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Multicenter Genetic Study of Retinitis Pigmentosa in Japan: II. Prevalence of Autosomal Recessive Retinitis Pigmentosa

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Abstract: Retinitis pigmentosa (RP) is a group of genetically heterogeneous diseases with autosomal recessive (AR), autosomal dominant, and X-linked modes of inheritance. Autosomal recessive retinitis pigmentosa (ARRP) is the most common form in Japan. A genetic analysis was done to determine the prevalence of ARRP indirectly, to provide an estimation of changing trends in the overall prevalence of RP. Data on the frequency of consanguinity and marriage year of normal parents of 59 ARRP patients were obtained from a nationwide multicenter survey of typical retinitis pigmentosa conducted in 1990. The gene frequency of ARRP was 0.01145 (Dahlberg's formula). In 1990, the number of young symptomatic ARRP patients decreased, while the number of patients aged 40 years and older increased. The total number of symptomatic ARRP patients in 1990 was nearly 21% higher than in 1970. Despite a dramatic decline in consanguinity in recent decades in Japan, the number of ARRP patients has increased. This increase is attributed to greater longevity and overall population growth. Our results suggest that the total number of RP patients has not decreased, and may even have increased. **Jpn J Ophthalmol 1997;41:7–11** © 1997 Japanese Ophthalmological Society

Key Words: Autosomal recessive inheritance, consanguineous marriage, gene frequency, inbreeding coefficient, prevalence, retinitis pigmentosa.

Introduction

Typical retinitis pigmentosa (RP) is one of the major causes of visual loss in advanced countries. It is a

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Table 1. Relationship of ARRP Patients

Relationship	Related		Unrelated	Unknown	Total
	First Cousins	Others			
Number of patients	14	3	34	8	59

genetically heterogeneous group of diseases that includes autosomal recessive (AR), autosomal dominant (AD), and X-linked (XL) modes of inheritance. The dramatic decline in consanguinity in recent decades in Japan,[12] has led to widespread speculation that the incidence of ARRP has likewise declined. As ARRP is the most common form of RP in Japan,[3–6] such a decrease would be expected to result in a lower prevalence of RP in the Japanese population.[3,5] However, greater longevity and overall population growth[7] seem to have contributed to an increase in numbers of both ARRP and RP patients as a whole. The multiplicity of factors makes precise determination of the prevalence of RP difficult. We have attempted to estimate changing trends in the overall prevalence of RP by analyzing ARRP in order to obtain data applicable to designing social care and rehabilitation services for RP patients.

Materials and Methods

Data on the parental relationship and marriage years of normal parents of ARRP patients were obtained from a nationwide multicenter survey of RP conducted in 1990.[8] Subjects and family history charts were the same as those used for the heterogeneity survey.[9] Among the 434 patients, 59 had one or more affected siblings with normal parents and were thus considered to be ARRP patients. The gene frequency (q) was calculated using Dahlberg's formula:

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

In this formula, variables k and c are the frequency of first-cousin marriages among the parents of ARRP patients and the general population, respectively. The variable c was calculated using both the distribution of marriage years of normal parents of the ARRP patients in this study and data on first-cousin marriages in the general population.[1,2]

The frequency of homozygotes (Q) was determined using the following formula:

$$Q = Fq + (1-F)q^2 \cdots \quad (2)$$

F is the inbreeding coefficient of the general population calculated from data on consanguineous marriages in the general population.[1,2]

The total number of symptomatic ARRP patients, excluding homozygotes without subjective symptoms, is calculated by multiplying the total Japanese population by Q times the percentage of symptomatic patients. The latter value was based on previous data[8] of cumulative percentage of age at which ARRP patients first experienced visual difficulty. The results of each 10-year age group were then combined to determine the overall prevalence of symptomatic

Table 2. Distribution of Parental Marriage Year for ARRP Patients and Inbreeding Data for the General Population

Marriage Year	Parental Marriage Year[a] for ARRP Patients in This Study (%)	General Population[1,2]	
		Frequencies of First-Cousin Marriages (%)	Average Inbreeding Coefficient (F)[b]
<1947.6.1[c]	41 (69.5)	46 (7.2)	0.00586
1947.6.2–1957.6.1[c]	7 (11.9)	96 (3.7)	0.00290
1957.6.2–1967.6.1[c]	5 (8.5)	38 (1.0)	0.00103
1967.6.2–1983.9.1[d]	6 (10.2)	27 (0.7)	0.00062
Total	59 (100.1)	207 (1.9)	

[a]Parental marriage year assumed to be 2 years before ARRP patient's birth.
[b]F is calculated from the data of consanguineous marriages in the general population.[1,2]
[c]Data from Imaizumi et al, 1975.[1]
[d]Data from Imaizumi, 1986.[2]

Table 3. Calculated Number of Symptomatic ARRP Patients in Japanese Population in 1970

Age	Average Inbreeding Coefficient of General Population (F)[a] ($\times 10^{-3}$)	Frequency of ARRP Homozygotes (Q)[b] ($\times 10^{-4}$)	Japanese Population Numbers in 1970[7] ($\times 10^{4}$)	Cumulative % of Symptomatic ARRP[8] (%)	Symptomatic ARRP Patients (N)
70 and over	5.86	1.974	434	100.0	857
60–69	5.86	1.974	668	98.9	1304
50–59	5.86	1.974	918	95.9	1738
40–49	5.86	1.974	1315	90.8	2357
30–39	5.86	1.974	1650	79.7	2596
20–29	5.86	1.974	1963	67.6	2620
10–19	2.90	1.639	1680	54.5	1501
<9	1.03	1.428	1685	24.2	582
Total					13 555

[a]F obtained from Table 2.
[b]Q calculated using formula (2).

ARRP patients in the Japanese population. These calculations were done for 1970 and for 1990 in order to compare the results.

Results

The k value in this survey was 27.5%, excluding 8 cases without information regarding the relationship of their parents (Table 1). The c value was 0.056, using the distribution of assumed parental marriage years for the 59 ARRP patients and the frequencies of first-cousin marriages in the general population (Table 2). The q value of ARRP was estimated as 0.01145. The calculated average inbreeding coefficient (F) for the general population is also shown in Table 2. The calculated number of symptomatic ARRP patients in Japan was 13 555 in 1970 (Table 3) and 16, 385 in 1990 (Table 4), with an increase of nearly 21%. A clear increase in the number of ARRP patients aged 40 years and older was found. This increase parallels the overall increase in the size of the Japanese population. In contrast to 1970, when the ARRP peak was seen in their twenties (Table 3), the majority of ARRP patients in 1990 were in their forties (Table 4). The decline in ARRP among young adults is significant in 1990 (Table 4). The frequency of homozy-

Table 4. Calculated Number of Symptomatic ARRP Patients in Japanese Population in 1990

Age	Average Inbreeding Coefficient of General Population (F)[a] ($\times 10^{-3}$)	Frequency of ARRP Homozygotes (Q)[b] ($\times 10^{-4}$)	Japanese Population Numbers in 1990[7] ($\times 10^{4}$)	Cumulative % of Symptomatic ARRP[8] (%)	Symptomatic ARRP Patients (N)
70 and over	5.86	1.974	978	100.0	1931
60–69	5.86	1.974	1183	98.9	2310
50–59	5.86	1.974	1578	95.9	2987
40–49	5.86	1.974	1961	90.8	3515
30–39	2.90	1.639	1666	79.7	2176
20–29	1.03	1.428	1670	67.6	1612
10–19	0.62	1.381	1846	54.5	1389
<9	0.62	1.381	1391	24.2	465
Total					16 385

[a]F obtained from Table 2.
[b]Q calculated using formula (2).

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gotes (Q) whose parents married before 1947, ie, those 40 years of age and over in 1990, was 1.974×10^{-4}. The same calculation for those <20 years of age yielded a rate of 1.381×10^{-4} (Table 4). In this 20-year period, the frequency of homozygotes (Q) decreased by 30%.

Discussion

Comparison of the number of patients between 1970 and 1990 shows that the prevalence of ARRP is increasing, with the majority of patients presently being middle-aged or elderly, while the incidence of ARRP in younger generations is decreasing due to declining consanguinity.

In recent decades, genetic analysis of diseases has been hampered by the small family size in Japan. Autosomal recessive inheritance is often difficult to verify without affected siblings. Approximately 50% of patients surveyed in recent studies were simplex cases.[8–10] We realize that 59 is a rather small number of subjects for conducting a genetic analysis of this type. The gene frequency (q) yielded by our data is, however, comparable to previously reported values: 0.0123,[11] 0.0092,[6] and 0.0078–0.0119.[3] Therefore, we consider our calculated q of 0.01145 to be reliable.

Formula (2), by which the frequency of homozygotes (Q) is calculated, can be applied when one causative gene is present.[3] When there are n causative genes, the Q must be multiplied by the value of n.[3] Molecular genetic studies have revealed at least four distinct genes causing ARRP[12–15] as well as interactions between mutations causing RP.[16] We anticipate that all causative genes and the detailed genetic mechanisms, which are presently unknown, will be identified in Japanese ARRP patients in the future. These discoveries will necessitate modifications of the formula (2). At present, however, we do not have sufficient data to attempt to modify the formula (2). The calculated numbers of symptomatic ARRP patients in Japan, approximately 13 600 in 1970 and 16 400 in 1990, may also be low estimates and require revision after further advances in molecular genetic studies of ARRP. However, comparison of the 1970 and the 1990 data is valid for demonstrating changing trends in the prevalence of ARRP in the Japanese population because the obligate gene, the gene frequency, and genetic mechanisms of ARRP have remained the same from 1970 to 1990. It is also essential to note that Q was determined only by the inbreeding coefficient (F), which has decreased in parallel with consanguinity. Patient number is affected by changes in Q and in total population numbers. Comparison of the number of patients between 1970 and 1990 is, therefore, unaffected by the numbers of causative genes responsible for ARRP.

In recent decades, no distinct factors operating to produce changes in the numbers of patients with XLRP and ADRP have been identified. Therefore, the incidences of RP with these inheritance patterns may have remained stable while the prevalences appear to have increased according to population growth. The lack of a decrease in the number of ARRP patients, despite a dramatic decline in consanguinity, suggests that the total number of RP patients has not decreased and may even have increased due to greater longevity and overall population growth. The elderly population was larger in 1993 than in 1990.[7] We assume that this trend will continue, resulting in an even larger total RP population, especially among the elderly. Our results suggest that rehabilitation services and social care for elderly RP patients with severe visual loss will become increasingly important in the near future.

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