Acta Medica Okayama

Volume 25, *Issue* 3 1971 *Article* 4

JUNE 1971

Estimation of the frequency of the recessive gene of acatalasemia in Japan

Masana Ogata* Sumiko Hayashi†

Shigeo Takahara‡

*Okayama University,

†Okayama University,

‡Okayama University,

Estimation of the frequency of the recessive gene of acatalasemia in Japan*

Masana Ogata, Sumiko Hayashi, and Shigeo Takahara

Abstract

The frequency of recessive gene, heterozygotes and homozygotes in Japanese acatalasemia were estimated as 0.0038, 7.5 X 10-3 and 3.0 X 10-5 by DAHLBERG'S formula, and estimated as 0.00087, 1.73 xl 0-3 and 4.23 X 10-6 by KIMURA'S formula. The frequency of recessive gene was calcu. lated from the frequency of hypocatalasemia obtained by the screening method as 0.00083, and it was almost identical with that calculated 1:'>y KIMURA'S formula. The number of acatalasemia was estimated as about 423 by KIMURA'S formula.

*PMID: 4263520 [PubMed - indexed for MEDLINE]

Acta Med. Okayama **25**, 193—198 (1971)

ESTIMATION OF THE FREQUENCY OF THE RECESSIVE GENE OF ACATALASEMIA IN JAPAN

Masana OGATA, Sumiko HAYASHI and
Shigeo TAKAHARA*

Department of Public Health, Okayama University Medical School, Okayama, Japan (Director: Prof. M. Ogata)

Received for publication, May 2, 1971

Acatalasemia, constitutional abnormality characterized by trace or lack of catalase enzyme in blood, was first discovered by TAKAHARA in 1947 (1). To date, 83 cases of acatalasemias from 44 Japanese families and 3 cases from a pure Korean family have been found in Japan.

From the kindredship of acatalasemia's parents, the frequency of the recessive gene, heterozygotes and homozygotes were calculated by the use of DAHLBERG's and KIMURA's formulas (2, 3). The results were presented in this paper.

MATERIALS AND METHODS

Materials:

Seventy-two cases of acatalasemia from 38 sibling groups of Japanese, whose kindred could be surveyed, were used as materials for calculation. In addition to this, 44 cases of hypocatalasemia and one case of acatalasemia found in 24192 persons by screening method were also surveyed as materials. Screening of hypocatalasemia was conducted by the method of TAKAHARA *et al.* (4).

Methods:

1) Estimation of the frequency of the recessive gene used by DAHLBERG's formula (2).

q: The frequency of the recessive gene responsible for acatalasemia.
k: The proportion of first cousin marriages among the parents of homozygotes individuals.
c: The proportion of first cousin marriages among the population as a whole.
α: The coefficient of inbreeding for the population.

* Department of Oto-Rhino-Laryngology, Okayama University Medical School, Okayama, Japan

From these elements, DAHLBERG's formula was derived, namely,

$$q=\frac{c(1-k)}{16k-15c-ck} \tag{1}$$

$$\text{The frequency of heterozygotes}=2q(1-q)(1-\alpha) \tag{2}$$

$$\text{The frequency of homozygotes}=q+(1-\alpha)q^2 \tag{3}$$

2) Estimation of the frequency of recessive gene used by KIMURA's formula (3).

x : The frequency of the recessive gene responsible for acatalasemia
f_i : The inbreeding coefficient
m_i : The number of sibling groups including of cases of acatalasemia
M : The total number of m_i
u_i : m_i/M
V_0 : The proportion of the sibling groups whose parents were not of inbreeding marriage among the population as a whole

KIMURA's formula is as follows.

$$V_0\sum_{i=0}\frac{u_i}{x+(1-x)f_i}-\frac{u_0}{x}=0 \tag{4}$$

The formula for the variance of estimate is as follows.

$$V_{\bar{x}}=\frac{\frac{1}{M}\left\{\left(\frac{V_0-1}{x}\right)^2u_0+V_0^2\left[\left(\frac{16}{1+15x}\right)^2u_2+\left(\frac{32}{1+31x}\right)^2u_2+\cdots\right]\right\}+\frac{u_0^2(1-V_0)}{V_0x^2N}}{\left\{V_0\left(\frac{u_0}{x^2}+\frac{15\cdot16\cdot u_1}{(1+15x)^2}+\frac{31\cdot32\cdot u_2}{(1+31x)^2}+\cdots\right)-\frac{u_0}{x^2}\right\}^2} \tag{5}$$

RESULTS

1) Estimation of the frequency of the recessive gene from DAHLBERG's formula.

The proportion of first cousin marriages among the parents of cases of acatalasemia (k) was 0.526 (20/38). The proportion of first cousin marriages among the population as a whole (c) is assumed from previous studies (5, 6) to be 0.06 in Japan, and the coefficient of inbreeding for the population (α) is also assumed from the previous studies (5) to be 0.004. Using these values and equation (1), the frequency of recessive gene was calculated to be 0.0038 and the frequency of heterozygotes and homozygotes were also calculated to be 7.5×10^{-3} and 3.0×10^{-5} respectively.

2) Estimation of the recessive gene frequency from KIMURA's formula.

KIMURA provided a more general maximum likelihood-type formula, which has the advantage of utilizing for the estimate all the data available concerning consanguinity in the parents of affected individuals. Further-

more, KIMURA derived the formula for the variance of the estimate value, which was not available in DAHLBERG's approach. In Japan, there are many types of inbreeding marriages as well as the first cousin marriages. So we used this method for estimation.

At first, we classified 38 sibling groups (72 cases of acatalasemia) according to the type of kindredship of parents of acatalasemic individuals as shown in Table 1 and those of the family relation with complicated blood relationship, as shown in Fig. 1. The proportion of the sibling groups whose parents were not of inbreeding marriages among the population as a whole (V_0) is assumed to be 0.9. Using these values and equations, the gene frequency (x) is estimated at 0.00087 with a standard error of 0.00052. The frequency of heterozygotes is estimated to be 1.73×10^{-3}, and a standard error is $\sigma_{\text{Het}}=\left(\frac{\delta\,\text{Het}}{\delta x}\right)\sigma x=2(1-\alpha)(1-2\bar{x})\,\sigma x=0.00103=1.03\times10^{-3}$. The frequency of homozygotes is estimated to be 4.23×10^{-6}, and a standard error is $\sigma_{\text{Hom}}=\left(\frac{\delta\,\text{Hom}}{\delta x}\right)\sigma x=[2\bar{x}+(1-2\bar{x})\alpha]\sigma x=2.98\times10^{-6}$. So, the frequency of recessive gene, heterozygotes and homozygotes are 0.00087 ± 0.00052, $(1.73\pm1.03)\times10^{-3}$ and $(4.23\pm2.98)\times10^{-6}$ respectively.

TABLE 1. THE TYPE OF KINDREDSHIP OF PARENTS OF ACATALASEMIC INDIVIDUALS

Consanguinity	inbreeding coefficient (fi)	number of cases of acatalasemia	number of sibling groups of acatalasemia	ui (mi/M)
1st cousin marriage	$\frac{1}{16}$	40	20	0.5263
1 1/2 cousin marriage	$\frac{1}{32}$	9	4	0.1053
2nd cousin marriage	$\frac{1}{64}$	2	1	0.0263
2 1/2 cousin marriage	$\frac{1}{128}$	2	1	0.0263
(A) (*)	$\frac{21}{256}$	1	1	0.0263
(B)	$\frac{5}{64}$	2	1	0.0263
(C)	$\frac{1}{512}$	2	1	0.0263
(D)	$\frac{5}{128}$	3	1	0.0263
non-consanguineous marriage	0	11	8	0.2105
Total		72	38	1.0000

(*): The cases of (A), (B), (C) and (D) are shown in Fig. 1.

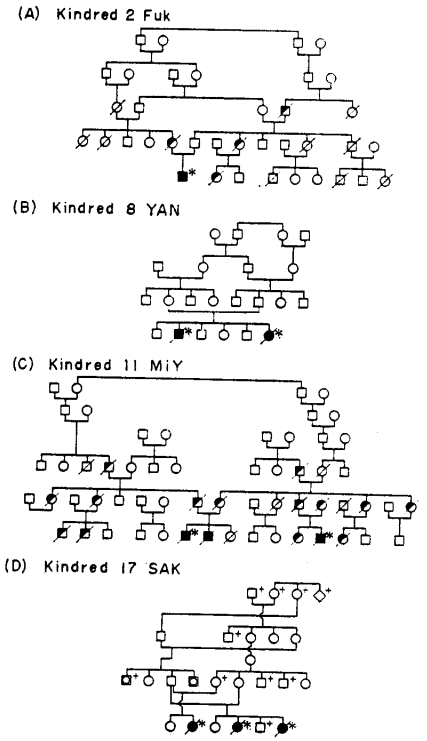

Fig. 1 The cases of the family relation with common ancestor in past due to the complicated blood relationship, and the calculations of inbreeding coefficient:
(A)*$\frac{1}{2^2}\times\frac{1}{2^2}+\frac{1}{2^3}\times\frac{1}{2^3}+\frac{1}{2^4}\times\frac{1}{2^4}=\frac{21}{256}$ (B)*$\frac{1}{2^2}\times\frac{1}{2^2}+\frac{1}{2^3}\times\frac{1}{2^3}=\frac{5}{64}$
(C)*$\frac{1}{2^4}\times\frac{1}{2^5}=\frac{1}{512}$ (D)*$\frac{1}{2^2}\times\frac{1}{2^3}+\frac{1}{2^3}\times\frac{1}{2^4}=\frac{5}{128}$

On the other hand, we calculated the frequency of heterozygotes using the results of screening. By screening method, 44 cases of hypocatalasemia and an acatalasemia were found in 24192 persons, and parents of 4 cases in 44 hypocatalasemias were inbreeding marriages. The frequency of heterozygotes $=(44-4)/(24192-4)=0.00165$. The expected value of the frequency of heterozygotes (Het) is as follows, $\mathrm{Het}=2\bar{x}(1-\bar{x})(1-\alpha)\approx 2\bar{x}$, $\bar{x}\approx\frac{\mathrm{Het}}{2}=0.00083$. This value is nearly equal to the value of $\bar{x}=0.00087$ which calculated from the equation (2).

DISCUSSION

The frequency of recessive gene of acatalasemia in Japanese calculat-

ed by DAHLBERG's formula is 0.0038 and that by KIMURA's formula 0.00087, and the former is 4 times as much as the latter. This is due to the fact that k value is underestimated. In Japanese acatalasemic family, the inbreeding marriages except first cousin marriage were found frequently. In DAHLBERG's formula, only proportion of first cousin marriage to all acatalasemic parents is used, and in the KIMURA's formula, inbreeding coefficient of all cases is used. Therefore, the latter is more adaptable than the former for estimating the frequency of recessive gene, homozygotes and heterozygotes of Japanese. The frequency of homozygotes calculated by DAHLBERG's formula is 3.0×10^{-5} and that by KIMURA's formula is 4.23×10^{-6}. About 423 persons of acatalasemia are estimated by the frequency of homozygotes by KIMURA's formula. As 83 persons out of 44 sibling groups have been found up to date, it is estimated that about 340 persons of non-detected acatalasemia shall be found among Japanese.

In 1963, HAMILTON (7) repored that gene frequency of acatalasemia is estimated at 0.006 by DAHLBERG's formula and 0.00082 with a standard error of 0.0053 by KIMURA's formula. As with only 17 sibling groups on which to base the gene frequency estimate, a large errow was to be expected in this case. As 44 sibling groups were used in our case, gene frequency is estimated at 0.00087 with a standard error of 0.00052, indicating that error is smaller than that of HAMITON's case. The value 0.00087 of gene frequency almost agrees with that calculated from the screening case.

CONCLUSION

The frequency of recessive gene, heterozygotes and homozygotes in Japanese acatalasemia were estimated as 0.0038, 7.5×10^{-3} and 3.0×10^{-5} by DAHLBERG's formula, and estimated as 0.00087, 1.73×10^{-3} and 4.23×10^{-6} by KIMURA's formula. The frequency of recessive gene was calculated from the frequency of hypocatalasemia obtained by the screening method as 0.00083, and it was almost identical with that calculated by KIMURA's formula. The number of acatalasemia was estimated as about 423 by KIMURA's formula.

ACKNOWLEDGEMENT

The authors wish to express profound gratitude to Dr. NORIKAZU YASUDA of Department of Population Genetics, National Institute of Genetics (Japan) for kind advice,

REFERENCES

1. TAKAHARA, S.: Progressive oral gangrene probably due to lack of catalase in the blood, *Lancet* **6**, 1101, 1952
2. DAHLBERG, G.: On rare defects in human populations with particular regard to inbreeding and isolate effects, *Proc. Roy. Soc. Edinburgh* **58**, 213, 1938
3. KIMURA, M.: Theoretical basis for the study of inbreeding in man, *Jap. J. Hum. Genet.* **3**, 51, 1958
4. TAKAHARA, S., HAMILTON, H. B., NEEL, J. V., KOBARA, T. Y., OGURA, Y. and NISHIMURA, E. T.: Hypocatalasemia, a new genetic carrier state, *J. Clin. Invest.* **39**, 610, 1960
5. NEEL, J. V., KODANI, M., *et al.*: The incidence of consanguineous matings in Japan, *Am. J. Hum. Genet.* **1**, 156, 1949
6. SCHULL, W. J.: A note on consanguineous marriages in the cities of Hiroshima and Nagasaki, *Jap. J. Hum. Genet.* **3**, 33, 1958
7. HAMILTON, H. B., NEEL, J. V., KOBARA, T. Y. and OZAKI, K.: The frequency in Japan of carriers of the rare recessive gene causing acatalasemia, *Jap. J. Hum. Genet.* **8** (3), 163, 1963