Familial Accumulation of Carriers of Au Antigen

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Summary. The sibs and parents of 83 Au-positive blood donors were tested in order to study the possible family clustering of Au positives in a population with a low frequency of carriers of Australia (Au) antigen. Tested by counter-electrophoresis the incidence of Au antigen in the parents of Au-positive persons is 5.4% and in the sibs 17.9%, compared to 0.15% in blood donors.

The hypothesis that the Au-carrier state is genetically determined was tested by calculating the proportion of Au-positive children in the families. The results are not inconsistent with a recessive mode of inheritance but do not allow definitive conclusions to be drawn.

Since Blumberg first presented his genetic hypothesis that the Au-antigen carrier state was inherited as an autosomal recessive trait the main data have come from two groups only, ie, that of Blumberg himself (Blumberg *et al*, 1966 and 1969) and that of Carbonara *et al* (1970). It is amazing that after 10 years there seems still to be great controversy about the significance of familial clustering of the carriers of Au antigen. One reason clearly is that, so far, the series systematically investigated all come from populations with a very high carrier frequency compared with those observed in countries where millions of blood donors are regularly screened.

The present series comes from a population with a relatively low frequency of carriers, ie, about 1.5 per thousand. The clustering in families is accordingly studied under conditions where the frequency is compared with a general population with very few carriers indeed.

Material and Methods

Screening of the Finnish Red Cross blood donors was started in 1969 using the Ouchterlony immunodiffusion method (Melartin, Myllylä, and Penttinen, 1970). The present series consists of two groups. In October 1970, all carriers who lived in the southern counties were asked to participate in the study. It soon became clear that due to the predominance of younger age groups in-

sufficient data would be obtained on the children. Another group of carriers, all over 30, was then contacted. These 210 carriers were asked to give information about their first-degree relatives who were then asked to give a blood sample. The number of living first-degree relatives was 916 and a sample was received from 743 of them. This report includes all the families in which both parents were investigated, a total of 83. The number of sibs was 195 and a sample was received from 173 of them.

While the *propositi* were selected using the immune diffusion technique only, the relatives were studied in addition with counter-immunoelectrophoresis* (Gocke and Howe, 1970) and a commercial radioimmunoassay† to obtain the most reliable results possible.

Results

Altogether there were 45 Au-antigen carriers among the 339 parents and sibs (Table I). This incidence is approximately 75 times higher than that in the general population. Due to limited family size identification of all pairs of heterozygous parents is not possible through families with one or more affected offspring. Consequently in order to test the genetic hypothesis presented by Blumberg the proportion of Au-positive children to all children must be mathematically corrected according to the mode of ascertainment. This correction has been

* IEP.

† Ausria-125, Abbott—RIA.

TABLE I
Au-ANTIGEN CARRIERS IN PARENTS AND SIBS
OF 83 FAMILIES

	Au-positive				
	Tested	IEP*		RIA†	
		Number	%	Number	%
Parents	166	9	5.4	14	8.4
Sibs	173	29	16.8	31	17.9

* IEP = counter-immunoelectrophoresis.

† RIA = radio immunoassay.

done (see Tables II and III) in two different mating types assuming that the ascertainment is complete (Li, 1961). The ratio obtained does not rule out a possibility of recessive inheritance with theoretical corresponding values of 0.50 and 0.25, respectively.

Discussion

The incidence of Au carriers appear to be age-dependent, the frequency being lower in young children and old adults (Lous, Skinhøj, and Olesen, 1970; Iwarson *et al*, 1972). In genetic terms, the

TABLE II
SEGREGATION OF Au ANTIGEN (Au₁) IN FAMILIES WITH AT LEAST ONE Au₁ (POSITIVE) CHILD
(MATING TYPE, NEGATIVE × NEGATIVE)

Family Size(s)	No. of Families (n _s)		No. of Children (sn _s = t _s)		Observed No. of Au ₁ (r _s)		Theoretical Total No. of Children ($C_s = \frac{t_s}{1 - (\frac{1}{4})_s}$)		Corrected Proportion of Au ₁ ($b_s = \frac{r_s}{C_s}$)	
	IEP	RIA	IEP	RIA	IEP	RIA	IEP	RIA	IEP	RIA
2	23	22	46	44	25	24	102.86	100.57	0.243	0.239
3	17	14	51	42	22	17	88.24	72.66	0.249	0.234
4	9	9	36	36	12	12	52.63	52.63	0.228	0.228
5	7	7	35	35	11	11	45.87	45.87	0.240	0.240
6	7	6	42	36	15	12	51.09	43.79	0.294	0.274
7	1	1	7	7	2	2	8.07	8.07	0.248	0.248
8	1	1	8	8	2	2	8.89	8.89	0.225	0.225
Total	65	60	225	208	89	80	357.66	332.48	0.249	0.241
	N		T		R		C		B	
									0.013 δ _B	0.014 δ _B

δ = standard error.

TABLE III
MATING TYPE, POSITIVE × NEGATIVE

Family Size (s)	No. of Families (n _s)		No. of Children (sn _s = t _s)		Observed No. of Au ₁ (r _s)		Theoretical Total No. of Children ($C_s = \frac{t_s}{1 - (\frac{1}{4})_s}$)		Corrected Proportion of Au ₁ ($b_s = \frac{r_s}{C_s}$)	
	IEP	RIA	IEP	RIA	IEP	RIA	IEP	RIA	IEP	RIA
2	3	4	6	8	4	5	8.00	10.67	0.500	0.469
3	2	5	6	15	4	9	6.86	17.14	0.883	0.525
4	2	2	8	8	6	6	8.53	8.53	0.703	0.703
5	—	—	—	—	—	—	—	—	—	—
6	—	1	—	6	—	3	—	6.09	—	0.492
Total	7	12	20	37	14	23	23.39	42.43	0.598	0.542
	N		T		R		C		B	
									0.077 δ _B	0.059 δ _B

penetrance of the Au_1 gene is incomplete at least in the young and the aged; in other words, there are people who will become carriers as well as those in whom, after carrying the antigen perhaps for long periods, it cannot be identified with the present methods.

Incomplete penetrance will affect the results of any genetic analysis. The effect is dependent on the age distribution of the family material. If the penetrance is not far from complete in the age groups, say, between 15 and 40 years, the incidence among sibs in this series—as in those of Blumberg and Carbonara and their coworkers—will give a reliable result. There is, however, another source of bias which affects the result the more the higher the frequency of Au-antigen carriers; that is, matings $Au_{neg} \times Au_{neg}$ which are negative by all testing methods but genetically can be $Au_{neg} \times Au_{pos}$. The number of these false negative matings rises with parental age and rising gene frequency. These matings show a normal/affected ratio of 0.50 instead of 0.25 which would compensate, or even over-compensate, the differences caused by incomplete penetrance in some of the sibs. In contrast to the frequencies in Indonesia and Sardinia which might well be four or five times higher, in Finland, the frequency of the Au_1 gene would hardly be higher than 0.15 and probably less.

Some evidence of the effect of incomplete penetrance in the mating distribution might be seen especially in the Sardinian series. There were 34 $Au_{neg} \times Au_{neg}$ and as few as 7 $Au_{pos} \times Au_{neg}$ matings. This ratio should be in complete penetrance, if Au_0 is denoted by p and Au_1 by q then $(2pq)^2:(q^2 \cdot 2pq)$ or $2p:q$. In Blumberg's series the ratio was higher, being 41:24. Whether this is a result of a difference between the gene frequencies,

age distribution, or some other factors cannot be decided.

The fact that the incidence of carriers among the sibs seems to be independent of the general incidence in the population studied is compatible with the genetic hypothesis. The same holds true of the incidence of carriers among the parents and children, which is much lower in Finland than in the high incidence countries. Facts which are incompatible with the genetic hypothesis will not be discussed in this preliminary report. These include, for example, higher incidence in spouses of the carriers and lack of antigen in one of identical twins of children in mating between two carriers. A detailed analysis of a larger epidemiological study is under preparation.

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