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GENETIC ANALYSIS OF HUMAN IMMUNITY PARAMETERS

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KEY WORDS: immunologic parameters; genetic analysis; heritability

Immunologic methods are widely used to study the genetic polymorphism of human populations. They are used in the study of human antigenic systems, such as blood groups, histocompatibility antigens, and immunoglobulins and their correlates with other immunologic, and also morphophysiological and biochemical features [6, 9, 15]. Their use as genetic markers, which has become traditional in population-genetic investigations, must be complemented by the study of the role of hereditary factors in the total phenotypic variation of immunity parameters in man which, in their nature, are multifactorial quantitative features. This problem can be solved by investigations on twins, and also by the genetic analysis of the structure of links between concrete features in pairwise comparisons of the relatives with different degrees of kinship, in the course of a genetic-epidemiologic investigation.

The few investigations already undertaken, namely on twins, have pointed to the important role of genetic factors in the formation of a particular level of certain immunologic parameters [4, 13, 14]. However, there have been virtually no genetic-epidemiologic investigations of the immunologic status in man.

In the investigation described below the authors have attempted for the first time to assess the role of hereditary factors in the total variation of certain immunologic characters in one of the circumpolar populations, a description of which was given previously [7].

EXPERIMENTAL METHOD

A sample representative for both sex and age, consisting of 372 persons (181 men and 191 women), aged 18-50 years, was studied. Eighty parent-child, 41 sib-sib, and 45 parent-parent pairs were formed from them.

The following immunologic parameters were determined by the usual methods: the relative numbers of T- and B-rosette-forming cells (T- and B-RFC) [10], the serum complement level [8], the serum β-lytic and lysozyme activity [1, 5], IgA, IgM, and IgG levels according to Mancini, and the titer of normal (heterophilic) antibodies to sheep's red blood cells.

Interfamilial correlation analysis included calculation [2, 3] of coefficients of phenotypic correlations in parent-child (r_{pc}), sib-sib (r_{ss}), and parent-parent (r_{pp}) pairs, averaged by Fisher's z-transformation. For immunologic parameters with significantly different r_{pp} values, r_{pc} and r_{ss} were corrected for assortative mating [2]. To assess genetic links between characters the coefficient of cross-correlation r^+ was used [3]:

$$r^+ = \frac{\sum_n^n (x_{np} - \bar{x}_p)(y_{nc} - \bar{y}_c) + \sum_n^n (y_{np} - \bar{y}_p)(x_{nc} - \bar{x}_c)}{\sigma x \, \sigma y 2(N-1)},$$

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TABLE 1. Coefficients of Phenotypic Interfamilial Correlations of Their Errors (Sr) for Immunologic Parameters

Parameter	Parents—children		Parents—parents	
	r_{cp}	S_{rcp}	r_{pp}	S_{rpp}
T-RFC	0,401*	0,160	0,144	0,206
B-RFC	—0,017	0,152	0,199	0,192
Complement	—0,193	0,182	0,644*	0,156
Lysozyme	0,190	0,192	—0,280	0,220
β-Lysins	0,080	0,204	—0,019	0,249
Heterohemagglutinins	0,262*	0,131	0,295	0,153
IgM	0,291*	0,121	—0,078	0,168
IgA	0,329*	0,113	0,472*	0,134
IgG	—0,045	0,115	0,052	0,157

TABLE 2. Coefficients of Phenotypic Correlation (r), Cross-Correlation (r^+), and Their Error (Sr) for Immunologic Parameters

Pair of features	r	Sr	r^+	S_{r^+}
T-RFC—heterohemagglutinins	—0,021	0,064	0,017	0,132
T-RFC—IgM	0,016	0,065	0,009	0,133
T-RFC—IgA	0,193*	0,063	0,055	0,126
Heterohemagglutinins—IgM	0,209*	0,055	0,314*	0,111
Heterohemagglutinins—IgA	0,083	0,054	0,267*	0,109
IgM—IgA	—0,093	0,055	0,166	0,113

Legend. Here and in Table 2: *$p < 0.05$.

where N is the number of parent-child pairs, x_{np} and y_{np} values of the 1st and 2nd features respectively, in the parents of the n-th pair, x_{nc}, y_{nc} the same in the child, and $\bar{x}_p$, $\bar{y}_p$, $\bar{x}_c$, and $\bar{y}_c$ the corresponding mean values.

EXPERIMENTAL RESULTS

Intrafamilial correlation analysis showed no significant correlations in the sib-sib pairs (r_{ss}) for any of the immunologic parameters studied. Coefficients of phenotypic correlations in parent-child and parent-parent pairs are shown in Table 1. Significant high and positive coefficients of correlation were obtained for parent-parent pairs for complement (0.64) and IgA (0.47) levels, which may be attributable to two main causes: either a predominant influence of environmental factors in determination of the levels of the parameters (for the parents were not genetically related), or assortative mating with respect to these features or their physiological correlates. Whatever the case, the high parent-parent correlations may distort assessment of the other familial correlations. Values of r_{cp} for complement and IgA levels were therefore calculated with the aid of correcting procedures [2]. As a result, r_{cp} for the complement level was found to be not significant, whereas for IgA it was 0.32 ($p < 0.05$). A significant role of hereditary factors was thus found from these two parameters for the IgA level.

Determination of interindividual differences by genetic factors also was established for T-RFC and the heterohemagglutinin and IgM levels. Estimates of the heritability (h^2) of these parameters, obtained by multiplying r_{cp} by 2 were 80, 52, and 85% respectively, i.e., not less than 50% of the total phenotypic variation of the above-mentioned immunologic features was due to genetic variation of the population. Similar results were obtained in investigations on twins for the complement level, when its heritability was about 80% [4], and on familial material a value of r_{cp} for IgM between 0.31 and 0.44 was obtained [12]. Other workers deny the importance of genetic factors in determinination of the IgM level [13].

Table 2 gives coefficients of phenotypic correlation between pairs of features studied. A definite degree of positive correlation was found only for two pairs: T-RFC—IgA and heterohemagglutinins—IgM. However, since the character of the phenotypic correlation could be due to the action of both common genetic and common environmental factors, absence of phenotypic correlations may be due to the opposite direction of action of genetic and environmental factors [11]. It was therefore interesting to study genetic correlations between features independently of the magnitude of their phenotypic correlations. For this purpose, the coefficient of cross-correlation r^+ was used as the estimate of genetic correlations between features [3]. Genetically common factors were found for at least the heterohemagglutinins—IgM ($r^+ = +0.314$, $p < 0.05$) the heterohemagglutinins—IgA ($r^+ = +0.267$, $p < 0.05$) pairs of features. This means that about 30% of genetic factors are common for heterohemagglutinin and IgA levels, on the one hand, and for heterohemagglutinin and IgM levels, on the other hand. Heterohemagglutinins are known to be normal antibodies, an evolutionarily very old adaptive mechanism. In the process of evolution IgM appeared earlier than IgG. It is this fact which suggests that these features may be firmly consolidated in the genotype and that correlations may be formed between them, for their evolution evidently took place along parallel lines.

This investigation is thus the first attempt to study phenotypic and genetic correlations between the principal parameters of immunity in a population with a unique genetic and

demographic structure, formed in the course of long-term adaptation to arctic conditions of life. It is important that information of this kind be collected on a large scale for other circumpolar populations and compared with the corresponding information for populations living in other climato-geographic regions.

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EXPERIMENTAL STUDY OF THE IMMUNOSUPPRESSIVE PROPERTIES OF VITAMIN D

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KEY WORDS: Vitamin D; T- and B-lymphocytes; natural killer cells; transplantation immunity

Vitamin D is widely and universally used for the prevention and treatment of vitamin D deficiency in children. Nevertheless, until very recently there was no information whatever in the literature on the effect of additional vitamin intake on activity of the immune system.

In 1982 the present authors showed for the first time in experiments on rats that vitamin D, in massive doses, causes atrophy of the thymus, inhibits the development of the delayed-

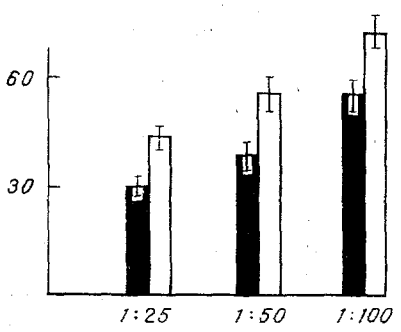

Fig. 1. Effect of vitamin D on NKC activity in mice. Abscissa, ratio of effector to target; ordinate, cytotoxicity index (in %). Unshaded columns — control; shaded — experiment.

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