The Genetics of Vitiligo

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Abstract. The genetics of vitiligo has been studied in 150 probands and their families. A familial concentration of the disease has been demonstrated which supports the concept that hereditary factors contribute to the etiology of vitiligo. Segregation analysis was not consistent with inheritance at a single autosomal or X-linked locus. Further analysis suggested that vitiligo is determined by multifactorial inheritance. An estimate of heritability of liability was found to be 72.4%, indicating that genetic factors play a significant role in the etiology.

Vitiligo affects all races and it is reported that it occurs in 1% of the population (Lerner, 1959: El Mofty, 1968). The frequency is probably the same in both sexes. However, racial differences in the incidence of vitiligo have been reported as being higher in those with racially pigmented skin (Levai, 1958).

Although the cause of vitiligo is unknown, various hypotheses have been evolved. The most widely accepted are the autoimmune (Cunliffe et al., 1968), the neurogenic (Lerner, 1959) and the melanocyte self-destruction (Lerner, 1971) theories. However, it was reported that between 30 and 40% of patients have a positive family history (Lerner, 1959), which indicates that a genetic factor is undoubtedly involved. For this purpose we planned a study of the genetics of vitiligo.

MATERIAL AND METHODS

The material for this study included 150 patients with vitiligo and their families. Living relatives of probands were classified as first-degree, second-degree, or third-degree relatives. First-degree relatives included parents, siblings, and children of the 150 probands. Second-degree relatives included aunts, uncles, and grandparents. Third-degree relatives comprised first cousins. The probands and the available living relatives were examined clinically. Some relatives who were not available for examination were recorded. Pedigrees were constructed and the genetic analysis performed using the mathematics of population genetics (Emery, 1976).

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Table I. Proportion of living relatives with vitiligo

<table>
<thead>
<tr>
<th>Relatives</th>
<th>Total</th>
<th>Affected</th>
<th>% affected ± SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mother</td>
<td>149</td>
<td>16</td>
<td>10.7 ± 1.4</td>
</tr>
<tr>
<td>Father</td>
<td>147</td>
<td>14</td>
<td>9.5 ± 2.1</td>
</tr>
<tr>
<td>Sister</td>
<td>384</td>
<td>32</td>
<td>8.3 ± 1.3</td>
</tr>
<tr>
<td>Brother</td>
<td>346</td>
<td>28</td>
<td>0.0 ± 1.2</td>
</tr>
<tr>
<td>All first-degree relatives</td>
<td>1 026</td>
<td>90</td>
<td>8.7 ± 0.4</td>
</tr>
<tr>
<td>Second-degree relatives</td>
<td>1 365</td>
<td>43</td>
<td>3.1 ± 0.6</td>
</tr>
<tr>
<td>Third-degree relatives</td>
<td>1 874</td>
<td>21</td>
<td>1.1 ± 0.3</td>
</tr>
<tr>
<td>Total</td>
<td>4 265</td>
<td>154</td>
<td>3.6 ± 0.2</td>
</tr>
</tbody>
</table>

RESULTS

The data concerning the frequency of vitiligo in the families of the 150 probands showed the incidence to be 24% (36 out of the 150 families). Of the 4265 relatives, 154 were affected (3.6%).

To test for autosomal dominant inheritance we used the method of Neel & Schull (Emery, 1976). Table II shows $\chi^2$ to be 23.1, which, with one degree of freedom, is more than 3.841. Thus there is a significant departure from the expected which is inconsistent with autosomal dominant inheritance.

To test for autosomal recessive inheritance we used Fisher's equation (Emery, 1976). In our sibships the probability was 0.103, SE 0.0013. It is therefore inconsistent with autosomal recessive inheritance. Furthermore, our data do not fit the hypotheses of x-linked inheritance. The female patients were found to constitute 57% of the probands. Moreover, there were two families in which both father and son were affected but the mothers were unaffected.

To determine if the proportions are consistent with the multifactorial inheritance; firstly, the curve of liability has been constructed (Fig. 1). The curve of the relatives is shifted to the right, showing that they have a higher mean liability. Secondly, the threshold trait among first-degree relatives (8.7%) approximates the square root of the frequency in the general population (10%). Thirdly, there is fairly close agreement between the observed relative frequency and that expected for multifactorial inheritance (Table III). However, the heritability was estimated to be 72.4%.

DISCUSSION

A genetic factor is undoubtedly involved in the development of vitiligo. 24% of our probands have a positive family history. The incidence of affected among their 4265 relatives is 3.6±0.2%, with a fall-off in frequency from the first-degree to second-degree to third-degree relatives. Lerner (1959) found that 38% of 198 patients with vitiligo had blood relatives, while Fitzpatrick (1964) quotes 35%. Mohr (1951) and Siemens (1953) observed the case in monozygotic twins.

Some workers reported the possibility of autosomal dominant inheritance (Mohr, 1951; El Mofty, 1968). However, our data are not consistent with...
any of the modes of inheritance with single-gene defects, and fulfill the criteria for multifactorial inheritance.

The liability curve shows that the genetic determinants can raise the frequency of disease among relatives of patients above that found in the general population. By specifying that the threshold remain fixed, the high frequency among relatives can be explained by a shift in mean liability from its position for the general population toward the threshold. Thus our analysis will consider vitiligo as a quantitative threshold trait with a familial concentration in terms of liability to and the threshold for vitiligo.

For multifactorial inheritance, Edwards (1960) has shown that the frequency of a threshold trait among relatives approximates the square root of the frequency in the general population. Data collected for this study are consistent with Edwards' hypothesis. Moreover the nearly equal relative observed and expected frequencies (Table III) fit with the model given by Penrose (1953).

Having decided that vitiligo appears to be inherited on a multifactorial basis, we estimated the heritability. The estimate of 72.4 % clearly indicates that genetic factors play a significant role in the etiology.

However, the heritable components in such a condition are alleles at an unspecified number of different loci, each contributing a small effect, which interacts with environmental variation to bring about the trait. Work on the genetics of pigmentation in the laboratory mouse revealed the influence of about 70 genes at approximately 40 loci (Fitzpatrick & Quevedo, 1971). Origin, spread and differentiation of melanoblasts, morphology of melanocytes and melanosomes, biosynthesis of tyrosinase and melanogenesis, and, finally, transfer to and arrangement of melanosomes in keratinocytes are each under the direction and influence of different genes.

### Table III. Frequency and relative frequencies of vitiligo in sibs

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Expected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gen. Pop (q)</td>
<td>Sibs (S)</td>
</tr>
<tr>
<td>0.01</td>
<td>0.082</td>
</tr>
</tbody>
</table>

### REFERENCES