The mode of inheritance of psoriasis: Evidence for a major gene as well as a multifactorial component and its implication for genetic counselling

Lennart Iselius¹ and Wick R. Williams²

¹ Department of Clinical Genetics, Karolinska Hospital, Stockholm, Sweden and Population Genetics Laboratory, University of Hawaii, Honolulu, HI 96822, USA
² Department of Medical Genetics, The University of Texas System Cancer Center, M. D. Anderson Hospital and Tumor Institute, Houston, TX 77030, USA

Summary. Complex segregation analysis of Lomholt’s family data on psoriasis on the Faroe Islands gave evidence for an additive major gene with gene frequency of 0.07 and penetrance 0.12 and 0.44 in the heterozygote and in the homozygote, respectively. In addition, there was a multifactorial component with heritability 0.87. The implications of these findings for genetic counseling are discussed and analytical risk figures are presented for chosen pedigrees.

Introduction

Psoriasis affects 1–3% of the general population in most Caucasian populations. The tendency for psoriasis to run in families is well known and a genetic component has long been suspected. The mode of inheritance has been under much debate and dominant, recessive as well as multifactorial inheritance has been suggested (review in Lomholt 1976). One genetic factor of importance for the development of psoriasis has been identified. In 1972 it was shown that there is an association between psoriasis and the HLA antigens B13 and B17. Later stronger associations have been found with CW6 and DRW7 (review in Baden and Hooker 1982). These findings have given new interest to studies of the genetics of psoriasis. Another reason for this increased interest is the development of new methods for analysis of the mode of inheritance of diseases, especially the mixed model of complex segregation analysis (Morton and MacLean 1974; Lalouel and Morton 1981), which allows for a major locus in addition to polygenes with an intergenerational difference and random environment. It was therefore considered of interest to reanalyse the data of Lomholt (1963), who performed a very thorough study of the prevalence, spontaneous course, and genetics of psoriasis on the Faroe Islands and on the basis thereof suggested a double recessive inheritance. Lomholt’s dataset has later been used by Ananthakrishnan et al. (1974) who claimed a multifactorial mode of inheritance. Kimberling and Dobson (1973) who also used Lomholt’s data, supported autosomal dominant inheritance. However, none of these studies was able to handle factors which complicate the segregation analysis like incomplete ascertainment, incomplete dominance, and monogenic effects in the presence of polygenes. In order to overcome these difficulties complex segregation analysis was used in the present paper to elucidate the mode of inheritance of psoriasis and to get segregation parameters for linkage studies with the HLA system, the results of which will be published separately (L. Iselius, J. Marcusson, and E. Möller, in preparation).

Material and methods

The material analyzed consists of 321 nuclear families from Lomholt’s study on the Faroe Islands (1963). The mode of ascertainment, criteria of diagnosis etc. are given in detail in Lomholt’s paper. Subjects living outside the district under study were not included in the analysis, since they were not personally examined by Lomholt.

Segregation analysis

The mixed model of segregation analysis features a major locus with two alleles, a continuous variable representing polygenic and/or cultural inheritance, and random error (Morton and MacLean 1974; Lalouel and Morton 1981). The phenotype may be defined by a continuous scale of liability underlying affection. The liability scale can have an arbitrary mean and variance but is here taken as 0 and 1, respectively. The major locus (a locus that causes a displacement of more than one phenotypic standard deviation between normal and abnormal genotypes) is specified by the gene frequency of the allele with higher liability q); the displacement between homozygotes measured in standard deviation units (i); the degree of dominance (defined so that displacement of the heterozygote is d x i) (d = 0 corresponds to a recessive gene, d = 0.5 to an additive gene, and d = 1 to a dominant gene). Multifactorial inheritance is parameterized in terms of H and H x Z representing juvenile and adult heritability, respectively. Polygenes and cultural inheritance are somewhat con-
founded using this parameterization, but it is not important if
the main goal of the study is to resolve a major locus. Esti-
mates of the parameters of the model are obtained by maxi-
mizing the probability density of the observed phenotypes of
the children conditional upon the phenotypes of the parents.

The general model has five parameters. Subhypotheses
can be tested by using a likelihood ratio test. For each hypo-
thesis we calculate \(-2 \ln L + c\), where \(\ln L\) is the log-likeli-
hood of the sample and \(c\) is a constant; if \(-2 \ln L_1 + c\) is the
value when \(m + k\) parameters are estimated, and \(-2 \ln L_2 + c\)
when only \(m\) of the \(m + k\) parameters are estimated, then
\((-2 \ln L_2 + c - (2 \ln L_1 + c) = 2 \ln (L_1/L_2)\) follows a \(\chi^2\)
distribution with \(k\) degrees of freedom testing a null hypothesis
on these \(k\) parameters.

Ascertainment correction

The pedigrees in Lomholt’s material were divided into their
321 component nuclear families for segregation analysis. The
ascertainment was taken as complete when the proband was a
parent. If the family was ascertained through a proband in the
children’s generation selection was taken as incomplete and
Fisher’s extension of the Weinberg proband method gave a
probability of ascertainment \((z) = 0.74\). If the family
did not have a proband but only one or more affected individ-
uals, selection was taken as truncate \((z = 1)\).

The concept of proband is usually sufficient for analysis in
nuclear families. For larger pedigrees the situation is more
complicated. The pedigree form will often be dependent on
the content, since the usual practice is to examine first degree
relatives of the proband and then to inquire whether any more
relatives are affected and in that case examine their first de-
gree relatives. To address this problem the concept of pointer
has been invented (Lalouel and Morton 1981). A pointer is
defined as an affected relative causing the particular nuclear
family to be ascertained. A pointer is always outside the
nuclear family to which it points. A nuclear family can have up
to three pointers (pointer to father, mother, and set of child-
ren). In the calculations the likelihood of the phenotypes of
the children are taken conditional upon both of the phenoty-
pes of the parents as well as on the phenotypes of the pointers.

The liability indicator

A quantitative phenotype may be covariate—adjusted for age
and sex effects, but this is not feasible for qualitative data
(e.g., normal versus affected). Instead, a discontinuous lia-
bility indicator is defined by polychotomizing a discriminant of
risk—in the present case chronological age. To the \(i\)th level of
the liability indicator corresponds an affection rate \(a_i\) in the
general population. These prevalence rates were calculated
from Lomholt’s paper and are given in Table 1.

<table>
<thead>
<tr>
<th>Table 1. Prevalence values for psoriasis for each liability class</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at last observation (years)</td>
</tr>
<tr>
<td>0–10</td>
</tr>
<tr>
<td>11–20</td>
</tr>
<tr>
<td>21–30</td>
</tr>
<tr>
<td>31–40</td>
</tr>
<tr>
<td>≥41</td>
</tr>
</tbody>
</table>

Table 2. Segregation analysis of psoriasis. (Non-iterated parameters within parentheses)

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>(-2 \ln L + C)</th>
<th>(H)</th>
<th>(Z)</th>
<th>(q)</th>
<th>(t)</th>
<th>(d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(q = 0, Z = 1)</td>
<td>1023.20</td>
<td>0.811</td>
<td>(1)</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>no major locus, no generational difference</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(q = 0)</td>
<td>1021.98</td>
<td>0.933</td>
<td>0.857</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>no major locus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d = 0)</td>
<td>1008.35</td>
<td>0.870</td>
<td>(1)</td>
<td>0.301</td>
<td>1.227</td>
<td>(0)</td>
</tr>
<tr>
<td>recessive major gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d = 0.5)</td>
<td>1003.90</td>
<td>0.875</td>
<td>(1)</td>
<td>0.0711</td>
<td>1.939</td>
<td>(0.5)</td>
</tr>
<tr>
<td>additive major gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(d = 1)</td>
<td>1005.68</td>
<td>0.884</td>
<td>(1)</td>
<td>0.0496</td>
<td>1.076</td>
<td>(1)</td>
</tr>
<tr>
<td>dominant major gene</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Generalized single locus</td>
<td>1025.81</td>
<td>(0)</td>
<td>(1)</td>
<td>0.0285</td>
<td>6.279</td>
<td>0.299</td>
</tr>
</tbody>
</table>

Results

The results of the segregation analysis are given in Table 2.
There was no significant evidence for an intergenerational dif-
ference for polygenic heritability \(\chi^2 = 1023.20 - 1021.98 =
1.22\); \(Z\) was therefore fixed at 1 in the rest of the analysis.

A solution for the general model in \(q, t, d, \text{ and } H\) could not
be obtained due to convergency problems. However, there was signifi-
cant evidence for a major locus \(\chi^2 = 1021.98 - 1003.90 =
18.08, P < 0.001\) with best fit for an additive gene \((d = 0.5)\).
The penetrance values were 0.12 for heterozygotes and 0.44
for homozygotes with the gene frequency \(q = 0.07\) and dis-
placement \(t = 1.94\). There was also significant evidence for a
multifactorial component with \(H = 0.87\) \((\chi^2 = 1025.81 -
1003.90 = 21.91, P < 0.001)\).

Discussion

The present study clearly shows that psoriasis is a heterogene-
ous disease from a genetic point of view. The evidence obtain-
ed for an autosomal additive gene with reduced penetrance
causing the disease in some families supports the results of
some previous studies. Thus, Abele et al. (1963) found evi-
dence for an autosomal dominant gene with reduced pene-
trance \((0.6)\) causing psoriasis in a large family from North
Carolina. Ward and Stephens (1961) also favored autosomal
dominant inheritance with reduced penetrance in their study
of a Utah kindred.