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Intrapair Differences of Physical Aging and Longevity in Identical Twins

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Abstract. The genetic and environmental contributions to physical aging (hair graying, balding, presbyopia) and longevity (age at death) were examined by within-pair comparison in monozygotic (MZ) and dizygotic (DZ) twins in later adulthood. Physical aging was investigated on 135 pairs of adult twins aged over 50. Hair graying and hair loss (baldness) showed significantly higher rates of concordance in the MZ twins than in the DZ twins. The intrapair difference of the degree of hair graying was negligible in 79%, slight in 15% and striking in 5% among the MZ pairs; while negligible in 40%, slight in 50% and striking in 10% among the DZ pairs. The intrapair difference of the degree of hair loss was negligible in 92%, slight in 8% (and striking in none) among the MZ pairs; while negligible in 69%, slight in 25% and striking in 6% among the DZ pairs. The age at onset of presbyopia showed a slightly higher rate of concordance in the MZ than in the DZ pairs. Longevity (age at death) was surveyed on 184 pairs of twins who died at over 40 years of age. The intrapair difference of longevity was 6.65 ± 5.6 years (maximum 18.0; minimum 0.04) in the MZ pairs, and 8.66 ± 7.2 years (maximum 18.6; minimum 2.9) in the DZ pairs. The MZ pairs showed a slightly smaller within-pair difference of longevity than the DZ pairs.

Key words: Physical aging, Longevity, Twins, Environment, Genetic factors

INTRODUCTION

The mechanisms of physiological aging and senescence are still unknown, although it is generally considered that genetic and environmental factors are interrelated in the

process of human aging. One of the most indicative research methods to investigate the nature-nurture problem is twin study. Monozygotic (MZ) and dizygotic (DZ) twins in later adulthood provide an outstanding opportunity to examine the influences of genetic and environmental factors on human senescence and longevity.

In the literature review, there is a very limited number of twin research studies on physical aging and longevity [18,19,23,24]. The twin studies by Kallmann [18,19] would appear to be the earliest and largest twin research on senescence and longevity. Shimizu's work [23,24] in Japan should also be noted as a pioneering study on senescence. Since those early twin studies were conducted over thirty years ago, more precise twin research is needed on senescence and human longevity in order to examine the genetic and environmental influences. In this study, as a preliminary report on senescence and longevity, the cohort study results of Kinki University Adult Twin Registry were reported.

METHODS

The subjects were 1982 pairs of adult twins in the Kinki University Adult Twin Registry [8-12]. These twins were follow-up surveyed for 13 years. Twin pairs in this panel were collected by several means, such as, newspaper advertisement, posters in hospitals, referral from nurse-midwives and follow-up of twin subjects in previous twin studies in collaboration with the retired researchers. 135 pairs living apart in the community volunteered to visit Kinki University Hospital for a comprehensive medical examination. The ages of these twins varied from 50 to 95 years; the majority were in their 50s or 60s. Zygosity was established from the results of the PTC (Phenylthiocarbamide) test and 9 blood systems: ABO, Rh (C, c, D, E, e), MN (M,N), Lewis (Le^a, Le^b), P (P_1), Duffy (Fy^a, Fy^b), Kidd (Jk^a, Jk^b), Kell (k) and Diego (Di^a). There were 76 MZ pairs (46 male and 30 female) and 21 like-sexed DZ pairs (18 male and 3 female).

Twenty-one unlike-sexed pairs were excluded from the data analysis in this study. The clinical examinations conducted at the University Hospital included: anthropological physical measurement, electrocardiogram, blood chemicals (90 items, such as serum lipids, Ig, etc), blood pressure, blood types, urine chemicals, audiometry, the Maudsley Personality Inventory, the Wechsler Adult Intelligence Scale, personal interview (on personal history, family history, etc) and a nutritional intake survey.

Concerning the data analysis, the variance analysis performed according to Snedecor et al [25] produced intraclass correlation coefficients. Skewness and kurtosis of the data distribution were tested by Fisher's cumulative method [5].

RESULTS

Within-pair hair graying was compared in both monozygotic and dizygotic pairs. Thirty-nine monozygotic pairs and 9 dizygotic pairs showed a certain degree of hair graying. Twin pairs who showed no hair graying at all were excluded from this comparison. The degree of hair graying was measured by the observed percentage of white hair. Measurement was conducted by a single examiner in order to avoid the influence of examiner

differences. The results of intrapair hair graying are shown in Table 1. In the male MZ pairs, there was a negligible difference in 25 pairs; a slight difference in 6 pairs and a striking difference in one pair. In the female MZ pairs, there was a negligible difference in 6 pairs and a striking difference in one pair. On the other hand, in the DZ pairs, there was a negligible difference in 4 male pairs, a slight difference in 5 male pairs and a striking difference in one female pair. The intrapair concordance rate was defined by the formula (None)/(None + Slight + Striking). The intrapair concordance rate was 79.4% in the MZ pairs and 40% in the DZ pairs. The intrapair concordance rate on hair graying was significantly higher in the MZ pairs than in the DZ pairs ($p < 0.01$).

Table 1 - Intrapair difference of hair graying

Difference	MZ**		DZ	
	Male pairs	Female pairs	Male pairs	Female pairs
None	25	6	4	0
Slight	6	0	5	0
Striking	1	1	0	1

** $p<0.01$

The results of intrapair comparison on hair loss (balding) are shown in Table 2. The monozygotic pairs, showed a negligible difference in 39 male pairs and 21 female pairs; a slight difference in 3 male pairs and 2 female pairs, and a striking difference in none. On the other hand, in the dizygotic pairs, there was a negligible difference in 9 male pairs and 2 female pairs; a slight difference in 4 male pairs; and a striking difference in one male pair. The intrapair concordance rate on hair loss was 92.3% in the MZ pairs and 68.7% in the DZ pairs. Again, the intrapair concordance rate on balding was significantly higher in the MZ than in the DZ pairs ($p< 0.05$).

Table 2 - Intrapair difference of hair loss (baldness)

Difference	MZ*		DZ	
	Male pairs	Female pairs	Male pairs	Female pairs
None	39	21	9	2
Slight	3	2	4	0
Striking	0	0	1	0

* $p<0.05$

As regards age at onset of presbyopia, the intraclass correlation coefficients were calculated for MZ and DZ twins. Table 3 shows the results. The intraclass correlation coefficient was 0.552 in the male MZ; 0.718 in the female MZ; and 0.455 in the male

Table 3 - Intraclass correlation coefficients of onset age of presbyopia in aging twins

	MZ*	DZ
Male	0.552**	0.455*
Female	0.718**	—

* $p<0.05$
** $p<0.01$

DZ twins. The values of all these intraclass correlation coefficients were significant. The age at onset of presbyopia showed a significant tendency of intrapair similarity in both the MZ and DZ twins. The difference of intraclass correlation coefficients was not significant between the MZ and DZ twins.

For the intrapair difference of age at death, the subjects were 20 pairs (17 MZ pairs and 3 DZ pairs), in which both twins died over the age of 40. These subjects did not include twins who died due to accidents or suicide. As shown in Table 4, for the MZ twins, the average intrapair difference of age at death was 6.56 ± 5.6 years (maximum difference 18.0, minimum difference 0.04). In the DZ twins, the average intrapair difference of age at death was 8.66 ± 7.2 years (maximum difference 18.9, minimum difference 2.9). The average intrapair difference of age at death was slightly smaller in the MZ pairs than in the DZ pairs, but not significant. The maximum difference was nil between the MZ and DZ twin pairs, while the minimum difference was slightly greater in the DZ than in the MZ pairs. Since the number of DZ pairs was very limited, it was not easy to compare between MZ and DZ pairs in this aspect of the study.

Table 4 - Intrapair difference of age at death in 184 pairs of adult twins who died over 40 years of age (excluding deaths due to accidents/suicide)

Difference	MZ	DZ
Average	6.56 ± 5.6 yr	8.66 ± 7.2 yr
Maximum	18.0	18.9
Minimum	0.04	2.9

Besides the above 20 pairs in which both twins died, there were 148 pairs in which one twin had died at over 40 years of age and the other one was still alive. Table 5 shows the average age at death for the twin pairs in which one or both had died (independent of cause). The average age of death of "both dead" twins was 68.2 ± 7.7 years in the male MZ pairs; 71.5 ± 8.2 years in the female MZ pairs and 66.0 ± 7.8 in the male DZ pairs. The average age at death of "one dead" twins was 58.3 ± 10.1 years in the male MZ pairs, 65.2 ± 10.1 years in the female MZ pairs; 62.4 ± 11.7 years in the male DZ pairs and 63.3 ± 7.3 years in the female DZ pairs. These were the average age at death

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Table 5 - Average age at death in adult twins who died at over 40 years of age. (including death due to accidents/suicide)

	Both dead		one dead & one alive	
	MZ	DZ	MZ	DZ
Male	68.2±7.7	66.0±7.8	58.3±10.1	62.4±11.7
Female	71.5±8.2	—	65.2±10.1	63.3± 7.3

values among twins who had died relatively earlier than the other subjects in the process of the follow-up study.

Regarding the cause of death, Table 6 shows the results of intrapair comparison (concordance) among twins over 40 years of age who had died. There were only two pairs who were concordant on the cause of death. Both pairs were MZ twins. The first concordant case was the pair who had died of myocardial infarction, in which one twin died at 65 years of age and the other at 63 years. Both had suffered from diabetes mellitus for a long time. The second concordant case was a pair involving lung cancer, in which one twin died at 78 years of age and the other twin died six months later. There were 30 twins (15 pairs) who were discordant on the cause of death in the MZ pairs of "both dead". The concordance rate of the cause of death was 11.7% in the MZ pairs. There was no concordant pair in the DZ twins. Concerning death due to cancer there were 3 pairs with lung cancer (1 concordant and 2 discordant); 5 discordant pairs with liver cancer; 2 discordant pairs with colon-rectum cancer; 1 discordant pair with cancer of the oesophagus; 1 discordant pair with kidney cancer: 1 discordant pair with cancer of the pancreas; 1 discordant pair with prostate cancer; 1 discordant pair with lymphatic tissue cancer; and one discordant pair with parotid cancer. There was a pair in which one twin died of lung cancer at the age of 78 and the other died of parotid cancer just 13 days later. Concerning the intrapair concordance of the cause of death very important information could be obtained through further study on the 148 pairs of "one dead and one alive" twins.

DISCUSSION

It is widely known that the experiments by Hayflick [13,14] were the first in scientific research on the limitation of human cell division and subsequently proposed a theoretical framework on human aging. Since then, the aging phenomenon has been investigated at various levels of physiological function. While research at the molecular level has been rapidly increasing in the last decade, a clear answer on the mechanisms of aging, has not yet been obtained. Although experiments with inbred-animals have been the major research method employed in the past, twin study has today become the most important research method on human subjects.

Twin study on aging was initiated by Kallman in New York [18,19]. His study is the pioneering legacy and remains the largest and most referred to twin study in this field.

Table 6 - Intrapair concordance of cause of death in twins who died over 40 years of age

Cause		Both dead				One dead (& one alive)	
		MZ		DZ		MZ	DZ
		Concor.	Discor.	Concor.	Discor.	Discor.	Discor.
Cerebral apoplexy			6		1	15	3
Cerebral infarction						5	2
Myocardial infarction		1*	3			15	7
CANCER	Lung	1**	2			5	
	Stomach				2	18	2
	Oesophagus		1			1	
	Liver		5			17	3
	Kidney		1		1	1	
	Colon, rectum		2			5	1
	Pancreas		1			2	1
	Prostate		1				
	Lymphatic tissue		1			1	
	Parotid		1				
	Leukemia					1	
	Mandibular					1	
	Brain					1	
Diabetes mellitus						3	1
Acute hepatitis						3	
Pneumonia						2	1
Kidney disorder						3	
Suicide						6	1
Accident			2		1	6	3
Other diseases			1		1	6	3
Unclear cause			3			2	1
Total		2	30	0	6	119	29

* Both twins were diabetic, and the disease course to death was similar within the pair.
** The intrapair difference of age at death was six months.

There is a great need to conduct a more precise larger-scale twin study on human aging and longevity, since the aging process is closely related to a number of diseases particular to later adulthood.

The authors have been conducting an adult twin cohort study since 1981 [8-12]. The twin subjects of that study group were basically population-based subjects collected from all over Japan. This study is a preliminary report on physiological aging, length of life span (age at death) and cause of death in those cohort twin subjects.

Concerning hair graying, previous reports by Shimizu [23,24] indicated a higher within-pair concordance rate in MZ twins than in DZ twins. The intrapair concordance rate in this present study was 79.4% in the MZ pairs and 40% in the DZ pairs. These

results are consistent with those of Shimizu. It was considered that the degree of hair graying was strongly influenced by genetic factors. It is interesting to note that in one MZ pair the hair definitely showed a mirror-image phenomenon. One twin had a white curling-hair spot of coin size on the right side of the head while the other had a white hair spot, the same size, curling in the opposite direction on the corresponding site of the left side of the head. There were several other MZ pairs whose hair graying looked like a mirror-image phenomenon. No DZ pair had hair showing a mirror-image phenomenon. These results indicated that the site of hair graying, as well as the degree of hair graying, was influenced by genetic factors.

In contrast, there were 2 MZ pairs (1 male and 1 female) who showed a striking within-pair difference in the degree of hair graying. Of the female pair, the twin who had had a hysterectomy showed the greater degree of hair graying which had advanced quickly after the operation. It was assumed that the hormonal change after hysterectomy induced the striking within-pair difference in this case. In the male MZ pair, the twin with the lower degree of hair graying was congenitally deaf; the other twin was not. One of the assumed causes of this intrapair difference is the difference of lifestyle environmental factors between the deaf twin and the healthy twin. It is also assumed that the physiological mechanisms relating to deafness contributed to the striking intrapair difference of hair graying in this case.

Concerning the degree of hair loss (balding), Shimizu [23] indicated a higher intrapair concordance rate in the male MZ than in the male DZ pairs. The difference was negligible in 92.3% of the MZ pairs and in 68.7% of the DZ pairs in this study. These results indicated that genetic components made the intrapair similarity significantly higher in the MZ than in the DZ pairs. The genetic influence was also strongly indicated by the results which showed that there was no pair with a striking intrapair difference in the MZ twin pairs.

No previous twin study was found concerning the onset age of presbyopia. In this study, the onset age of presbyopia was based on the age when the subject started to use eye glasses for presbyopia. The results showed no significant difference of intraclass correlation coefficients between the MZ and DZ twin pairs (MZ:0.552, DZ:0.455). A strong influence of environmental factors was indicated in the onset age of presbyopia. The moderately high levels of intraclass correlations seen in both the MZ and DZ pairs suggested that the intrapair similarity of various lifestyle factors affected the onset age of presbyopia.

In the comparison of age at death in this study, there were only a few pairs who died at a similar age within the pair. Kallmann et al [18] reported the mean intrapair difference of age at death to be 36.9 months in MZ pairs and 78.3 months in DZ pairs and also indicated the involvement of a strong genetic influence. On the other hand, Jarvik et al [16] who conducted the 12-year follow-up study of Kallmann's subjects (75 MZ pairs and 88 DZ pairs) reported that there was no significant difference in the age at death for the male twins between the MZ pairs (62.5 months) and DZ pairs (65.0 months). They also reported that the female twins showed a significant intrapair difference between the MZ (55.4 months) and DZ (80.9 months) pairs, but the difference was only significant among the twins who died between 60 and 69 years and not significant among the twins who died in their 70s or 80s. The results shown by Jarvik would seem very important and interesting to human longevity research. It was suggested that genet-

ic factors had a strong influence only among the female twins who died early in their 60s. In this study, the mean intrapair difference was 6.56 years in the MZ pairs. This value was only slightly greater than that (4.9 years in the total MZ) in Jarvik's report. The results of this study and Jarvik's study [16] were considered as showing environmental factors to have a strong influence and genetic factors to have a mild influence on the length of human life span. The slight difference between the two studies might be explained by the difference in the ages of the subjects. The subjects in this study included twins who died in the earlier over 40 age group.

Concerning the intrapair comparison of causes of death, few previous reports exist [3,16], while a fairly large number of previous reports exist on the comparison of disease incidence in twins [1,2,4,6,7,15,22]. Faire's report [3] on death by cerebral apoplexy and cerebral infarction seem most suggestive. He compared the observed rates with the expected rates of intrapair concordance of death by cerebral vascular disease. He suggests a strong environmental influence by showing no significant difference between the observed rate and expected rate. There was no concordant pair for cerebral vascular disease in this study. It can be said that the results in this study and those of Faire's study show a similar tendency of strong environmental influence. On the other hand, the concordance rate on the incidence of cerebral vascular disease was somewhat different from the concordance rate on death by cerebral vascular disease in Harvald's report [7]. He reported that the concordance rate of cerebral vascular disease was slightly higher in MZ twins (23.8%) than in DZ twins (12.5%), and also indicated a mild genetic influence. The consideration arrived at was that the incidence of cerebral vascular disease had some genetic involvement, while death by cerebral vascular disease was strongly influenced by non-genetic factors.

As regards the incidence of myocardial infarction, the works of Harvald [7] and Cederlof [2] seem most suggestive. The results of these previous twin studies indicate a weak genetic influence and a strong environmental influence. In our study, there was only one concordant MZ pair, in which both twins had diabetes mellitus as a basic health problem. It was therefore considered that the metabolic dysfunction due to diabetes mellitus had induced myocardial infarction in this particular case.

On the concordance for the incidence of cancer, Harvald [6] reported a very low concordance rate both in MZ (5.6%) and DZ (3.3%) twins, except for breast cancer in the MZ twins (19.0%). In this study, there was only one concordant pair for lung cancer, and the total concordance rate for cancer was similarly low (6.25%). In the lung-cancer concordant pair, some common factors relating to lung cancer were considered to be involved in its development, since both twins died at the same age.

As a total, concerning the cause of death, the within-pair concordance rate was only 11.7% in the MZ and 0% in the DZ pairs. It was therefore assumed that genetic components were not duely observed in the majority of twins deaths, but only in the very limited number of pairs whose deaths were due to specific diseases.

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