about 20 to 38%) of PV fitted a double recessive hypothesis and for the remaining larger proportion (62 to 80%), the mode of inheritance for the susceptibility to PV remains unknown.

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