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Genetic and Environmental Determinants of Healthy Aging

Life at the Extreme Limit: Phenotypic Characteristics of Supercentenarians in Okinawa

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Background. As elite representatives of the rapidly increasing ''oldest-old'' population, centenarians have become an important model population for understanding human aging. However, as we are beginning to understand more about this important phenotype, another demographic group of even more elite survivors is emerging—so-called ''supercentenarians'' or those who survive 110-plus years. Little is known about these exceptional survivors.

Methods. We assessed the Okinawa Centenarian Study (OCS) database for all information on supercentenarians. The database includes dates of birth and year of death for all residents of Okinawa 99 years old or older and a yearly geriatric assessment of all centenarians who consented, enabling prospective study of age-related traits. Of 20 potential supercentenarians identified, 15 had agreed to participate in the OCS interview, physical examination, and blood draw. Of these 15, 12 (3 men and 9 women) met our age validation criteria and were accepted as supercentenarians. Phenotypic variables studied include medical and social history, activities of daily living (ADLs), and clinical phenotypes (physiology, hematology, biochemistry, and immunology).

Results. Age at death ranged from 110 to 112 years. The majority of supercentenarians had minimal clinically apparent disease until late in life, with cataracts (42%) and fractures (33%) being common and coronary heart disease (8%), stroke (8%), cancer (0%), and diabetes (0%) rare or not evident on clinical examination. Functionally, most supercentenarians were independent in ADLs at age 100 years, and few were institutionalized before the age of 105 years. Most had normal clinical parameters at age 100 years, but by age 105 exhibited multiple clinical markers of frailty coincident with a rapid ADL decline.

Conclusion. Supercentenarians displayed an exceptionally healthy aging phenotype where clinically apparent major chronic diseases and disabilities were markedly delayed, often beyond age 100. They had little clinical history of cardiovascular disease and reported no history of cancer or diabetes. This phenotype is consistent with a more elite phenotype than has been observed in prior studies of centenarians. The genetic and environmental antecedents of this exceptionally healthy aging phenotype deserve further study.

***Key Words*:** Supercentenarian—Longevity—Healthy aging—Phenotype—Okinawa—Japan.

FOR most of human history centenarians were a rare phenomenon. However, they are now among the most rapidly increasing demographic groups in developed countries (1,2). Since the early 1960s, the Japan Ministry of Health, Labour and Welfare has been tracking the population of centenarians in Japan. The prevalence of centenarians was low throughout Japan when they first began to be counted in 1963 with only 153 persons recorded nationwide (3). However, as Robine and colleagues (4) have shown, larger birth cohorts combined with lower mortality rates among the oldest old population have resulted in a rapid increase in this special demographic group. Consequently, a ''new generation'' of centenarians has arisen in Japan, and the total population of persons 100 years old or older reached 32,295 with a centenarian prevalence rate of 25.28 centenarians per 100,000 in 2007 (3). Because Japan is among the world's most rapidly aging countries, this demographic explosion of centenarians may yield important lessons for other rapidly aging countries (5–7).

Interestingly, a new and growing subpopulation of exceptionally aged individuals has arisen within the centenarian population. Gerontologists have recently defined this new demographic group as ''supercentenarians'' because they have achieved the previously unattainable age of 110 years or

more (8–10). This population has generated interest because of its potential to unlock genetic or other keys to healthy aging and longevity. As exceptional survivors at the tail end of an increasingly extended human survival curve, they may help us understand the driving forces behind the impressive increases in human survival, and perhaps aid us in forecasting new trends in aging (9,10). Finally, the morbidity patterns of these exceptional survivors may contribute to our understanding of morbidity and disability at older ages.

Recently, sufficient numbers of supercentenarians have appeared to justify study of their demographic (11) and familial characteristics (12). However, despite the fact that, by some estimates, as many as 1000 supercentenarians have been identified worldwide (13), the numbers that have been age-validated with strict criteria are much lower (11), and there has been little systematic study of their phenotypic characteristics, especially with regard to anthropometric, physiological, and clinical data. Moreover, other than a few isolated case reports, we found only one case series study of their phenotypic characteristics, such as incidence and prevalence of chronic diseases and functional status. This valuable study, by Schoenhofen and colleagues (14), was the first to report clinical histories and current functional status of supercentenarians. However, to our knowledge, no published study presents data from direct geriatric examination of more than one individual, and the aforementioned study, although important, relied mainly on self- or proxy reports of morbidity and function (14). Also, although informative work has been done on phenotypic characteristics, we have not been able to identify any study that assessed clinical blood work as a phenotype (i.e., serum or plasma studies) in more than one such individual. Finally, to our knowledge there has not been a single population-based, prospective clinical study of centenarians who later became supercentenarians—an event that is much more demographically challenging than becoming a centenarian. Therefore, we believe that further study of this exceptional demographic group is warranted.

Okinawa, the 47th prefecture of Japan, is well known for the longevity of its inhabitants. In 2007, 792 centenarians were counted from a total population of 1,368,000, resulting in the highest recorded centenarian prevalence in Japan, at 58 per 100,000 (3). All persons turning 100 years within the fiscal year in Japan (between April 1st and March 31st and counted yearly on September 30th) in Okinawa prefecture have been part of the Okinawa Centenarian Study (OCS) database since 1976 ($n = 3768$ as of 2007). Approximately 900 of these have been enrolled in the study thus far and have participated in an interview, clinical examination, and blood draw. For this study, we identified all potential supercentenarians reported to have lived in Okinawa from the OCS database. In total, 20 potential cases were identified. Of these 20, 15 had participated in the first stage of the interview given by the OCS. We were not able to further investigate the remaining five because of refusal to participate or prior death. Of these 15, 12 (3 men and 9 women) were age-validated with stringent validation criteria (see Participants and Methods), and their phenotypic characteristics were further studied in the current report. The other five potential cases had birth and death data supplied by government officials. We examined (1) sociodemographic characteristics of age-validated supercentenarians, including their frequency, gender, age at death, and living situations; (2) other age-related biomedical phenotypes, including past and present medical history, morbidity, and functional status; and (3) blood biochemistry, hematology, physiology, and immunology, to better understand biological phenotypes associated with healthy aging and exceptional longevity.

Participants and Methods

This study was conducted under ongoing Institutional Review Board approval from Okinawa International University. Informed consent was received from all study participants in Okinawa, and permission was granted from local municipalities and/or participants to review private documents such as the *koseki* (family register) or medical records.

Participant Identification and Validation

The OCS began recruitment of centenarians in 1976, and study protocol consists of an annual geriatric examination (including activities of daily living [ADLs], instrumental ADLs [IADLs], and blood draw), as well as anthropometric, demographic, psychological, social, and other parameters. The details of the OCS protocol have been reported elsewhere (6,15,16).

The first centenarian participant who became a supercentenarian was enrolled in 1985. All supercentenarians who took part in the current study were assessed between 1992 and 2007. Most supercentenarians were examined and followed from the time they reached the age of 99 years, but some entered the study at later ages. Therefore, study participants were seen on one or more occasions from as early as age 99 years until death (most were seen on three or more occasions).

Age validation was performed on several levels. First, participants were required to possess a valid family registration (*koseki)* document, which lists the proband's date of birth, birth order, location of birth, and other important demographic information; second, participants were required to provide at least one other document that listed the proband's age at an important life event (e.g., marriage certificate, driver's license); third, age needed to be credible after reconstruction of a family pedigree (pedigree included ages of birth and death, birth order, as well as cause of death of parents, siblings, and children of the supercentenarian); fourth, life history reconstruction needed to be credible. This reconstruction included major milestones, such as school graduations, marriage, military service, and career milestones. Finally, animal year of birth (*eto*) according to the traditional Chinese calendar, a valuable means of age identification in East Asian cultures, had to match official year of birth as recorded in the *koseki* (17). All documents must have been consistent with stated age (as reported by proband or health care proxy) to accept the proband as a validated supercentenarian.

Phenotypic Data

The phenotypic data for this study were collected as part of the ongoing OCS described above. Data were collected

during visits to study participants' places of residence. In addition to a geriatric physical examination, the OCS protocol includes assessment of ADL (assessed by physical examination and proxy); IADL; social and demographic characteristics including life history, medical history, dietary habits, family history, kinship diagram (pedigree); and health habits such as smoking and alcohol consumption. A 12-lead resting electrocardiogram is recorded and blood samples are collected.

ADL Assessment

ADLs are assessed with the Inoue Index, an expanded version of the Barthel Index, which is in common use throughout Japan (18). This index measures three major domains of function: physical, sensory, and cognitive. Each domain contains several items that are evaluated individually at one of five levels: completely independent (5), independent but slow (4), independent with difficulty (3), partially dependant (2), and completely dependant (1). Seven physical items are evaluated: self-feeding, bowel continence, bladder continence, standing, bathing, dressing, and range of mobility. In addition, two sensory items (visual and auditory acuity) and two cognitive items (self-expression and comprehension of conversation) are evaluated. In total, 11 items are surveyed with a maximum possible score of 55 and a minimum possible score of 11. Total ADL scores of participants are scored at one of five levels as follows: completely dependent (11 points); partially dependent (12–22 points); independent with difficulty (23–33 points); independent but slow (34–44 points); or completely independent (45–55 points).

Statistical Analysis

A mixed model regression (19) was used to analyze change over time for body mass index (BMI), ADLs, and other clinical measures (such as biochemistry, hematology, physiology, and immunology). These data are presented in Tables 3 and 4. Individual measures were regressed against age for each person. This model estimated the trends of change for every person and treated the estimated trends as a random variable. Overall mean of the trends was estimated, and the average yearly change was assessed. This model requires that each participant in the analysis has at least 3 data points (from a minimum of three separate geriatric assessments at different ages).

Results

In total, 20 alleged supercentenarians (3 men and 17 women) were identified. Age at death ranged from 110 to 112 years. Fifteen of these alleged supercentenarians were further investigated by our study team (as indicated above) and of these 15, 12 (3 men and 9 women) were age validated using the above protocol and were included in the current study. Unfortunately, we could not perform our additional age validation protocol on the five other alleged supercentenarians as they had either died before we were able to enroll them as study participants or were otherwise unavailable; we could only confirm dates of birth and dates of death as reported by public officials.

Table 1. Age at Death of Supercentenarians in Okinawa 1992–2007

Age of Death	Men ($N = 3$)	Women ($N = 13$)
110	1	6
111	1	4
112	1	3
113	0	0
Mean	111 y 62 d ± 378 d	111 y 88 d ± 344 d

Note: Twenty potential cases were identified. Three cases did not meet our age validation criteria, and one female participant is still living, leaving 16 cases with birth and death data supplied by public officials. Twelve of these cases were further examined during a home visit.

Table 1 shows the age at death of supercentenarians in Okinawa. Nineteen of twenty potential cases are now deceased. One 110-year-old woman was still alive at the time of this study and is therefore not included in the table. Three potential supercentenarians were eliminated because they did not meet our additional age validation criteria, as described above, leaving 16 cases with death data.

Table 2 shows the social history, medical history, and health habits of the 12 Okinawan supercentenarians whom we were able to age-validate and examine with OCS protocol. As can be seen from the table, the majority of supercentenarians had little to no formal education. When compared to the only other supercentenarian study with such data, that of a U.S. population, the Okinawan supercentenarians were poorly educated. Eighty-six percent of the Okinawans had < 8 years of education, and 57% had no formal education whereas almost half of U.S. supercentenarians (47%) had at least 8 years of education (14). Most lived with family at the age of 100 years, but by the time they were 110 years old all but one had moved into a long-term care facility or hospital.

Supercentenarians also appear to have delayed clinically apparent diseases until very late in life. The majority (83%) did not report, nor did we determine through our clinical examination, a major, clinically apparent disease (e.g., coronary heart disease, stroke, cancer) until at least age 105. Cataracts were the most commonly reported condition (42%), and the average age of onset was less than 80 years. Pneumonia became more common with advancing age, and one third of the participants reported having experienced this condition. This finding is important to note because pneumonia, not cardiovascular disease or cancer, has been reported to be the leading cause of death in Japanese centenarians (20,21).

Table 2 also displays health habits of supercentenarians. Approximately half (42%) of the supercentenarians had a history of smoking; however, of those participants who did smoke, most began later in life and tended to smoke < 20 cigarettes per day and/or quit by their 70s (data not shown). Only one third of the supercentenarians had a history of regular alcohol consumption, and they tended to be social drinkers who drank moderately (data not shown). Five of 12 supercentenarians (42%) never drank alcohol or smoked during their lifetimes.

Table 2. Medical and Social History of Supercentenarians

Social History	
Education, y ($n = 7$)	
None	4 (57%)
≤8 y	2 (29%)
9–12 y	1 (12%)
>12 y	0
Living situation, at age 100 y ($n = 11$)	
With family	8 (73%)
Nursing home	2 (18%)
Hospital	1 (9%)
Living situation at age 110 y ($n = 8$)	
With family	1 (12.5%)
Nursing home	5 (62.5%)
Hospital	2 (25%)
Past Medical History (ICD 9) ($n = 12$)*	Cases n (%) and Average Age (year range) at Diagnosis
Cataracts (366)	5 (42%): <80
Fracture (800–829)	4 (33%): 80–100
Pneumonia (486)	4 (33%): 1: <80, 3: >100
Dementia (290)	3 (25%): 80–100
Tuberculosis (010–018)	1 (8%): <80
Malaria (084)	1 (8%): <80
Hypertension (401)	1 (8%): 80–100
Heart disease (410–414)	1 (8%): >100
Stroke (430–438)	1 (8%): >100
COPD (490–496)	1 (8%): 80–100
Cancer (140–239)	0
Diabetes mellitus (250)	0
Hyperlipidemia (272)	0
Parkinson's disease (332)	0
Health Habits ($n = 12$)	
Ever smoked	5 (42%)
Ever drank alcohol	4 (33%)
Never drank alcohol and/or smoked	5 (42%)

Notes: Study participants may have been seen at any age between 99 and 111 years and on one or more occasions. Not all information was available on all study participants at every examination.

*In order of frequency.

COPD = chronic obstructive pulmonary disease.

Table 3. Average ADL Scores of Supercentenarians

Number of Cases	$N = 9$	$N = 7$	$N = 4$
Mean age, range (y)	100.6 (99–103)	104.8 (104–107)	109.3 (108–111)
Feeding	4.7 ± 0.9	4.1 ± 1.5	1.8 ± 0.5
Bowel	4.3 ± 1.3	3.5 ± 1.9	1.4 ± 0.6
Urination	4.4 ± 1.3	3.5 ± 1.9	1.4 ± 0.5
Standing	3.6 ± 1.3	3.3 ± 1.7	1.5 ± 0.7
Movement	3.4 ± 1.3	3.0 ± 1.2	1.3 ± 0.2
Bathing	3.4 ± 1.3	3.1 ± 1.2	1.8 ± 0.5
Dressing	4.0 ± 1.3	2.8 ± 1.5	1.3 ± 0.4
Hearing	3.4 ± 1.2	3.0 ± 0.9	2.3 ± 0.5
Sight	3.9 ± 1.2	3.1 ± 1.4	2.0 ± 0.7
Expression	4.4 ± 1.2	4.0 ± 1.5	2.7 ± 0.8
Understanding	4.2 ± 1.6	4.0 ± 1.3	3.1 ± 0.7
Total ADL score	43.7 ± 11.4	37.4 ± 13.2	20.5 ± 3.5

Note: Maximum score for each category is 5; minimum possible is 1. Total activities of daily living (ADL) score is the average of the summed ADL scores of participants (maximum 55, minimum 11). Total ADL saw an average yearly change of –3.3 per year ($p = .004$).

Table 3 displays the ADL scores of supercentenarians at various ages. As they aged, some participants received a clinical diagnosis of cognitive impairment (three were clinically diagnosed with dementia). All but one was ADL independent at the age of 100. However, they had begun to show clear deficits, particularly in functions that required motor skills (standing, movement, bathing) and sensory acuity (visual and auditory perception). Most participants rapidly lost functionality between ages 105 and 109, such that by age 110 years, they were extremely frail and in need of major care support.

Table 4 shows longitudinal trends (estimated yearly change) in clinical biochemistry, hematology, physiology, and immunology of the supercentenarians as they aged from 99 to 111 years. BMI appears to have progressively dropped as they transitioned from centenarians to supercentenarians (a risk factor for mortality in most elderly persons), suggesting increased frailty or undiagnosed morbidity. Total cholesterol continued to fall with advancing age, also a possible marker of frailty, but high-density lipoprotein appeared to be maintained at relatively high levels, consistent with a previously reported lipoprotein phenotype of exceptional longevity in centenarians (6,22). Total protein, hematocrit, albumin, hemoglobin, and red blood cell count progressively dropped to below the normal adult range by age 110 years. Several of these measures have been suggested as candidate biomarkers of aging, and most are commonly associated with frailty (23). Serum immunoglobulin A, a possible indicator of intestinal inflammation and/or potential deficits in the mucosal defense system, rose with increasing age. Uric acid and creatinine, measures of renal function, remained at high normal or exceeded normal levels in line with the extreme ages of the participants. In addition, there was a marked decrease in blood pressure as they aged, although this change did not reach statistical significance. Remarkably, most indicators appeared within the normal adult range, at least until approximately age 105 years.

Discussion

Previous studies of phenotypic characteristics of supercentenarians are few, and of these, most are single case studies (24–26). To our knowledge, only one case series that includes information on medical and functional characteristics of a group of supercentenarians exists in the gerontological literature and that study, although important, did not involve direct clinical examination but rather reports from proband, family, and (where available), medical records (14). Thus, the current study helps to further characterize the supercentenarian phenotype by adding novel, prospectively collected data on morbidity and physical, cognitive, and social function obtained from direct interview, observation, and clinical examination. Furthermore, because this is a population-based study of supercentenarians (the first to appear in the gerontological literature), it is less likely to suffer from selection bias and more likely to be representative of the supercentenarian phenotype. Finally,

Table 4. Clinical Phenotypes of Supercentenarians in Okinawa: Longitudinal Trends

Physiology	Age Range 99–103 y ($N = 10$) Mean	*SD*	Age Range 104–107 y ($N = 7$) Mean	*SD*	Age Range 108–111 y ($N = 4$) Mean	*SD*	Estimated Yearly Change	Statistical Significance *p* Value	Normal Range
Age at examination, y	100.9	1.5	104.8	0.6	109.4	0.5	–	–	N/A
BMI, kg/m^2	21.47	2.78	18.81	1.58	17.43	0.59	−0.6	.029	17–25
BP (systolic), mm Hg	142	24	128	17	119	18	−2.1	.24	<129
BP (diastolic), mm Hg	74	9	70	13	64	5	−0.9	.21	<84
Hematology									
Hematocrit, %	36.7	3.26	33.88	3.62	31.21	4.05	−0.7	.014	34–46
Hemoglobin, g/dL	11.72	1.2	11	1.51	9.92	1.18	−0.2	.023	11–15
RBC, $\times 10^4/\mu L$	374.8	48.1	338.6	35.5	329.2	76.9	−4.5	.22	350–500
WBC, $\times 10^4/\mu L$	4931	1077	5090	645	4721	1107	42.3	.55	3500–9000
Platelets, $\times 10^4/\mu L$	21.38	6.10	22.65	3.75	22.18	5.82	0.5	.09	13–35
Biochemistry									
Nonfasting glucose, mg/dL	100	17	116	13	102	29	−1.5	.17	<200
Total protein, g/dL	7	0.57	6.47	0.32	6	0.3	−0.09	.0005	6.5–8.5
Albumin, g/dL	4.09	0.36	3.84	0.47	3.26	0.33	−0.7	.018	3.8–5.1
Cholesterol, mg/dL	198.4	52.0	177.4	48.0	160.9	20.0	−4.7	.12	120–219
LDL, mg/dL	116.8	28.1	101.9	41.1	87.4	7.8	–	–	<139
HDL, mg/dL	49.1	15.1	48.6	12.7	50.1	7.9	0.5	.70	40–80
Triglycerides, mg/dL	141.4	65.8	115.4	53.4	92.5	22.3	−2.6	.36	30–149
TC/HDL, ratio	4.24	1.05	3.71	0.79	3.33	0.52	0.01	.034	<4.5
Uric acid, mg/dL	6.38	2.34	6.27	0.84	5.49	1.68	−0.15	.063	2.5–6
Creatinine, mg/dL	0.99	0.18	1.04	0.14	0.98	0.16	−0.02	.19	.47–.79
GOT (AST), IU/L	20.2	3.7	18.8	3.8	22.1	3.0	–	–	5–38
GPT (ALT), IU/L	9.7	1.6	9.7	2.5	13.8	6.2	0.6	.098	4–43
Immunology									
IgA, mg/dL	322	104	391	127	436	205	12.3	.039	150–310
IgG, mg/dL	1598	444	1630	389	1354	152	16.3	.64	800–1800
IgM, mg/dL	102.2	36.6	110.4	34.1	90.2	26.8	−3.5	.034	80–180

Notes: Average yearly change is estimated from mixed model analysis, which regressed individual measures against age for each individual, and estimated the overall mean of the regression coefficient, which is presented here as the average yearly change. Because of small sample size, the average yearly change for low-density lipoprotein (LDL) and gamma glutamyltranspeptidase (GOT) could not be estimated.

BMI = body mass index; BP = blood pressure; RBC = red blood cells; WBC = white blood cells; HDL = high-density lipoprotein; TC = total cholesterol; AST = aspartate aminotransferase; GPT = glutamate pyruvate transaminase; ALT = alanine aminotransferase; IgA = immunoglobulin A; IgG = immunoglobulin G; IgM = immunoglobulin M.

it is the only study to report detailed hematological, physiological, biochemical, and immunological data from clinical blood work.

Previous work has demonstrated that the majority of public claims of supercentenarian status (particularly for individuals claiming to be 115 years old or older) do not have sufficient evidentiary support to be considered valid (27–35). Therefore, demographers Robine and Vaupel (11) advocate set criteria for age validation of supercentenarians. The highest category of validation is three stars, which indicates that the birth record and the death record have been brought side by side and checked to verify age. Two stars indicate that age, date of birth, and date of death are officially communicated by the public officials in charge of vital statistics. One star indicates that two different documents exist that verify age. All data must be consistent and have no age ambiguity. The strictest criteria (three stars) are almost impossible for Japan (and Okinawa) because strict privacy laws govern access to *koseki* (birth) and death documents, making side by side comparisons practically impossible. Otherwise, three star status could likely be claimed for all 12 age-validated supercentenarians in this study. However, we can claim at least two star status for all 12 age-validated study participants as well as for the four cases for whom dates of birth and death were communicated to us by public officials. A fifth case is still living (with valid documentation). Our additional validation criteria on the 12 age-validated cases who received a home visit and examination add further credibility that our study participants were indeed supercentenarians. The fact that three alleged supercentenarians did not meet our additional, stricter age validation criteria underscores the need for rigorous age validation procedures at these extreme ages, even among nations with the most reliable age registration systems, such as Japan (27).

From the current study of Okinawa's supercentenarians we can observe that the majority experienced few major, clinically apparent diseases before the age of 100 years. Cataracts and fractures were the most common age-associated morbidities. Coronary heart disease and stroke (cardiovascular diseases) were rare and did not appear clinically until after 100 years of age. These findings are in

agreement with the previously reported case series, which also reported cataracts and osteoporosis as the most common diseases among supercentenarians and cardiovascular disease as rare (14). These findings are also consistent with morbidity patterns among centenarians in Okinawa (20) and elsewhere who have reported delayed onset of several clinically apparent, age-associated diseases (36–38). As suggested by previous studies (14,36), earlier expression of particularly lethal diseases of aging (cardiovascular disease and cancer) would markedly diminish odds for survival to such exceptional ages, and it may be necessary to delay such morbidity (and its associated disability) until even later in life for a person to survive to 110 years or more. Consistent with the low prevalence found in prior work, clinical evidence of cancer (non-skin), Parkinson's disease, and diabetes was not found in this study (36–38).

Lack of clinical evidence of major cardiovascular disease (or other comorbidities) in supercentenarians does not necessarily indicate lack of underlying pathology. Autopsy reports on centenarians or supercentenarians indicate several underlying subclinical comorbidities, including subclinical cardiovascular disease, calcification of major arteries in areas of turbulent blood flow (e.g., aorta), respiratory damage, amyloid deposition in various tissues, immune dysfunction, and gastrointestinal disorders, among other pathology (20,21,39,40). Nevertheless, these exceptional survivors do seem to be more resilient or better able to delay or adapt to major chronic disease, and thus maintain biological function significantly longer. For example, clinical evidence of myocardial ischemia or serious heart failure appears rare (14,20,27). Under these circumstances, it is more likely that underlying frailty and lack of physiological reserve might predispose such individuals to accidents (such as falls), intestinal problems (such as malabsorbtion), and respiratory infections (such as pneumonia), which can suddenly claim them. Indeed, pneumonia has been reported to be the leading cause of death in Japanese centenarians (20,21), and these diseases become relatively more common among the oldest old population as contributing factors or direct causes of death compared to middle-aged or younger elderly persons (26,39,40).

It has been previously reported that centenarians experience a compression of disability until late in life, partly because disability in the oldest old population is a strong predictor of mortality (36). The current prospective study extends these previous findings to supercentenarians. All but one of our participants functioned independently at high ADL levels at age 100 (data not shown), although decline was rapid from age 105 onward. By age 110 years all were in need of major support with ADLs as would be expected at these extreme ages. Interestingly, the previously reported case series study of ADL levels in supercentenarians in the United States found that 41%, despite their extreme age, required only minimal assistance with ADLs or were independently functioning (14). A possible reason for this discrepancy in findings is that our sample was population based, whereas the U.S. study (14) relied on media reports, the internet, or families for study volunteers, likely skewing the sample toward healthier participants. Selection bias is common in studies of the oldest old population, largely because healthier participants tend to be easier to recruit. In *population-based* studies of centenarians, generally $< 30\%$ can be considered independent in ADLs (18,41–43). In addition, because the data for the U.S. study were gathered by proxy rather than direct examination, there is a greater likelihood of underreporting of morbidity and disability. As exceptional survivors at the extreme end of the centenarian distribution, it is unlikely that supercentenarians are more independent with ADLs than are younger members of the centenarian cohort, despite their apparent delay in morbidity and disability (18).

It has been suggested that supercentenarians may be more homogenous with regard to some phenotypes of aging, particularly those relating to morbidity and function (14). Therefore, it is interesting to note that the morbidity findings of the present study were similar to those of the previous case series study of supercentenarians. Both samples suffered little from clinically significant coronary heart disease, stroke, or cancer, yet cataracts and osteoporosis (or osteoporotic fracture) were common. Indeed, delaying or avoiding clinical expression of more lethal diseases (coronary heart disease, stroke, and cancer) may be a hallmark of supercentenarianism. High physical and cognitive function until very late in life, a hallmark of healthy aging, also appears to be important (44). As exceptional survivors among an already highly selected group, supercentenarians may be a valuable resource for uncovering genetic, lifestyle, or other antecedents of healthy aging.

These findings are also noteworthy in light of the low levels of formal education (a factor often associated with high morbidity) (44–46) in the Okinawan supercentenarians. Given the link between education (and other socioeconomic status indicators) and longevity, it is especially interesting to note that these participants overcame this social disadvantage and the majority achieved 105 years of age with relatively good function.

Strengths of this study include a population based design, relatively high case ascertainment (15 of 20 potential participants were assessed), a prospective design with longitudinal data collection, thorough phenotyping with direct clinical examination, and extensive age validation. A limitation of this study is that not all of Okinawa's supercentenarians could be enrolled for detailed study. Three of 20 potential cases were eliminated, and it was not possible for us to enroll, or carry out further extensive age validation, on five other cases because they had either died or were otherwise unavailable. The small number of cases made it difficult to demonstrate statistically significant differences over time in several of the clinical characteristics, but the general pattern of changes with rapid late-life decline, particularly after age 105 years, was consistent with a compression of major clinical morbidity and disability and rapid deterioration at the end of life. Another limitation is that the extremely small number of men made gender comparisons untenable.

It is, as yet, unclear what allows supercentenarians to achieve at least a decade of life beyond the age of 100, a feat that is more difficult to achieve than that of surviving to age 100 itself (5,10). We speculate that genes, lifestyle, and psychosocial factors may be important, including a good

long-term care environment. High quality long-term care from the time that centenarians became frail may have been an important survival factor that helped centenarians to achieve supercentenarian status in Okinawa and throughout Japan. It appears clear that supercentenarians have an extraordinary number of years of independence, but it also appears that significant long-term care resources will still need to be devoted to the care of such exceptional survivors as they reach the end of their extremely long and healthy lives.

Conclusion

Supercentenarians in this study displayed a healthy aging phenotype with delay of clinically apparent major age-associated diseases and disabilities until very late in life. They demonstrated little clinical history of cardiovascular disease and reported no history of cancer (non-skin) or diabetes. These findings suggest that supercentenarians have a more elite phenotype of healthy aging than has been observed in previous studies of centenarians. The genetic and environmental antecedents of this exceptionally healthy aging phenotype are unclear and merit further study.

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