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Multicenter Genetic Study of Retinitis Pigmentosa in Japan: I. Genetic Heterogeneity in Typical Retinitis Pigmentosa

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Abstract: A nationwide, multicenter study of typical retinitis pigmentosa (RP) was carried out in collaboration with 18 hospitals throughout Japan to obtain current information for genetic counseling. We analyzed the genetic heterogeneity of RP based on the parental consanguinity of 434 probands registered during a 6-month period in 1990. A gradual decline in the frequency of consanguineous marriage was recognized among the normal parents of RP patients. The relative frequencies of inheritance patterns were estimated as: autosomal recessive, 25.2%; autosomal dominant, 16.9%; X-linked, 1.6%; and simplex, 56.3%. A comparison of these results with previous reports in Japan revealed a decline in the relative frequency of autosomal recessive cases and an increase in simplex cases. This suggests a decrease in the incidence of autosomal recessive retinitis pigmentosa in Japan, as well as the necessity for exhaustive investigations aimed at identifying inheritance patterns for RP patients seeking genetic counseling. **Jpn J Ophthalmol 1997;41:1–6** © 1997 Japanese Ophthalmological Society

Key Words: Consanguinity, genetic counseling, genetic heterogeneity, retinitis pigmentosa.

Introduction

Typical retinitis pigmentosa (RP) is a group of genetically heterogeneous diseases including autosomal dominant (AD), autosomal recessive (AR), and X-linked (XL) inheritance patterns. The course is intractable, with no effective treatment at present. Genetic counseling is an important aspect of patient

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care, in addition to rehabilitative services and psychological support.

Previously reported data indicate that autosomal recessive retinitis pigmentosa (ARRP) is the most common form in Japan.[1–4] Over the past few decades, however, there has been a dramatic decline in consanguineous marriage.[5,6] In addition, family size has decreased markedly.[7] Simultaneously, industrialization and the economic demands of modernization have contributed to migration of the population into cities from rural areas. These social changes are likely to have modified the genetic aspects of this disease. We recently reported a genetic analysis of RP patients in a preliminary collaborative study involving 14 hospitals, where members of the research committee on chorioretinal degeneration practiced.[8] The present study was designed to evaluate the relative frequencies of different inheritance patterns in RP patients throughout Japan to obtain information applicable to genetic counseling. Inbreeding data were also analyzed in each area and for every decade.

Materials and Methods

A nationwide, multicenter study of typical RP was done by the research committee on chorioretinal degeneration,[9] under the sponsorship of the Ministry of Health and Welfare of Japan. Seventeen university hospitals and one prefectural hospital participated in this survey (Figure 1). A uniform clinical data sheet was used that included age at onset, disease pro-

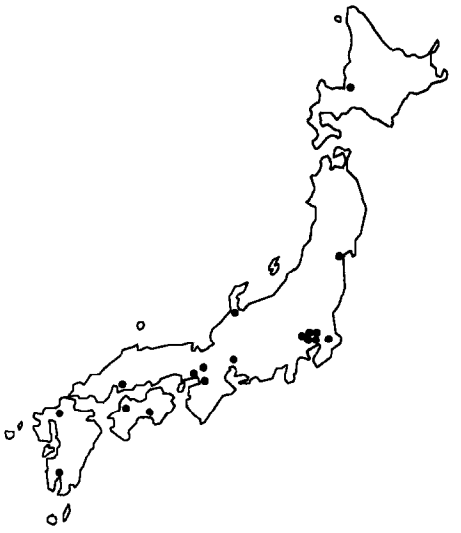

Figure 1. Geographic distribution of participating hospitals: Black dots indicate location of 18 participating hospitals.

Table 1. Individual Family History Chart

Parent	Consanguinity	1. No 2. Yes (1C, 1 1/2C, 2C, others, unknown) 3. Unknown
	Affected parent	1. No 2. Yes (father, mother) 3. Unknown
Siblings	Number of siblings excluding proband (elder brother, younger brother, elder sister, younger sister)	___persons
	Affected siblings	1. No 2. Yes (Number: elder brother___, younger brother___, elder sister___, younger sister___) 3. Unknown
Children	Number of children	___persons
	Affected children	1. No 2. Yes (Number: son___, daughter___) 3. Unknown
Other affected relatives		1. No 2. Yes Paternal · · · grandfather, grandmother, uncle, aunt, nephew, niece, male cousin, female cousin Maternal · · · grandfather, grandmother, uncle, aunt, nephew, niece, male cousin, female cousin Others (specify relationship)_____ 3. Unknown

1C: first cousins, 1 1/2C: first cousins once removed, 2C: second cousins.

Table 2. Distribution of Parental Relationships and Average Inbreeding Coefficient in Each Group

Group	Parental Relationship: Related 1C (%)	1 1/2 C	2C	Other	Total (%)	Unrelated	Unknown	Total	Average Inbreeding Coefficient (α_i)[a]
I	3 (5.9)	0	0	1	4 (7.8)	39	8	51	0.00436
II	14 (23.7)	1	0	2	17 (28.8)	34	8	59	0.01777
III	2 (9.1)	1	1	0	4 (18.2)	17	1	22	0.00818
IV	2 (16.7)	0	0	0	2 (16.7)	10	0	12	0.01042
V	25 (8.8)	3	5	14	47 (16.6)	230	6	283	0.00626
VI	0 (0.0)	0	0	0	0 (0.0)	7	0	7	0.0
Total (%)	46 (10.6)	5 (1.1)	6 (1.4)	17 (3.9)	74 (17.1)	337	23	434 (100.0)	

1C: first cousins, 1 1/2C: first cousins once removed, 2C: second cousins.

[a] α_i was given by the following formula in cases with known parental relationship in each group: α_i = (number of patients with parental 1C marriage × 1/16 + number of patients with parental 1 1/2 C marriage × 1/32 + number of patients with parental 2C marriage × 1/64) ÷ total number of patients in each group.

gression, visual acuity, refractive error, findings of fundus, electroretinogram, dark adaptation, visual field, and ocular complications, such as cataract, glaucoma, and others. Patients who registered between April 1 and September 30, 1990, showing typical RP characteristics were included in this study. Criteria were: (1) progressive visual disturbance including night blindness, visual field loss, and retention of good or fair central vision until relatively late in the natural course of disease progression; (2) extinguished or severely diminished amplitudes on electroretinogram attributable to diffuse degenerative atrophy of the retina; and (3) ophthalmoscopically visible narrow retinal arterioles and various degrees of bone-spicule pigmentary clumping. Patients with the following diseases were excluded: atypical RP, such as the central and sectorial forms; retinitis punctata albescens; Leber's congenital amaurosis; choroidal dystrophies, including choroideremia and gyrate atrophy; retinal degeneration as part of a systemic syndrome, such as Usher's and Refsum's syndromes; and sequelae of non-hereditary diseases. After applying the above criteria, 534 registered RP patients remained. After excluding younger patients in any family in which multiple patients had been registered, as well as those who did not provide a detailed family history, 434 respondents (205 men and 229 women, each the eldest patient in his/her family, ranging in age from 7 to 84 years with a mean of 45.7 ± 17.2 years) had provided sufficient information for this genetic analysis.

Data concerning the types and frequencies of parental consanguineous marriages and the year of marriage were analyzed. We used family history charts (Table 1) to analyze inbreeding, using a modification of the Matsunaga method.[8] Subjects were divided into 6 groups according to the following family history criteria: (I) at least one affected parent; (II) affected siblings, both parents normal; (III) affected relatives other than parents and siblings; (IV) siblings and other relatives affected, both parents normal; (V) no known affected relatives; and (VI) male patients with affected male relatives on the maternal side.

Group II was considered to represent ARRP. The proportion of ARRP in each group (yi) is given by the following formula.[1]

$$y_i = (\alpha_i - \alpha)/(\alpha_2 - \alpha) \cdots\cdots \quad (1)$$

In this formula, α_i, α_2, and α are the average inbreeding coefficients of each group, group II, and the general population in Japan, respectively. The α was calculated using the average inbreeding coefficients of previously reported inbreeding data for the general population,[5,6] then weighted according to the marriage year distribution of patients' parents in this study. In group I, subtracting the rate of ARRP cases from total cases yields the rate of ADRP cases. In groups III and IV, subtracting the rate of the ARRP cases from the total yields the rate of ADRP cases, since the XL cases are in group VI. In group

Table 3. Distribution of Parental Marriage Year

Parental Marriage Year[a]	Number of Patients (%)
<1947.6.1	284 (65.5)
1947.6.2–1957.6.1	66 (15.2)
1957.6.2–1967.6.1	34 (7.8)
1967.6.2–1983.9.1	50 (11.5)
Total	434 (100.0)

Marriage-year group based on general population data.[5,6]

[a] Parental marriage year assumed to be 2 years before patient's birth.

Table 4. Frequencies of Consanguineous Marriages According to Marriage Year in General Population and Calculated Average Coefficient of Inbreeding

Marriage Year	Relationship							Average Coefficient of Inbreeding
	Related[5,6]					Unrelated[5,6]	Total[a]	
	1C (%)	1 1/2C	2C	2 1/2C	Other			
<1947.6.1[b]	46 (7.2)	16	24	—	18	536	640	0.00586
1947.6.2–1957.6.1[b]	96 (3.7)	25	44	—	55	2352	2572	0.00290
1957.6.2–1967.6.1[b]	38 (1.0)	29	39	—	37	3646	3789	0.00103
1967.6.2–1983.6.1[c]	27 (0.7)	10	21	9	13	3815	3895	0.00062
Total	207 (1.9)	80	128	9	123	10349	10896	

1C: first cousins, 1 1/2C: first cousins once removed, 2C: second cousins.
[a]Total number of marriages excluding those with unknown relationship.
[b]Data obtained from Imaizumi et al, 1975.[5]
[c]Data obtained from Imaizumi, 1986.[6]

V, subtracting the rate of the ARRP cases from the total yields the rate of simplex cases.

Results

1. Relative Frequencies of Each Inheritance Pattern

The parental relationship distribution and calculated α_i are shown in Table 2. The parental marriage-year distribution, according to previously reported general population data,[5,6] is shown in Table 3. The relationship data for the general population[5,6] and average coefficient of inbreeding calculated in each marriage year are shown in Table 4. The α value was calculated to be 0.00443.

The y_i and the frequencies of each inheritance pattern are shown in Table 5. In group I, the y value was negative, indicating that all cases were AD. In group II, all 59 cases were considered to be AR. In group III, y was calculated to be 0.2811. The total number in group III was 22. Therefore, the calculated number of AR was $22 \times 0.2811 = 6.2$, and the remaining 15.8 were thus assumed to be AD. In group IV, the number of AR was calculated to be 5.4 and the remaining 6.6 were considered to be AD. In group V, the calculated number of AR was 38.8 and the remaining 244.2 were assumed to be simplex cases. In group VI, there were 7 cases identified as XL. Therefore, the relative frequencies of the inheritance patterns for AR, AD, XL, and simplex were estimated to be 25.2, 16.9, 1.6, and 56.3%, respectively.

2. Changes in Frequency of Consanguineous Marriage Among Normal Parents of Patients

The frequency of consanguineous marriage was high during the 1947–1957 period. Subsequently, a gradual decline was noted for each 10-year period, except in the post-1977 marriage-year group in which the patient number was too small, only nine (Table 6).

3. Geographical Distribution of Parental Consanguinity

The frequency of consanguineous marriage was negligible in Hokkaido, while Kyushu had the highest

Table 5. Proportion of ARRP (y_i) in Each Group and Frequency of Each Inheritance Pattern

Group	y_i	Proband		Number of Patients	Inheritance Pattern			
		Male	Female		AD	AR	Spl	XL
I	—	27	24	51	51.0	—	—	—
II	1.0	34	25	59	—	59.0	—	—
III	0.2811	6	16	22	15.8	6.2	—	—
IV	0.4490	5	7	12	6.6	5.4	—	—
V	0.1372	126	157	283	?	38.8	244.2	?
VI	—	7	0	0	—	—	—	7
Total		205	229	434	73.4	109.4	244.2	7
(%)				(100.0)	(16.9)	(25.2)	(56.3)	(1.6)

AD: autosomal dominant, AR: autosomal recessive, Spl: simplex, XL: X-linked.

Table 6. Frequencies of Consanguineous Marriage Among Normal Parents of Patients According to Parental Marriage Year

	Parental Relationship							
	Related							
Year[a]	IC (%)	1 1/2C	2C	Other	Total (%)	Unrelated	Unknown	Total (%)
<1947.6.1	30 (11.9)	2	4	9	45 (17.8)	199	9	253 (100.0)
1947.6.2–1957.6.1	10 (17.9)	1	1	4	16 (28.6)	38	2	56 (100.0)
1957.6.2–1967.6.1	1 (3.2)	0	0	3	4 (12.9)	26	1	31 (100.0)
1967.6.2–1977.6.1	1 (2.9)	2	0	0	3 (8.8)	28	3	34 (100.0)
>1977.6.2	1 (11.1)	0	1	0	2 (22.2)	7	0	9 (100.0)
Total (%)	43 (11.2)	5	6	16	70 (18.3)	298	15	383 (100.0)

IC: first cousin, 1 1/2C: first cousin once removed, 2C: second cousin.
[a]Marriage-year group based on general population data.[5,6]

Table 7. Frequencies of Parental Consanguinity by Geographic Area

	Parental Relationship							
	Related							
Area	1C (%)	1 1/2C	2C	Other	Total (%)	Unrelated	Unknown	Total (%)
Hokkaido	0 (0.0)	0	0	0	0 (0.0)	6	0	6 (1.4)
Tohoku	1 (6.3)	0	0	0	1 (7.6)	12	3	1 (3.7)
Kanto	14 (8.8)	1	2	5	22 (14.7)	128	9	159 (36.6)
Chubu	6 (9.2)	0	0	1	7 (12.3)	50	8	65 (15.0)
Kinki	15 (11.7)	3	3	9	30 (23.8)	96	2	128 (29.5)
Chugoku	1 (11.1)	0	0	0	1 (11.1)	8	0	9 (2.1)
Shikoku	1 (8.3)	0	1	0	2 (16.7)	10	0	12 (2.8)
Kyushu	7 (20.6)	1	0	1	9 (27.3)	24	1	34 (7.8)
Unknown	1	0	0	1	2	3	0	5 (1.1)
Total (%)	46 (10.6)	5	6	17	74 (17.1)	337	23	434 (100.0)

1C: first cousins, 1 1/2C: first cousins once removed, 2C: second cousins.

Table 8. Percentages of Each Retinitis Pigmentosa Inheritance Pattern in Japan

Authors (Reported Year)	Tanabe[12] (1972)	Ohba et al[2] (1975)	Matsunaga et al[1] (1977)	Hayakawa et al[10] (1989)	Fujiki et al[8] (1990)	This Study
Investigation Period	1960–1964	1972–1975	1974–1976	1980–1988	1989	1990
Spl				50	34.6	56.3
AR	54.6	88.5*	67	31	47.6	25.2
AD		10.6	30	12	17.3	16.9
XL		0.9	3†	5	0.5	1.6
Undetermined				2		
f: No. of families p: No. of patients	1650f[a]	104f[b]	588f[c]	385p[d]	181f[e]	434f

[a]Inbreeding analysis of collaborative data from 9 university hospitals and 1 public hospital.
[b]Data from Tokyo University analyzed by classification of family tree hereditary pattern (*includes 61 simplex cases).
[c]Inbreeding analysis of collaborative data from 12 university hospitals and 1 public hospital (†includes phenocopies).
[d]Data from Juntendo University analyzed by classification of family tree hereditary pattern.
[e]Inbreeding analysis of collaborative data from 13 university hospitals and 1 prefectural hospital.

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rates for first-cousin marriages (20.6%) and total consanguineous marriages (27.3%) (Table 7), though the difference did not reach statistical significance.

Discussion

The trend toward smaller family size in recent decades[7] has decreased the number of siblings of patients; therefore it is very difficult to distinguish AR from simplex cases. With male patients, the possibility of XL inheritance must also be considered. Individuals now tend to live in small family units, often far from second- and third-degree relatives, making it very difficult to obtain information on affected members in AD and XL families. Simplex cases appear to include AR without affected siblings, as well as AD and XL without known affected relatives. The calculated frequencies of AR, AD, and XL types in this study may therefore be lower than the actual values. Nonetheless, our data reflect the current relative frequency of each inheritance pattern.

Despite a decline in first-cousin marriages among the general population[5,6] (Table 4), a high frequency of consanguineous marriage among patients' parents was recorded in 1947–1957 (Table 6). This period includes the postwar baby boom.[7] With the exception of this period, and the post-1977 period in which there are only nine subjects, the consanguinity rate has shown a steady decline. The incidence of AR therefore is believed to have decreased in recent decades.

The frequencies of consanguineous marriages of patients' parents varied according to geographic area. We found the highest frequency in Kyushu, the lowest in Hokkaido. This geographic distribution tendency is consistent with that of consanguineous marriages for the general population in Japan.[6]

A decrease in the relative frequency of AR is apparent, when the results of this study and data reported in the 1990s[8–10] are compared with those obtained in the 1970s[1–4] (Table 8). The proportion of AR in group V was 60% in the report by Matsunaga et al,[1] but was 13.7% in this study (Table 5). This suggests that AR may not account for the majority of simplex cases in recent decades. The decrease in AR has not, however, led to relative increases in the frequencies of AD and XL (Table 8). This is considered to be attributable to difficulties in diagnosing AD and XL, as discussed above. In Japan a large proportion of patients has been dealt with as AR cases in genetic counseling when their inheritance pattern was unknown.[11] These results show the necessity for making greater efforts to identify inheritance patterns for RP patients seeking genetic counseling.

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