The current status of 492 adult women with Turner syndrome: a questionnaire survey by the Foundation for Growth Science

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Abstract. Current status and its background of Adult Turner Syndrome (TS) are not clarified well. Via a questionnaire survey of 492 adult women with TS, this study investigated the association between menstruation, Kaufmann therapy (menstrual induction therapy), social status (education, employment & marriage), complications, transition from pediatric to adult care, and sex chromosome karyotype using statistical methods. Spontaneous menarche occurred in 22.0% and more frequently among patients with the 45,X/46,XX karyotype. Over 60% of these subjects, menstruation did not persist regularly. Kaufmann therapy was performed in 69.4%; the most common formulation was a conjugated estrogen and progesterone combination. Marriage and higher education advancement rates were low in adults with TS, whereas their employment rate was similar to that of the age-matched general female population. Patients receiving Kaufmann therapy had higher complication rates, greater education length, and higher employment rates. The higher-education advancement rate was observed among patients with 45,X/46,X,Xi and 46,X,Xi karyotypes. Transition from pediatrician to adult specialist was not smooth, subjects were treated in pediatric departments (60.7%), gynecological department (21.4%), internal medicine departments (13.3%), and others. While reason is not clear, the largest number of TS patients are treated in general pediatrics and the percentage of receiving Kaufmann therapy and having complication were significantly lower than in pediatric and adult department of endocrinology (& metabolism). This Study revealed many novel findings of adult TS.

Key words: Adult Turner Syndrome, Social status, Menstruation, Transition, Sex chromosome

TURNER SYNDROME (TS), which results from the complete or partial loss of one X chromosome, affects 1 in every 2,000 to 2,500 live female births [1, 2]. The principal features of TS are short stature and ovarian dysfunction, while growth hormone therapy and sex hormone therapy (to induce secondary sex characteristics) are the mainstay of treatment in childhood for those afflicted [2, 3]. Women with TS are likely to have various complications—these include metabolic, autoimmune, cardiovascular, urinary system, bone and joint, otorhinolaryngological, central nervous system, and psychological diseases (among others), in addition to hypogonadism [1, 3-7]. These complications affect their daily lives and may influence the outcomes in education, employment, and marriage.

Many girls with TS develop various complications as described above, which often continue into adulthood. Therefore, in order to provide appropriate care for women with TS, a smooth transition from pediatric to adult specialists is important [1, 8, 9]. We believe that the follow-up of complications by specialists is essential in enhancing quality of life, providing appropriate treatment of complications, and improving longevity for women with TS. However, although many TS girls do receive appropriate treatment, the issue of transition—from pediatric to adult care—has not been fully realized, and social and health aspects surrounding the issue have not been sufficiently addressed [8, 9].

In this study, we administered a questionnaire to attending physicians for TS patients to evaluate: the rate of spontaneous menarche, and its association with sex hormone therapy; social status (education [mean length of education], employment, and marriage); the association between social status, complications, and Kaufmann therapy; and transition from pediatric to adult care. In TS, the severity of the phenotype, affected organs, and intellectual performance differ according to the sex chromosome karyotype [3]. Therefore, we further examined the association between the karyotype and additional selected variables.
Methods and Subjects

The questionnaire survey was conducted with 1,656 women with TS (from 544 facilities) born on or before August 1, 1993, who had received human growth hormone (hGH) therapy for short stature, and who reached the age of 17 years by August 1, 2009. The deadline for registration was December 31, 2010.

The questionnaire was sent to the attending physicians; the survey asked about spontaneous menarche, estrogen therapy, Kaufmann therapy (i.e., Menstrual induction therapy), education, employment, marriage, and department where the patient was being treated (Table 1) [6, 7]. The responses of 492 cases that contained satisfactory data were included in the analysis. The data were compared with those of the general female population of Japan, as reported by the Ministry of Education, Culture, Sports, Science and Technology; the Labour Force Survey conducted by the Ministry of Internal Affairs and Communications in 2009 (Date of Publication 2010); and the 2010 Population Census in Japan conducted by the Ministry of Internal Affairs and Communications: 2010 [10-12]. In addition, the associations between karyotypes and some variables were also examined to determine the association between genotype and the current status in women with TS. The chromosomal karyotype of each patient was taken from the Foundation for Growth Science database.

The certificate of approval of manuscript submission was obtained from The Foundation for Growth Science.

Data were expressed as mean ± standard error of mean (SE). In the statistical analysis, for comparison of proportion or of the mean values of groups the Fisher’s exact test or the Wilcoxon non-parametric analysis were used. Statistical significance was accepted at \( p < 0.05 \) and JMP version 9.02 (SAS Institute Inc.) was used.

Results

Current status of adult women with TS

1) Patients characteristics

Among 492 cases, majority of the subjects (\( n = 437 \)) were aged between 20 and 39 years (the lowest age recorded was 17.1 years, the highest age was 42.5 years), and the median was 26.7 years, upper quartile and lower quartile 22.9 years and 30.1 years old, respectively. The distribution of karyotype in these subjects was reported previously [7].

2) The rate of spontaneous menarche and the proportions of patients receiving estrogen therapy/Kaufmann therapy

A total of 455 responses were obtained for the question about spontaneous menarche occurrence. Of the 455 subjects, 100 (22.0%) had spontaneous menarche. This rate was slightly higher than that reported by Tanaka et al. (14.6%) [13] but similar to the rate reported by Hibi et al. (21.3%) [14].

Estrogen therapy (used to induce puberty) was performed in 283 (66.4%) of 426 subjects, whereas the remaining 33.6% did not receive such therapy. The mean age at the start of estrogen therapy was 15.9 ± 0.1 (SEM) years. The details of formulations were described in 264 subjects. The most common estrogen used was conjugated estrogen (mainly estrone) (71.2%), followed by synthetic estrogen (15.9%), estradiol (11.4%; with a transdermal patch used in 90% of subjects), and estriol (1.5%). On the other hand, Kaufmann therapy (used to induce menstruation) was performed in 306 (69.4%) of 441 subjects, and the mean age at the start of the therapy was 18.1 ± 0.2 years. The details of formulations were described for 268 subjects: the most common formulation was a combination of conjugated estrogen (estrone) and progesterone (61.9%), followed by a combination of synthetic estrogen and progesterone (20.9%), a combina-

Table 1 A sheet for the questionnaire survey regarding Turner syndrome

| Question | Description |
|----------|-------------|
| 1) Estrogen therapy to induce secondary sex characteristics (Yes - No) | If answered Yes: Age (years months) and height (cm) at the start of the therapy Name of formulation ( ) |
| 2) Kaufmann therapy (Yes - No) | If answered Yes: Age (years months) and height (cm) at the start of the therapy Name of formulation ( ) |
| 3) Currently employed (Yes - No - Unknown) |
| 4) Final education level (junior high school - high school - technical school - junior college - university - graduate school) |
| 5) Marital history (Yes - No), current marital status (Married - Single) |
| 6) Department where the patient is treated (multiple selection is allowed) (General pediatrics, pediatric endocrinology and metabolism, general internal medicine, adult endocrinology and metabolism, pediatric and adult endocrinology and metabolism, gynecology, others (specify) ) |
tion of estradiol and progesterone (4.1%; with a transdermal patch used in 90.9%), and a combination of estriol and progesterone (0.4%), estrone alone (0.8%), and progesterone alone (11.9%). Of the 100 women with spontaneous menarche, 62% were receiving Kauffmann therapy. Of the 441 subjects who answered the question concerning Kauffmann therapy, 341 reported no spontaneous menstruation, while 97 (28.4%) of the 341 did not receive the therapy.

The rate of spontaneous menarche in subjects not receiving Kauffmann therapy was 28.1%, which was slightly higher than that observed among those receiving Kauffmann therapy (20.3%)—although there was no statistically significant difference between the two ($p = \text{NS}$).

The rate of spontaneous menarche was calculated for each karyotype: the rate was highest in subjects with 45,X/46,XX (35.7%) ($p < 0.0002$), and significantly lower in subjects with 45,X monosomy (15.9%) ($p < 0.023$). These findings were consistent with other reports [3, 13, 15].

There were no significant differences in other karyotypes between the observed and expected number of cases (Table 2).

3) Advancement rate (university/junior college)

Among the 228 women with TS, 42.5% attended university or junior college (28.9% and 13.6%, respectively). Among the remaining subjects, 7.5% attained junior high school education, 28.5% attained high school education, 21.1% attained technical school education, and 0.4% attained nursing school education.

The advancement rate to universities/junior colleges was significantly higher in subjects with 45,X/46,X,Xi karyotype (56.3%) and those with 46,X,Xi karyotype (43.5%), when compared with the expected rate (both: $p < 0.001$).

4) Employment rate

In 250 women with TS, 153 (61.2%) were working, 57 (22.8%) were not working after graduation, and 40 (16.0%) were studying at school. The employment rate was 72.9%, excluding students (153 out of 210).

The employment rate was approximately 70% across all karyotype groups, with no significant differences observed among these groups.

5) Marriage rate compared to the general female population

In 125 women with TS aged between 25 and 35 years, 11 (8.8%) were married (as of 2010). There were no significant differences in the marriage rate among karyotypes.

6) Analysis of factors influencing social status (length of education, employment rate, and marriage rate) (Table 3, 4)

Table 3 shows the list of complications, along with their frequencies, in women with TS. Of 492 TS women, 318 (64.6%) had at least one complication, and the mean number was 2.1 in the latter. The most common complication was decreased bone density, followed by chronic thyroiditis and dyslipidemia, which have been reported in previous studies [6, 7].

Analysis of the associations between complications and social variables showed that the presence of complications was not associated with length of education, employment rate, or marriage rate (Table 4). The presence of hearing loss or obesity (BMI $\geq 25$ kg/m$^2$) was also not associated with the above three social variables.

On the other hand, the complication rate, length of education, and employment rate were significantly higher in patients receiving Kauffmann therapy than among those not receiving it ($p < 0.0001$, $p < 0.003$, and $p < 0.0009$, respectively); however, there was no significant difference in marriage rates between those who have and have not received Kauffmann therapy ($p = \text{NS}$) (Table 4).

7) Departments where subjects were treated (Table 5, 6)

Table 5 shows the departments where TS patients were treated at the time of this study. A total of 481 patients

| Karyotype        | Cases (%) of karyotype | Observed cases | Expected cases | $p^{*2}$ |
|------------------|------------------------|----------------|----------------|---------|
| 1) Other 45,X mosaic*1 | 138 (30.3%)            | 40 (29.0%)     | 30.3           | 0.8862  |
| 2) 45,X Monosomy | 132 (29.0%)            | 21 (15.9%)     | 29.0           | 0.0234**|
| 3) 45,X/46,X,Xi | 77 (16.9%)             | 11 (14.3%)     | 16.9           | 0.8347  |
| 4) 45,X/46,XX    | 28 (6.2%)              | 10 (35.7%)     | 6.2            | 0.0002**|
| 5) 46,XXi        | 41 (9.0%)              | 8 (19.5%)      | 9.0            | 0.0935  |
| 6) Others        | 39 (8.6%)              | 10 (25.6%)     | 8.6            | 0.0098**|

*1. Percent of karyotype is based on 455 patients with Turner syndrome.
*2. Observed vs. Expected.
*3. Excluding 45,X/46,X,Xi and 45,X/46,XX.
*4. $p = \text{Statistically significant.}$
Table 3  Complications and their frequencies in women with Turner syndrome

| Complication                  | Number of responses | Number of cases with each complication | Proportion of each complication*1 | Complication rate*2 |
|-------------------------------|--------------------|---------------------------------------|----------------------------------|--------------------|
| Chronic thyroiditis           | 424                | 107                                   | 16.2%                            | 25.2%              |
| Decreased bone density        | 231                | 99                                    | 15.0%                            | 42.9%              |
| Dyslipidemia                  | 433                | 82                                    | 12.4%                            | 18.9%              |
| Liver dysfunction             | 442                | 51                                    | 7.7%                             | 11.5%              |
| Cardiovascular anomaly        | 424                | 50                                    | 7.6%                             | 11.8%              |
| Urinary tract anomaly         | 363                | 43                                    | 6.2%                             | 11.8%              |
| Scoliosis                     | 392                | 33                                    | 5.0%                             | 8.4%               |
| Hypertension                  | 404                | 31                                    | 4.7%                             | 7.7%               |
| Hearing loss                  | 402                | 25                                    | 3.8%                             | 6.2%               |
| Diabetes mellitus             | 440                | 82                                    | 3.6%                             | 5.5%               |
| Other autoimmune diseases     | 390                | 16                                    | 3.2%                             | 4.2%               |
| Epilepsy                      | 433                | 12                                    | 1.8%                             | 2.8%               |
| Bone and joint complications  | 433                | 7                                     | 1.1%                             | 1.6%               |
| Schizophrenia                 | 433                | 4                                     | 0.6%                             | 0.9%               |
| Delayed mental development    | 433                | 4                                     | 0.6%                             | 0.9%               |
| Other complications           | 433                | 68                                    | 10.3%                            | 15.7%              |

Complications Total               —                —                                       —                                    —                 

*1: Number of cases with each complication/total number of cases with complications.
*2: Number of cases with each complication/total number of responses.

Table 4  Relationship between social status and complications among TS patients

| Complication        | Complication*1 | Mean length of education*2 (Yr) | Employment rate | Marriage rate |
|---------------------|----------------|---------------------------------|-----------------|--------------|
| Kaufmann therapy    | Yes (N = 306)  | 13.8 ± 0.1 (N = 167)            | 127/161 (78.9%) | 8/206 (3.9%) |
|                     | No (N = 135)   | 12.8 ± 0.3 (N = 58)             | 23/44 (52.3%)   | 2/75 (2.7%)  |
|                     | p: 0.0001*3    |                                 |                 |              |
| Complication*1      | Yes (N = 318)  | 13.6 ± 0.2 (N = 162)            | 109/152 (71.7%) | 7/202 (3.5%) |
|                     | No (N = 174)   | 13.5 ± 0.3 (N = 66)             | 44/58 (75.9%)   | 3/85 (3.5%)  |
|                     | p: 0.9123      |                                 |                 |              |
| Obesity             | Yes (N = 106)  | 13.8 ± 0.2 (N = 58)             | 33/46 (71.7%)   | 2/67 (3.0%)  |
|                     | No (N = 320)   | 13.5 ± 0.2 (N = 158)            | 104/143 (72.7%) | 6/195 (3.1%) |
|                     | p: 0.3930      |                                 |                 |              |
| Hearing loss        | Yes (N = 25)   | 13.3 ± 0.4 (N = 12)             | 6/9 (66.7%)     | 1/11 (9.1%)  |
|                     | No (N = 377)   | 13.5 ± 0.2 (N = 191)            | 129/180 (71.7%) | 8/249 (3.2%) |
|                     | p: 0.5432      |                                 |                 |              |

*1 Patients having at least one complication.
*2 Mean length of education from 1st grade of elementary school to graduation of junior college or university.
*3 p = Statistically significant.
were treated across 565 departments (including duplications). The most common departments reported included pediatric departments (pediatric endocrinology and metabolism, general pediatrics, pediatric neurology, and pediatric cardiology) (60.7%), followed by gynecological department (21.4%), internal medicine departments (adult endocrinology and metabolism, general internal medicine, cardiovascular medicine, and gastroenterology) (13.3%), and other departments (4.6%) (the total percentage exceeds 100% because of duplication). The percentages of patients treated in the department of pediatric endocrinology and adult endocrinology and metabolism were 28.1% and 8.3%, respectively. In Devernay’s study [9], the proportion of patients treated by pediatric endocrinology is lower (11%), whereas those by adult endocrinology and metabolism (29%) and gynecologist (53%) are higher compared to our study.

Analysis of variables according to department showed that the complication rate and the proportion of subjects receiving Kauffmann therapy did not differ significantly between the departments of pediatric endocrinology and adult endocrinology and metabolism (78.0% and 76.3%, vs. 87.2% and 78.3%, respectively); meanwhile, these values were significantly lower in the general pediatrics (53.2% and 44.0%, respectively) than in the above two departments (Table 6).

In patients who were treated in gynecological department, while the complication rate was significantly lower than the above two specialist departments (63.6%), proportion of Kauffmann therapy (79.0%) did not differ among the three groups of departments (Table 6).

The mean length of education received after junior high school graduation was 4.4 ± 0.2 years for those treated in the department of pediatric endocrinology, 4.6 ± 0.2 years for those treated in the department of general pediatrics, 4.3 ± 0.4 years for those treated in the department of adult endocrinology and metabolism, 4.2 ± 0.3 years for those treated in the department of internal medicine, and 4.9 ± 0.2 years for those treated in the department of gynecology, with no statistically signifi-

### Table 5 Departments where women with TS are treated

| Department                              | Number of cases*1 | Percentage |
|-----------------------------------------|-------------------|------------|
| **Pediatric departments Total**         | 343               | 60.7%      |
| Pediatric endocrinology                 | 159               | 28.1%      |
| General pediatrics                      | 190               | 33.6%      |
| Pediatric neurology                     | 2                 | 0.4%       |
| Pediatric cardiology                    | 1                 | 0.2%       |
| **Gynecological department**           | 121               | 21.4%      |
| **Internal medicine departments Total** | 75                | 13.3%      |
| Adult endocrinology and metabolism      | 47                | 8.3%       |
| General internal medicine               | 22                | 3.9%       |
| Cardiovascular medicine                 | 5                 | 0.9%       |
| Gastroenterology                        | 3                 | 0.5%       |
| **Other departments Total**             | 26                | 4.6%       |
| Otorhinolaryngology                     | 4                 | 0.7%       |
| Orthopedics                             | 6                 | 1.1%       |
| Ophthalmology                           | 1                 | 0.2%       |
| Psychiatry                              | 9                 | 1.6%       |
| Psychosomatic medicine                  | 1                 | 0.2%       |
| Dermatology                             | 3                 | 0.5%       |
| Surgery                                 | 1                 | 0.2%       |
| Cardiac surgery                         | 1                 | 0.2%       |
| **Total**                               | 565               | 117.5%*3   |

*1 A total of 481 responses were obtained regarding the department where patients are treated.
*2 The details of total departments were shown below.
*3 The total percentage exceeds 100% because of duplication.
cant differences observed.

**Discussion**

There are no known large-scale studies that were previously conducted on the present status of TS in adult women and its related factors. This is the largest questionnaire survey conducted in Japan, which attempted to investigate these issues in detail and revealed many novel findings.

At first, over 60% of Turner Syndrome, spontaneous menstruation was often short-term. Compared to the general female population, the rates of educational advancement and marriage in women with TS were lower; however, there was no significant difference in their employment rates. The transition from pediatric care to adult internal medicine or adult endocrinology and metabolism is not smooth. Patients receiving Kauffmann therapy had higher complication rates, greater education length, and higher employment rate. In specialist of

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**Table 6** Comparison between departments regarding the complication rate and proportion of patients receiving Kaufmann therapy

| Department                        | Complication (patients having at least one complication) | Kaufmann therapy | Each Department Compared*2 |
|-----------------------------------|----------------------------------------------------------|------------------|---------------------------|
|                                   | No. of responses | No. of cases | Percentage | p | No. of responses | No. of cases | Percentage | p |                                      |
| Pediatric departments             | 343             | 221         | 64.4%      | 0.9123     | 157             | 93          | 59.2%      | 0.0073*     | Gynecological department               |
|                                   |                |             |            | 0.0090*     |                |             |            | 0.0314*     | Internal medicine departments            |
| Pediatric endocrinology           | 159             | 124         | 78.0%      | 0.2129     | 76              | 58          | 76.3%      | 1.0000      | Adult endocrinology and metabolism        |
|                                   |                |             |            | 0.0084*     |                |             |            | 0.7032      | Gynecological department               |
| General pediatrics                | 190             | 101         | 53.2%      | 0.1121     | 84              | 37          | 44.0%      | 0.0257*     | General internal medicine               |
|                                   |                |             |            | <.0001*     |                |             |            | <.0001*     | Pediatric endocrinology                 |
|                                   |                |             |            | <.0001*     |                |             |            | 0.0045*     | Adult endocrinology and metabolism       |
| Gynecological department         | 121             | 77          | 63.6%      | 0.9123     | 62              | 49          | 79.0%      | 0.0073*     | Pediatric departments                   |
|                                   |                |             |            | 0.0021*     |                |             |            | 1.0000      | Internal medicine departments            |
|                                   |                |             |            | 0.0084*     |                |             |            | 0.7032      | Pediatric endocrinology                 |
|                                   |                |             |            | 0.0015*     |                |             |            | 0.9385      | Adult endocrinology and metabolism       |
| Internal medicine departments     | 75              | 63          | 84.0%      | 0.0090*     | 34              | 27          | 79.4%      | 0.0314*     | Pediatric departments                   |
|                                   |                |             |            | 0.0021*     |                |             |            | 1.0000      | Gynecological department               |
| General internal medicine         | 22              | 16          | 72.7%      | 0.1121     | 8               | 7           | 87.5%      | 0.0257*     | General pediatrics                      |
| Adult endocrinology and metabolism| 47              | 41          | 87.2%      | 0.2129     | 23              | 18          | 78.3%      | 1.0000      | Pediatric endocrinology                 |
|                                   |                |             |            | 0.0015*     |                |             |            | 0.9385      | Gynecological department               |

*1 All asterisks indicate statistical significance (p < 0.05).
*2 The proportion in the department shown at the left side was compared with each department shown at the right side.
pediatric or adult endocrinology the percentage of receiving Kauffmann therapy and having complication were higher than in general pediatrics. Regarding karyotypes, spontaneous menstruation was highest in subjects with 45,X/46,XX and lowest in those with 45,X monosomy. The advancement rate was high in subjects with 45,X/46,Xi and those with 46,X,Xi.

In the present study, 69.4% of the subjects were receiving Kauffmann therapy. Among those who experienced spontaneous menarche, 62% were also receiving this therapy; this was also observed in much younger patients with TS [13]. Pasquino et al. reported that 84 (16.1%) of 522 women with TS had experienced spontaneous menarche, but that only 30 (36%) of the 84 experienced regular menstruation, accounting for only 6% of all cases [15]. These findings suggest that a certain number of women with TS who experience spontaneous menarche might become irregular and transient menstruation, or early menopause, i.e. premature ovarian failure. It is notable that, a substantial percentage (28.4%) of subjects who did not experience spontaneous menarche were not receiving Kauffmann therapy.

The most common formulation used in both estrogen therapy and Kauffmann therapy for women with TS, in the present study, was conjugated estrogen, and was similar to that reported in the Unites States, where many clinicians use conjugated estrogen to induce puberty in women with hypogonadism [16]. Conjugated estrogen—which is a mixture of estrogens—mainly consists of estrone sulfate. Since both conjugated estrogen and estradiol are metabolized in the liver, the level of estrone in the body becomes higher than that of estradiol. On the other hand, some studies report that a 17β-estradiol (E₂) transdermal patch is most suitable for inducing puberty as levels of E₂, E₁, and E₃ increase in distributions approximate to physiological conditions of the user [17, 18].

The guidelines on inducing puberty and menstruation in women with TS have been proposed previously [1, 17, 19, 20]. In the present study, the mean ages of patients at the start of estrogen therapy (15.9 years) and at the start of Kauffmann therapy (18.1 years) were older than the recommended ages—an issue which needs to be addressed. In the future, further studies are required to determine the most beneficial formulation, dose, and route of administration in terms of metabolic effects, psychosocial outcomes, adult height achievement, development of uterus, and prevention of adverse drug reactions.

The advancement rate in women with TS in Japan attending university/junior college was 42.5%, which was lower than that observed in the general female population (54.3%), as reported in the School Basic Survey 2010 that included new and past high school graduates [10]. In Denmark, the advancement rate to university among women with TS (data from 2009) was 64.8%, which was similar to that in the general female population (66.3%) [21]. In the United States, the advancement rate to university in women with TS (data ranging from 2001 to 2010) was very high, at 70.0%, and was much higher than that observed among the general female population (30%) [22].

In this study, the employment rate in women with TS was 72.9%, which was not significantly different from that of the general female population aged between 15 and 44 years (68.6%), according to data on 13,790,000 women obtained from the general female population of 20,100,000 [11]. The employment rate in women with TS in Japan was higher than that recorded in Belgium (45.1%) and comparable to that of Norway (68%; where the employment rate among the general female population was 77%) [23, 24]. In the United States, the previously reported employment rate among women with TS was very high, at 80.4%, which was higher than that of the general female population (70.0%) [22]. Gould et al. suggest that the higher advancement rate and employment rate in women with TS in the United States may reflect the lower rates of having children and marriage among this population, which grants more time to invest in educational and employment aspirations, when compared to the general female population who often have to devote their time to caring for children, as well as maintaining a relationship with them [22].

In this study, the marriage rate in women with TS was 8.8%, which was significantly lower than that of the general female population, when adjusted for age (50.6%, 4,379,844 people out of 8,650,644 people) [12]. In Belgium (in 2004), the marriage rate among women with TS was 7.9%, which is comparable to that observed in Japan (the marriage rate in the general female population in Belgium was 42.6%) [23]. The marriage rates among women with TS in the United States [22] and Denmark [21] are 46% and 60.2%, respectively, which are much higher than that observed in Japan; although, they were lower than those of the general female populations (78.0% in the United States and 88.5% in Denmark). The reasons for the lower marriage rate in women with TS are not well understood. Although the health-related quality of life of women with TS is reported to be normal, it is considered that high levels of shyness, social anxiety, low self-esteem, low sexual confidence, and tendencies of social isolation may be associated with lower marriage rates in this population [8, 9]. Since the above characteristics are reportedly associated with delayed sexual maturation due to hypogonadism, it is recommended that puberty should be
induced at a physiologically appropriate age [8]. Clinicians should be aware that women with TS need to be educated—through opportunities such as outpatient services and meeting of patients’ association—on their ability to enjoy marriage.

Regarding the association of karyotypes, the reason of higher rate of 45,X/46,XX and lower rate of 45,X monosomy in TS with spontaneous menstruation, and higher rate of 45,X/46,X,Xi and 46,X,Xi in advancement rate requires to be clarified.

It is noteworthy that patients receiving Kauffmann therapy display a higher complication rate, advancement rate (length of education), and employment rate than those not receiving it. Although the reason for this is unclear, it is speculated that women with TS are likely to have a higher awareness of their health condition owing to their frequent visits to medical institutions for various complications and ovarian dysfunction. Such interactions with physicians may help motivate them to pursue higher education and secure employment.

Although the reason of the lower proportion of complication and Kauffmann therapy in general pediatrics is unclear, it is speculated that patients with complications requiring treatment are likely to be not examined well or to be transferred to internal medicine departments, and that general pediatricians do not actively recommend Kauffmann therapy.

A multivariate analysis shows that treatment with an endocrinologist is the sole predictive factor for long-term follow-up [9]. One reason for the lower frequency of transitions from pediatric to adult care in Japan is the lack of endocrinologists to treat TS. Since, individuals with TS are likely to have various complications; it is desirable that, after experiencing growth and puberty, patients are treated by multiple specialists collaborating together in order to maximize the health and longevity of those with TS [1, 25]. In order to provide a better follow-up, a smoother transition, appropriate care for various complications, and better education among adult women with TS, the establishment of an electronic health record system for adult care providers and multidisciplinary adult care centers has been proposed [26-28].

This is the largest and original questionnaire survey conducted in Japan, which attempted to investigate current status of adult TS and its related factors, and demonstrated many novel findings. However, there are several limitations such as interview survey regarding the reason of lower marriage rate, higher education and employment rate in patients with Kauffmann therapy including familial finance status, and the inadequate transition from general pediatrician. The reason of premature ovarian failure, and of association between specific karyotypes and spontaneous menarche or advancement rate should also be elucidated.

We believe that a collaboration among specialists is essential for long-term follow-up because women with TS have a higher risk of developing complications requiring multidisciplinary care.

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Disclosure

The authors have no potential conflict of interest to declare.

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