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GENETIC ASPECTS OF SERUM IgE LEVELS IN ATOPIC FAMILIES

By

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Atopy is known as a form of human hypersensitivity in which there is evidence of genetic predisposition (1, 3, 23, 28). Immunoglobulin E (IgE) plays a decisive role in atopic diseases (10, 12). Nothing is known about hereditary control of IgE synthesis in man.

According to *Spain & Cooke* (23) and *Bucher & Keeler* (4) atopy is inherited as a simple mendelian dominant. In contrast *Adkinson* (1) interpreted her findings favouring a recessive mechanism. It was *Bray* (3) who found a bimodal distribution of the onset of atopic diseases. Partially based on this observation *Wiener* (28) proposed a genetic model which points out that atopy is transmitted by a single gene disseggregating into two alleles, A and a, where A determines non-atopy, and a atopy. Based on *Wiener's* hypothesis of disposition in atopy we studied the serum IgE levels in members of atopic families in comparison with the serum levels of 50 unselected persons. These results should supply further information about the mode of genetic transmission of atopic predisposition and IgE synthesis. Results are evaluated according to a model of *Bazara* (2).

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MATERIALS AND METHODS

Test groups: Serum IgE levels of 49 persons belonging to 12 atopic families were assayed. At the time of the IgE determination 20 persons of this group suffered from atopic diseases such as atopic eczema, allergic bronchial asthma, or hay fever. Six others had histories of atopic diseases. None of the patients, who were all diagnosed in dermatological clinics, had been treated with cortisone in the last three months before IgE determination. The sera of 50 blood donors served as controls.

In preliminary studies we compared the sensitivity and reproducibility of two tests for IgE determination, the radioactive single radial immunodiffusion and the radioimmunosorbent test (RIST). Because of the higher sensitivity we chose the RIST as method for IgE determination. All levels reported here were done by RIST.

Radioimmunosorbent technique was carried out as described by *Wide & Porath* (27) and modified for IgE determination by *Johansson et al.* (14). The test set which we received from 'Pharmacia', Uppsala, contained anti-myeloma protein-ND labelled with ^{125} Iodine with a specific activity of about $50\mu\text{Ci}/\mu\text{g}$. The test system was controlled with the IgE standard 69/204 received from the WHO International Reference Centre for Immunoglobulins, Lausanne.

Radioactive single radial immunodiffusion was performed as described by *Rowe* (21): sheep-anti-human-IgE-serum, obtained from 'Pharmacia', Uppsala, diluted 1:1000 was immersed in Noble agar (Difco Laboratories, Detroit) to a final agar concentration of 3 per cent. The gamma-globulin fraction of a rabbit-anti-serum was separated by precipitation with 16 per cent sodium sulfate and afterwards labelled with ^{125} Iodine (Farbwerke Hoechst AG, Frankfurt/Main) according to *McConahey & Dixon* (19). After dialysis the trichloroacetic acid precipitable radioactivity was measured in a well-type gamma ray scintillation detector (Frieske & Hoepfner FHT 660 B 1 S).

RESULTS AND DISCUSSION

The serum IgE levels in a group of non-selected adults showed the following: the mean level in this group, 209 U/ml, range 83–650, is in good agreement with the results of *Johansson* (13) (248 ng/ml, range 66–1830), *Gleich et al.* (9) (193 ng/ml), and *Bazaraal et al.* (2) (205 U/ml, range 19.4–810). Although we expected a Gauss distribution of IgE levels in the random population, we found a multimodal distribution. Considering the distribution curve the IgE levels deviate among three maxima. According to the maxima the total was divided into three groups, denoted as A^2 , $2Aa$ and a^2 . The

TABLE 1

Presumptive Gene Frequencies Derived from Clinical Data and IgE Levels.

Genotype	Wiener et al. (28) clinical data	Bazara! et al. (2) IgE level	Own results IgE level
AA	0.7225	0.7473 (0.7473)	0.7600 (0.7600)
Aa	0.2550	0.2315 (0.2344)	0.2200 (0.2236)
aa	0.0233	0.0210 (0.0183)	0.0200 (0.0164)

Theoretical frequencies calculated from $\sqrt{A^2}$ according to the *Hardy-Weinberg* law are presented in brackets.

mean values of each group differ statistically significant ($p = < 0.01$). The proportions among the three groups $A^2 : 2Aa : a^2$ are 0.76 : 0.22 : 0.02 and fit the *Hardy-Weinberg* law, which describes the frequencies of two alleles, dis-segregating at a single genetic locus. The theoretical frequencies derived according to *Hardy-Weinberg* from $\sqrt{A^2} = 0.8717$ are 0.7600 : 0.2236 : 0.0164 which is in agreement with our experimental findings. Recently *Bazara! et al.* (2) reported about analogous findings in the distribution of IgE levels in normal adults which he obtained from his own and *Johansson's* results (12). The proportions of frequencies among the three groups are very similar to our results (Table 1).

An extensive clinical analysis of atopic diseases in respect to heredity was performed by *Wiener et al.* (28). He interpreted his data supposing that a single alleomorphic gene is responsible for the expression of atopy. He proposed that those patients, in which atopic diseases become manifest before puberty are homozygous in respect to the allele a. Heterozygous individuals are either healthy transmitters of the gene a or show atopic manifestation later in life. In this genotype group (Aa) one sixth will manifest symptoms after puberty, five sixth not at all. The gene frequencies published

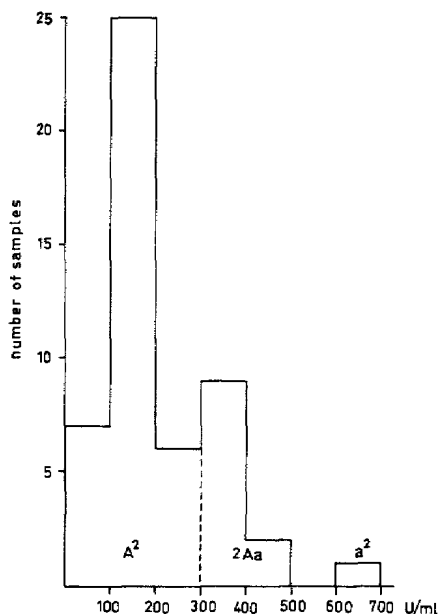


Fig. 1.

Frequency distribution of IgE levels in 50 unselected blood donors. According to the maxima the samples were divided into three groups denoted as A^2 , $2Aa$, and a^2 . The frequencies of the three groups $A^2 : 2Aa : a^2$ are $0.76 : 0.22 : 0.02$ and fit the Hardy-Weinberg distribution with the calculated hypothetical frequencies $0.7600 : 0.2236 : 0.0164$ calculated from $\sqrt{A^2}$.

by *Wiener et al.* (28) are in good agreement with our own findings and those of *Bazaraal et al.* (2), based on the frequency distribution of IgE levels in a random population. In both studies the actual gene frequencies are in accordance with the theoretical frequencies calculated according to *Hardy-Weinberg*.

We examined if the individual IgE levels of different genotypes in atopic families run parallel to the statistical results in the random population. Fig. 2 shows the levels of 49 persons belonging to 12 atopic families. Excessive high

levels originated from individuals suffering from two or more manifestations, either at the same time or alternatively which has been described previously by *Juhlin et al.* (15). According to *Wiener's* theory (28) patients having their onset of atopic disease before puberty were distributed to genotype aaF (see Fig. 2) whereas the ones with onset after puberty and healthy parents of atopic children with genotype aaF were distributed to genotype AaF. The genotype of nine healthy children from atopic families could not be determined since they might belong as well to genotype AAaF as to AaF. The frequency distribution of IgE levels in the atopic family group is plotted down in Fig. 3. It can be noted that the distribution of IgE levels of the two genotypes are signif-

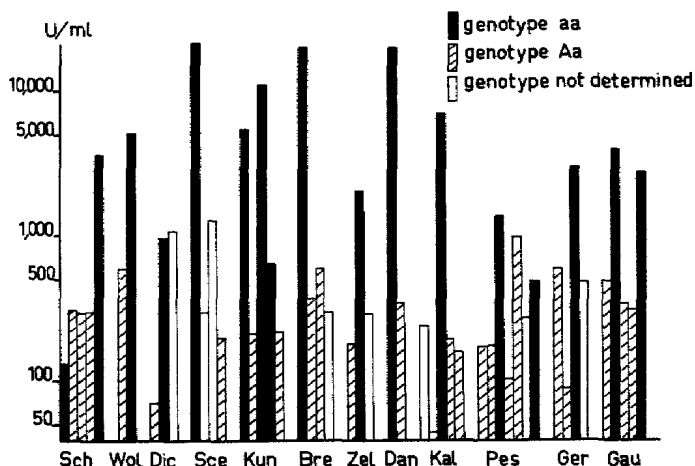


Fig. 2.

IgE-levels (U/ml) of members of atopic families. According to *Wiener's* theory (6) individuals having their onset of atopic disease before puberty were distributed to genotype aa (black columns). Individuals with onset of disease after puberty and healthy parents having children of genotype aa were distributed to genotype Aa (hatched columns). In nine cases the genotype of healthy children could not be determined, since they might either belong to genotype AA or Aa.

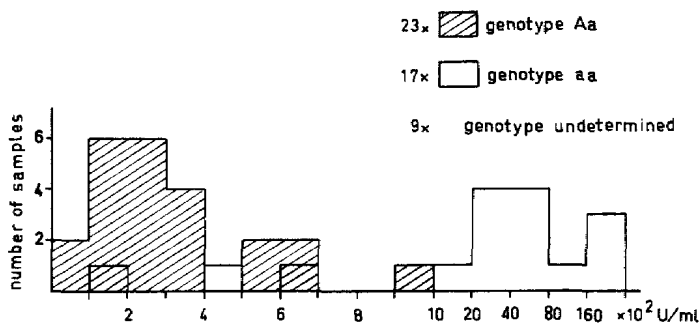


Fig. 3.

Frequency distribution of IgE-levels (U/ml) in members of atopic families. IgE level and genotype of individual members of atopic families were plotted down in this figure. The genotype was determined by help of clinical data according to Wiener (28). Individuals with onset of atopic disease before puberty were distributed to genotype aa, the ones with onset after puberty to genotype Aa. Healthy parents of children with genotype aa had to be joined to genotype Aa. The genotype of nine healthy children could not be determined (see text).

icantly different ($p = < 0.01$), even with overlapping in a few cases. Furthermore, they are in accordance with the analogous genotypes aa_N and Aa_N in the random population. The calculation of significance against genotype aa_N proved to be difficult, since this group comprised only one person, because of the rarity of this genotype in a random population.

The numerical distribution of the different genotypes in atopic families and in the unselected population are specified in Table 2.

The *Hardy-Weinberg* law describes mathematically the frequencies in a population of two alleles belonging to one genetic locus. Basing on clinical statistics *Wiener* found gene frequencies in the occurrence of atopic diseases which fitted the *Hardy-Weinberg* law. In our own studies we found group distributions of IgE levels in a normal population which also fitted the *Hardy-Weinberg* law. If one compares the

TABLE 2

Mean IgE Levels of Different Genotype and Calculation of Significance Among the Different Groups.

	Genotype	n	Mean level and variance	Significance at percentage level		
				AA _N	Aa _N	aa _N
Random population	AA _N	38	154 ± 55		<0.01	*)
	Aa _N	11	358 ± 54	<0.01		*)
	aa _N	1	650	*)	*)	
Members of atopic families					Aa _F	aa _F
	Aa _F	23	322 ± 220			<0.01
	aa _F	17	644 ± 7170		<0.01	
				AA _N	Aa _N	aa _N
	Aa _F			<0.01	NS	*)
	aa _F			<0.01	<0.01	*)

*) Since genotype aa_N is represented by one person calculation of significance is statistically not allowed.

percentage proportions of the three groups in our results with those of *Wiener's* study a remarkable identity is evident. Since IgE plays a decisive role in pathogenesis of atopy, our results support evidence for a common genetic control of IgE level and atopic disposition. This control seems to be exerted by two alleles belonging to one locus. It would be of interest to get information about the antigenic relationship between IgE molecules, synthesized by different genotypes. Possibly they differ in the sense of allotypes, as it is known in the case of IgG where allelic control was demonstrated (8).

In animal experiments *Levine* (17) could show that reagin production in mice is under genetic control of two alleles belonging to one locus. The reagins of the rat (24), mouse (6), guinea pig (7), rabbit (11), dog (22), and monkey

(20) share common physicochemical properties with human IgE. Serological cross reactions between rat- and human IgE could be established by two different investigators, (16, 18) suggesting a common phylogenetic origin of IgE in the different species. Recalling *Levine's* findings (17) one might assume that genetic regulation of IgE production is similar in species with common IgE properties.

Adaptive immunity also exerts regulatory influence on the IgE level, since severity of an atopic disease is not always accompanied by an appropriate rise of IgE level (15, 26). Further elucidation of these regulatory functions are to be expected by studies on the feedback mechanism performed by other specific immunoglobulins, as for instance the blocking antibodies on IgE synthesis. Promising are studies of *Tada & Okumura* (25) who demonstrated the suppressive effect of specific homologous γ S-gammaglobulins on rat reagins.

SUMMARY

Serum IgE levels were determined in members of atopic families and in a random population. The distribution of IgE levels in the random group follows the *Hardy-Weinberg* law, which describes the segregation of two alleles at a single locus. The frequencies of the alleles derived from our results are in good agreement with those of other investigations based on clinical data. According to *Wiener* members of the atopic families were divided into homozygous and heterozygous. Both groups show different distribution patterns of their IgE levels. Our results supply evidence for the possibility that the predisposition to atopy and synthesis of IgE is under identical gene control.

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