Prevalence of diverse complications and its association with karyotypes in Japanese adult women with Turner syndrome—a questionnaire survey by the Foundation for Growth Science—

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Abstract. The reported prevalence of complications in Turner Syndrome (TS) was highly variable because of the rarity and the limited numbers analyzed. Again, possible presence of other complications that are not described as specific for TS, is also speculated. To resolve these issues, a questionnaire survey was conducted in hGH treated 492 patients with adult TS (17–42 years). The possible association with these complications and karyotypes were also analyzed. The complications and their prevalence were as follows: chronic thyroiditis (25.2%), inflammatory bowel disease (1.8%), congenital cardiovascular anomaly (11.8%), urinary tract malformation (11.8%), low bone mineral density (BMD) (42.9%), scoliosis (8.4%), hearing loss (6.2%), epilepsy (2.8%) and schizophrenia (0.9%). The majority of prevalence of these diseases in TS was higher than in the general population. In distribution, the most frequent karyotype was 45,X monosomy (28.9%), followed by 45,X/46,X,Xi (16.9%), 46,X,Xi (9.1%), and 45,X/46,XX (6.3%), while other mosaic 45,X was noted in 29.9%. Regarding the karyotype, cardiovascular anomaly was more frequent in the 45,X group and less in the 46,X,Xi group. Urinary tract malformation and epilepsy were frequently associated with the chromosome 45,X. The prevalence of low BMD was noticed more in the chromosome 46,X,Xi and 45,X/46,XX, and less in other mosaic 45,X. In conclusion, the more exact prevalence of diverse complications was clarified and it exceeded the prevalence of the majority of complications in general population. As novel findings, it was observed that the prevalence of epilepsy was significantly high, and epilepsy and low BMD were frequently associated with the specific karyotypes.

Key words: Adult Turner syndrome, Diverse complications, Prevalence, Karyotype, General population

TURNER SYNDROME (TS) is a condition observed in females, caused by complete or partial absence of an X chromosome, and clinically characterized by short stature and ovarian dysfunction [1-5]. Treatment of TS patients during childhood primarily involves growth hormone and sex steroid therapies to improve appearance and maturation of secondary sex characteristics [1, 5, 6]. Patients with TS often suffer throughout their life from disease-related complications of varying severity with extensive influence on metabolism, autoimmunity, cardiovascular system, urinary tract, ear/nose, central nervous system, and mental/social aspects. Managing these complications is necessary throughout their lives [1-5].

However, the reported prevalence of these complications is very variable due to the comparative rarity and limited numbers of TS analyzed. In addition, possible presence of other morbidity that is not described as specific for TS is speculated.

Based on a questionnaire survey, we have observed a high complication rate of diabetes mellitus, hypertension, dyslipidemia, and hepatic dysfunction in association with increased body mass index (BMI) among patients with TS compared with age-matched normal female population, and also observed further BMI elevation due to the combination of multiple complications [7]. In addition, a markedly higher prevalence of these lifestyle-related chronic diseases was noted in patients with BMI equal to or higher than 25 kg/m² [7], as was previously indicated.
in the comparison between obese and non-obese patients with Turner syndrome by Sakakibara et al. [8]. In this study, we have tried to clarify the exact prevalence of diverse complications in a large number of TS through a questionnaire survey and have compared the prevalence with the national health surveys or with large scale studies. Comparisons of association between each complication and chromosomal karyotype were also conducted. The analysis clarified the more exact prevalence of diverse complications, a novel morbidity and specific relations between complications and karyotypes in TS.

### Materials and Methods

The study included 1,656 patients with TS (from 544 facilities) born before August 1, 1993, who had received human growth hormone (hGH) therapy for short stature, and who had reached the age of 17 years by August 1, 2009. A questionnaire was sent to the attending physician of each patient, consisting of an inquiry about the presence/absence of various complications as shown in Table 1. The detailed content of the questionnaire were previously reported [7]. The responses of 492 cases that contained satisfactory data were included in the analysis. The informations of chromosomal karyotype were obtained from the database of the Foundation for Growth Science (FGS) in Japan. To use each data for academic purpose, agreement was obtained at the registration to FGS.

An overwhelming majority (437 cases) of these 492 cases included patients aged between 20 and 39 years (lowest age 17, highest age 42, mean age 26.6 ± 0.2 years).

The results were expressed as Mean ± standard error of the mean (SE). The association of each complication and karyotype was statistically analyzed between groups with and without complication. For statistical analysis, Fisher’s exact test was used in the comparison of incidences. Statistical significance was accepted at $p < 0.05$ and JMP version 9.0.2 (SAS Institute Inc.) was used.

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**Table 1** A sheet for questionnaire survey in Turner syndrome

<table>
<thead>
<tr>
<th>Patient name</th>
<th>Date of birth</th>
<th>yr / mo / day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Registration No.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Please circle to appropriate one and fill out the blank.

- Presence or absence of Complications
- Thyroid autoimmune (Yes · No)
- Thyroid replacement (Yes · No)
- Treatment (insulin or oral antidiabetic agent)
- Its type (I. II, others), anti-pancreatic antibody (Yes · No)
- Treatment (Yes · No)
- Treatment (Yes · No)
- Hearing aid (Yes · No)
- Name of disease ( )
- Treatment (Yes · No) and the therapeutic modality ( )
- Treatment (Yes · No) and the therapeutic agents ( )
- Name of disease ( )
- The name and its complication
- (double ureters, horse shoe kidney, others, and secondary urinary tract lesions)
- Name of disease ( )

*These life style diseases are previously reported (Ref. 7)
When the comparison of data between TS patients and general female population was difficult, the latter data were shown as a reference value.

Results

Cytogenetic analysis

In chromosomal analysis in 492 cases, 45,X monosomy was observed in 142 cases (28.9%), 45,X/46,X,Xi in 83 cases (16.9%), 46,X,Xi in 45 cases (9.1%), 45,X/46,XX in 31 cases (6.3%), and other mosaicisms containing 45,X in 147 cases (29.9%) and the others in 44 cases (8.9%) [7]. Thus, 45,X was the most frequent karyotype.

Prevalence of complications

a) Autoimmune diseases: chronic thyroiditis, inflammatory bowel disease and others

Out of the 424 patients with TS, 25.2% (n = 107) had chronic thyroiditis (Table 2). The prevalence of chronic thyroiditis increased according to aging, i.e. 16.4% (10/62 cases) in their late teens, 23.9% (62/304 cases) in their twenties, 33.0% (34/125 cases) in their thirties. In these three decades, the prevalence was significantly higher in the thirties compared to the late teens (p < 0.05), while significant difference was not observed between the thirties and the twenties (p = 0.34), or the twenties and the teens (p = 0.24).

Among the 107 patients with chronic thyroiditis, 33.6% (n = 36) were receiving thyroid hormone replacement. These 36 patients accounted for 8.5% of all patients with TS. Moreover, of 95 thyroid autoantibody positive cases, 23 (24.2%) were receiving thyroid hormone replacement therapy. Regarding the association of chronic thyroiditis and karyotype, 46,X,Xi was relatively frequent (13/107 cases; 12.1%) compared to cases without the disease (24/317 cases; 7.6%), although the difference was statistically not significant (p = 0.17).

Complications related to autoimmune diseases other than the chronic thyroiditis were observed in 4.2% (n = 16) of the 385 patients with TS, including seven cases of hyperthyroidism (1.8%), four cases of ulcerative colitis (UC) (1.0%), three cases of Crohn’s disease (CD) (0.8%), and one case of necrotizing lymphadenitis (0.3%). In one case, the name of the autoimmune disease was not cited. Thus, UC and CD (inflammatory bowel diseases) were the predominant autoimmune diseases noted in addition to the thyroid disease in the present study. Moreover, the prevalence of each of these diseases was 10 folds or more higher than the prevalence among the general population in Japan in 2008 (UC: n = 121,000, 0.1%; CD: n = 32,000, 0.03%) (Table 2) [9]. On the other hand, one of the four cases with UC had the karyotype 46,X,Xi, while another case of UC had 45,X/46,X,Xi. Moreover, two in three cases with CD had 46,X,Xi and 45,X/46,X,Xi (Table 2). Statistical analysis of the percentage of karyotype distribution was not possible because of the small sample size.

b) Cardiovascular disease

Congenital cardiovascular anomaly (CVA) was noted in 11.8% (n = 50) of the 424 patients with TS (Table 2). As the prevalence of congenital CVA among the general population in Japan is reported to be approximately 1.0% [10, 11], the above-mentioned prevalence among the patients with TS was considerably high. Table 3 summarizes the details of congenital CVA among patients with TS. Aortic coarctation (CoA) was the most frequent (n = 12, 2.8%), followed by aortic regurgitation (n = 6, 1.4%), bicuspid aortic valve (BAV; n = 5, 1.2%), and ventricular septal defect (VSD; n = 5, 1.2%). Indeed, the frequency of CoA, BAV and VSD were markedly high compared with that in the general population (0.027% for CoA, 0.3% for BAV and VSD) (Table 2) [10, 11]. Accurate data regarding the prevalence of aortic regurgitation are not available [10].

Out of the 50 cases with congenital CVA, 11 had received treatment (surgery, n = 7; medical therapy, n = 2; and unknown treatment, n = 2). Moreover, in comparison with the cases without CVA, we found that karyotype 45,X was the most frequent in cases with CVA (28/50, 56% vs. 98/374, 26.2%; p < 0.001), while 46,X,Xi was the least frequent (0/50, 0%) vs. 98/374, 26.2%; p < 0.001) (Table 2). When analyzing the prevalence in relation to the anomaly’s site, we found that CoA was often seen in cases with karyotype 45,X (CoA vs. non-CVA: 9/12, 75.0% vs. 98/374, 26.2%; p < 0.01), while its prevalence was lowest in cases with other mosaic 45,X (1/12, 8.3% vs. 121/374, 32.4%; p = 0.11). In three of the five cases with BAV, the karyotype was 45,X. However, no significant differences were observed in karyotypes between the cases with BAV and without CVA.

c) Urinary tract malformation

Urinary tract malformation was seen frequently among patients with TS (43/363, 11.8%). Horseshoe kidney was the most frequent malformation (n = 19, 5.2%), followed by renal dysplasia (n = 7, 1.9%), hydronephrosis (n = 7, 1.9%), and double ureter (n = 6, 1.6%) (Tables 2, 4). The
prevalence of urinary tract malformation and horseshoe kidney among patients with TS was evidently higher than the prevalence among the general population in Japan (0.47% and 0.25%, respectively) [12, 13].

Out of the 43 patients with urinary tract malformation, 44.2% (n = 19) had karyotype 45,X; this percentage is higher than that among other cases without urinary tract malformation (93/320, 29.1%), although the difference was not statistically significant (p = 0.053; Table 2). Out of the 19 cases with horseshoe kidney, 36.8% (n = 7) had karyotype 45,X, also exceeding the percentage of other cases without urinary tract malformation cited above (p: statistically not significant). The number of cases with renal dysplasia or hydronephrosis was too small to yield any statistical significance, but the karyotype 45,X was seen in 57% (n = 4) of the seven cases with renal dysplasia, while it was 29% (n = 2) in the seven cases

with hydronephrosis. In the cases with double ureter, there was no bias related to any particular karyotype.

d) Osteoporosis

Out of the 231 patients with TS (aged 17 to 37 yr) who were reported about bone mineral density (BMD), 42.9% (n = 99) had low BMD (Table 2). The prevalence of low BMD was 47.1% (16/34 cases) in their late teens, 39.7% (56/141 cases) in their twenties, 48.2% (27/56 cases) in their thirties, and there were observed no statistical differences among these three decades. The prevalence of osteoporosis in general female’s early forties in Japan is reported to be 0.8% (31 × 10^3/3,867 × 10^3) [14]. Low BMD in this study might include osteopenia [T-Score between −1.0 and −2.5SD of Young Adult Mean (YAM)] and osteoporosis [T-Score ≤ −2.5SD of YAM], and the ratio of osteopenia and osteoporosis in TS is reported about 2:1(5). Therefore, the prevalence of osteoporosis

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Table 2  Prevalence of complications and its association with karyotype in patients with Turner syndrome

<table>
<thead>
<tr>
<th>Complication</th>
<th>Turner syndrome</th>
<th>General population</th>
<th>p</th>
<th>Karyotype characteristic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic thyroiditis</td>
<td>25.2</td>
<td>N.D.</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Ulcerative colitis</td>
<td>1.0</td>
<td>0.1^2</td>
<td></td>
<td>46,X,Xi in 1, 45,X/46,X,Xi in 1 among 4 cases</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>0.8</td>
<td>0.03^2</td>
<td></td>
<td>46,X,Xi in 1, 45,X/46,X,Xi in 1 among 3 cases</td>
</tr>
<tr>
<td>Cardiovascular diseases</td>
<td>11.8</td>
<td>1.0^2</td>
<td></td>
<td>45,X frequent (p &lt; 0.001), 46,X,Xi less frequent (p &lt; 0.01)</td>
</tr>
<tr>
<td>Coarctation of aorta</td>
<td>2.8</td>
<td>0.027^2</td>
<td></td>
<td>45,X frequent (p &lt; 0.001)</td>
</tr>
<tr>
<td>Bicuspid aortic valve</td>
<td>1.2</td>
<td>0.3^3</td>
<td></td>
<td>45,X in 3, other mosaic 45,X in 1 among 5 cases</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>1.2</td>
<td>0.3^2</td>
<td></td>
<td>45,X in 3, other mosaic 45,X in 2 among 5 cases</td>
</tr>
<tr>
<td>Urinary tract anomaly</td>
<td>11.8</td>
<td>0.47^1</td>
<td></td>
<td>45,X frequent (p = 0.053)</td>
</tr>
<tr>
<td>Horseshoe kidney</td>
<td>5.2</td>
<td>0.25^2</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Low bone mineral density</td>
<td>42.9</td>
<td>0.8^4</td>
<td></td>
<td>46,X,Xi and 45,X/46,X,Xi frequent (both p &lt; 0.05), other mosaic 45,X less frequent (p &lt; 0.01)</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>8.4</td>
<td>0.42^6</td>
<td></td>
<td>None</td>
</tr>
<tr>
<td>Hearing loss</td>
<td>6.2</td>
<td>0.04^6</td>
<td>&lt;0.001</td>
<td>None.</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>2.8</td>
<td>0.17^6</td>
<td>&lt;0.0001</td>
<td>45,X frequent (p &lt; 0.01), other mosaic 45,X less frequent (p &lt; 0.05)</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>0.9</td>
<td>0.5^6</td>
<td>= NS</td>
<td>Mosaic 45,X other than 45,X/46,X,Xi and 45,X/46,XX in 3 of 4 cases</td>
</tr>
</tbody>
</table>

*1 N.D.: Not available.
*2 General population for all ages.
*3 General female population for all ages.
*4 Osteoporosis in general female’s early forties.
*5 Junior high school girls in general.
in TS seems very high (probably over 17 times).

While every TS patients received hGH treatment, BMD reduction was observed similarly between cases with early estrogen therapy (12–14 years) (n = 26/52, 50%) and cases with late estrogen therapy (≥15 years) (n = 40/88, 45.5%) for pubertal induction.

Of these 99 patients with osteoporosis, 18.2% (n = 18) were receiving medical therapy, other than estrogen replacement, such as activated vitamin D, bisphosphonate, selective estrogen receptor modulator, and calcium lactate, 56.6% (n = 56) were not receiving medical therapy, and the medical therapy was unknown in the remaining 25 patients. Among these 231 patients with TS, spontaneous menstruation was observed in 43 patients (18.6%). The rate of spontaneous menstruation was statistically not different between cases with (n = 16/99, 16.2%) and without low BMD (n = 27/132, 20.5%).

Regarding the effect of body size on BMD, which was probably determined by two-dimensional DEXA

<table>
<thead>
<tr>
<th>Table 3 Cardiovascular diseases in Turner syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>a) Incidence of CVD</td>
</tr>
<tr>
<td>(+)</td>
</tr>
<tr>
<td>(−)</td>
</tr>
<tr>
<td>b) Site of Lesion*1</td>
</tr>
<tr>
<td>Aorta</td>
</tr>
<tr>
<td>Aortic Valve</td>
</tr>
<tr>
<td>Ventricle</td>
</tr>
<tr>
<td>Mitral Valve</td>
</tr>
<tr>
<td>Atrium</td>
</tr>
<tr>
<td>Pulmonary artery</td>
</tr>
<tr>
<td>Others</td>
</tr>
<tr>
<td>c) Treatment</td>
</tr>
<tr>
<td>(+)</td>
</tr>
<tr>
<td>(−)</td>
</tr>
<tr>
<td>unknown</td>
</tr>
</tbody>
</table>

*1 In a case of tetralogy of Fallot, each disorder was described to the respective site of lesion.
*2 Four cases had more than one complication, i.e. three lesions in one case, two lesions in three cases, and the details of disorder were not cited in three cases.

Table 4 Urinary tract abnormalities in Turner syndrome

| a) Incidence of Urinary Tract Anomalies | N | % |
| (+) | 43 | 11.8% |
| (−) | 320 | 88.2% |

| b) Disease Name | N | % |
| Horseshoe kidney | 19 | 5.2% |
| Renal dysplasia | 7 | 1.9% |
| Hydronephrosis | 7 | 1.9% |
| Double ureter | 6 | 1.6% |
| Malrotation (kidney) | 3 | 0.8% |
| Wandering kidney | 2 | 0.5% |
| Duplicated kidney | 1 | 0.3% |
| Duplicated pelvis | 1 | 0.3% |
| Polycystic kidney | 1 | 0.3% |

* Some cases had more than one complication.
method, there was no difference in the prevalence of low BMD between the group of 150 cm and over (44.8%, n = 58, Mean Ht 152.3 ± 0.3 cm) and the group less than 150 cm (38.3%, n = 120, Mean Ht 144.6 ± 0.3 cm) among the 178 cases reported adult height.

When analyzed in relation to karyotypes, in comparison with no BMD reduction cases, BMD reduction was seen more frequently in patients with 46,XX,XX (17/99 vs. 10/132, p < 0.05) or 45,XX/46,XX,XX (21/99 vs. 14/132, p < 0.05), but less frequently in patients with other mosaic 45,XX (21/99 vs. 49/132, p < 0.01) (Table 2).

e) Scoliosis

Scoliosis was seen in 8.4% (n = 33) of the 392 patients with TS. Considering the previously reported prevalence of complications of scoliosis among the general junior high school girls in Japan (0.42%, 141/33,557) (Table 2), the prevalence of this complication in our study was very high; however, exact comparison is not possible because of the age differences and possible undiagnosed cases in the present questionnaire study. The relative rate of karyotype 45,XX and 46,XX,XX in scoliosis cases were slightly higher than those in non-scoliosis cases (36.4%, 12/33 vs. 29.5%, 106/359 and 12.1%, 4/33 vs. 8.6%, 31/359, respectively), but those differences were not statistically significant (p = 0.43 and p = 0.52) (Table 2).

f) Hearing loss

Hearing loss was noted in 6.2% (n = 25) of the 402 patients with TS. The prevalence of hearing loss was 0% (0/55 cases) in their late teens, 7.5% (19/253 cases) in their twenties, 6.5% (6/93 cases) in their thirties, and the prevalence in the twenties was significantly higher than that of the teens (p < 0.05), while there were no significant differences between the thirties and twenties (p = 0.82) or teens (p = 0.08).

Hearing loss affects 0.04% (n = 8,000) of the total female population aged between 15 and 39 years in Japan (n = 19,376,000) according to the MIAC statistics in 2008 (Table 2) [16]. Our results suggested that the prevalence of hearing loss among patients with TS is considerably high compared with the general population (p < 0.001). Responses concerning presence/absence of use of hearing aid were collected from 22 cases, but none of them was using a hearing aid. In the rate of karyotype in patients with hearing loss, 45,XX/46,XX,XX was the highest (28.0%, 7/25) compared to non-hearing loss patients (14.3%, 54/377), but the difference was statistically not significant (p = 0.08) (Table 2).

g) Epilepsy

Complication by epilepsy was present in 2.8% (n = 12) of the 433 patients with TS. In the general population in Japan, onset of epilepsy occurs before the age of 20 years in 80% of all cases [17]. It has been reported that epilepsy occurs in 0.15% of the entire female population between 0 and over 90 years and in 0.17% (33 × 10^11/19,376 × 10^3 females) of those aged between 15 and 39 years in Japan, and the prevalence of TS was significantly higher than the latter (p < 0.0001) (Table 2) [18]. Based on these previous reports, the prevalence of complication by epilepsy among patients with TS was considerably high in our study. When the association with the karyotype was evaluated, we found that the rate of karyotype 45,XX was markedly higher in the epilepsy group (8/12) compared with the epilepsy-free group (115/421, p < 0.01), while the prevalence of this complication was significantly lower in patients with other mosaic 45,XX (epilepsy vs. non-epilepsy: 0/12 vs. 134/421, p < 0.05) (Table 2).

h) Schizophrenia

Schizophrenia was present in 0.9% (n = 4) of the 433 patients with TS. Considering that 0.5% (n = 103,000) of the total female population aged between 15 and 39 years in Japan (n = 19,376,000) had schizophrenia according to the MIAC statistics (Table 2) [16], the prevalence of this complication among patients with TS was slightly high, but not statistically significant. The karyotypes in three of these four cases were mosaic 45,XX other than 45,XX/46,XX,XX and 45,XX/46,XX,XX (Table 2).

i) Other complications

In other comorbidities in TS patients, high prevalence of bone/joint complications (n = 7, including four cases of congenital hip dislocation), mental retardation (n = 4), colorectal cancer (n = 2) and one case of gonadoblastoma were observed.

Discussion

As far as we know, there are no comparative studies on a large scale regarding the prevalence of diverse complications between TS patients and general population. By this questionnaire survey, the more exact prevalence of diverse complications was clarified and it exceeded the prevalence of the majority of complications in Japanese general population. Further, as novel findings, it was observed that the prevalence of epilepsy was significantly high, and it was frequently associated with the chromosome 45,XX. The prevalence of BMD reduc-
tion was more associated with the chromosome 46,X,Xi and 45,X/46,X,Xi and less in mosaic 45,X. This study will offer invaluable information for physicians involved in managing and studying patients with TS.

In cytogenetic studies, the chromosome karyotype 45,X among patients with TS in Japan has a lower frequency than that reported in the United Kingdom and Belgium, while karyotypes 46,X,Xi, 45,X/46,X,Xi and other mosaic 45,X have a higher frequency [19, 20]. Annual evaluation of the frequency of karyotype 45,X based on which more than 400 cases were analyzed in Western countries (including the above-cited reports) showed continuous decreases by the year, recording 50% until 1982 [21], 46% until 1989 [20], and 36% between 2006 and 2013 [19, 22]. This resembles the trend of change in Japan where chromosome analysis has been carried out relatively extensively as a means for screening female individuals with short statures [23].

In the present study, the prevalence of chronic thyroiditis among patients with TS was close to that observed in the general female population screened in Japan (25.2–31.4%) [24, 25]. However, these individuals had a mean age of about 50 years, and chronic thyroiditis generally becomes apparent with age as was observed in this study [24]. Moreover, 8.4% of the patients with TS were overt hypothyroidism in this study, while the percentage in the above-mentioned reference was low (0.4–0.9%). Based on these observations, we suggest that the prevalence of chronic thyroiditis among the patients with TS is considerably high. The positive rate of chronic thyroiditis in TS is reported to be 20–67% among the population including children and adults in foreign countries [26, 27], while the prevalence of clinically overt hypothyroidism is reported to be 12–31.4% [6, 26]. Both of these percentages are considerably high compared to our study, while similar observation was recently reported in Japan [28].

Therefore, periodical evaluations of thyroid autoantibodies and thyroid function are required during the follow-up of patients with this syndrome. An association between chronic thyroiditis and the chromosome karyotype 46,X,Xi among patients with TS has been reported [1]. While the present study revealed no statistically significant relationship between chronic thyroiditis and any karyotypes as was reported by Bettendorf et al. [29].

According to reports from Western countries, the prevalence of inflammatory bowel disease was very high in the TS patients (2.6%), while the prevalence of CD is higher than UC, contrary to the finding in the present study [1, 30]. In a large-scale analysis of the data from US military personnel and their families (10.2 million in total) [31], the prevalence for UC was 0.2% and 0.15% for CD; both lower than the prevalence in the TS group but much higher than the prevalence among the general population in Japan. In previous reports, such cases often had chromosome karyotype 46,X,Xi [1]. Indeed, our study has also revealed karyotype 46,X,Xi in two of the four cases with ulcerative colitis and two of the three cases with CD, thus suggesting a high percentage of cases having the karyotype 46,X,Xi.

The prevalence of congenital cardiovascular anomalies (cardiovascular diseases) among TS patients was evidently higher than that in the general population in Japan, as observed in the analysis of both the overall prevalence and the prevalence at each site (i.e. aorta and ventricle). It is worth noting that the prevalence of CoA and BAV among patients with TS is quite high in Western countries. According to data analyzed by Elsheikh et al. and Donadille et al. [1, 32], the prevalence of CoA was 6.9 to 9%, while that of the BAV 12 to 21%, both markedly exceeding the prevalence in the present study (particularly high prevalence of BAV).

Concerning the karyotype, a significantly high percentage of patients with heart malformation had karyotype 45,X monosomy, while karyotype 46,X,Xi was significantly less frequent, which is similar to the previous report [1].

Although cardiovascular anomaly is well known as a cause for sudden death in patients with TS, aortic anomaly is often symptom-free [5]. Therefore, it seems necessary to request periodical complete evaluations by cardiology specialists at hospitals with sufficient and advanced medical equipment.

In the present study, the prevalence of both entire urinary tract malformation and horseshoe kidney was evidently higher than the national average [12, 13]. However, the prevalence of structural anomalies of the kidney among TS patients in Western countries is much higher (20–43%) [1-5], far exceeding the prevalence for each type of renal malformation in Japan. Among the kidney malformations, horseshoe kidney was the most frequent, which is in line with past reports [1, 5]. Recently, it was reported that X-linked inhibitor of apoptosis protein (XIAP) mRNA expression in TS was higher in mosaic karyotype and renal malformation than those without [33]. However, as this abnormality does not explain all the TS phenotype, further studies are required to elucidate the developmental mechanism of the malfor-
mation.

Albeit not statistically significant, the present study revealed a higher percentage of karyotype 45,X cases in patients with urinary tract malformation. This is consistent with a previous report suggesting that kidney malformation is more likely to be found in patients with karyotype 45,X [1]. When analyzed by anomaly type, we noted that horseshoe kidney, renal dysplasia, and hydronephrosis were often associated with karyotype 45,X, although no significant difference was noted between patients with and without malformation. There was no bias to any particular karyotype among cases complicated by double ureter.

In the present study, the prevalence of osteoporosis was considered to be very high in TS compared to the general female’s early forties in Japan [14].

In Western countries, the frequency of bone mass reduction and bone density reduction among patients with TS is quite high. According to a recent report [5], out of 43 patients (mean age 31) 22 (51.2%) displayed osteopenia, and 10 (23.2%) did osteoporosis, namely an overwhelming majority (74.4%) of patients with TS showed bone density reduction.

Despite the reports suggesting that BMD is normal in patients with spontaneous menstruation [3, 34], the present study revealed no statistical difference in the BMD reduction rate between patients with or without spontaneous menstruation. In patients with TS, spontaneous menstruation, if present, is not always continuous and often leads to amenorrhea [3, 35, 36]. This manifestation may be associated with BMD reduction among patients with TS.

It is known that early estrogen therapy and human GH (hGH) therapy can improve the reduced bone mass and density as well as high fracture rate seen in TS [1, 3, 37]. However, in the present study, bone density reduction was observed in 42.9% of all cases despite treatment with hGH during childhood. In addition, bone density reduction was noted even in cases where estrogen therapy, in addition to hGH, has been administered, to induce the development of secondary sex characteristics at relatively young ages. These results suggest that the application of hGH and estrogen therapies starting from early childhood might improve bone mass and density to some extent, but cannot achieve normal bone density in a reliable manner [38-41]. Relating to this, many authors are speculating a presence of endogenous bone defects in TS patients [1, 38, 40, 42].

In this study, there were no differences in the BMD reduction rate between groups over 150 cm and below 150 cm. It might be necessary to correct the partial volume effect due to body size using peripheral Quantitative CT (pQCT) which allow precise measurement of three-dimensional bone density [43].

Because osteoporosis associated with TS becomes noticeable during childhood, periodical BMD evaluations are indispensable during the follow-up of patients at outpatient clinics. In cases with BMD reduction, the percentage of karyotype 46,X,Xi and 45,X/46,X,Xi was significantly high compared with cases without BMD reduction, while the percentage of other mosaic 45,X was significantly low. It is desirable to clarify the exact mechanism inducing osteoporosis due to complete or partial absence of X-chromosome.

Scoliosis or kyphosis is often seen in patients with TS. The prevalence of this kind of deformity was markedly high in TS patients as compared with the general junior high school girls in Japan [15]. According to the international reports, scoliosis was seen relatively frequently (12–28%) among patients with TS [44-46]. If mild cases are also included, the prevalence increased to 59% of all cases with TS [47]. This complication develops at the age of 10 years and increases with aging. However, no association with hGH therapy has been noted [44, 47]. The reduced expression of short stature homeobox (SHOX) gene is accompanied by dysmorphism of the skeletal growth plate in patients with TS. Therefore, abnormality of such a gene is also anticipated in cases showing scoliosis associated with TS. However, in congenital cases or cases of idiopathic scoliosis clinically and radiologically resembling the cases of TS, the expression of this gene in the vertebral body growth plate is enhanced, rather than reduced. Thus, it is difficult to explain the scoliosis associated with TS simply based on SHOX gene abnormality [48]. When analyzed by karyotype, no significant association was noted between scoliosis and karyotypes.

Hearing loss can disturb the daily living, psychosocial well-being and cause social isolation of the patients with TS [2, 49]. In the present study, the prevalence of hearing loss among patients with TS (6.2%) was evidently higher than in the general female population of the corresponding age. The prevalence of hearing loss among patients with TS varies greatly between 12 and 67% according to international reports, but it is considerably higher than in Japan [30, 50].

In this study, we could not confirm the age dependency of hearing loss in TS. However, according to a
detailed analysis by age among patients with TS at the same Swedish university, the prevalence of hearing loss was very high, i.e. 45.0% at age 16–34 and 61.2% at age 35 and over, indicating a sharp elevation with aging. Moreover, the percentage of hearing aid users was 26.5% in the group aged 35 and over [51, 52], while there was no hearing aid user in our study. The reason for these discrepancies of the rate of hearing loss and hearing aid users between Japanese and Western TS patients remains unexplained. It has been previously reported that patients with hearing loss often had karyotype 46,X,Xi, while the mosaic karyotype was the least prevalent [1]. Such a trend was noted also in the present study, although there was no significant difference between patients with or without hearing loss.

This study revealed at first time to our knowledge that the prevalence of epilepsy among Japanese patients with TS was significantly higher than that among the general female population [18]. To date, few reports have been published concerning epilepsy in TS in foreign countries [53], and the incidence of this complication was reported only in one study in which an electroencephalogram suggesting idiopathic epilepsy was noted in one of the 64 cases (1.6%) [54]. As for the karyotype bias, only karyotype 45,X was markedly higher in the patients presented with epilepsy, while the incidence of this complication was significantly low in cases showing other mosaic 45,X karyotypes.

The prevalence of schizophrenia was slightly higher among patients with TS (0.9%) compared with the general female population of the corresponding age (0.5%). No global analysis has been conducted concerning the incidence of schizophrenia among patients with TS. However, among 6,483 female patients with schizophrenia Turner syndrome was observed in 11 patients, and is 3-fold more frequently in schizophrenic females than in the general female population [55]. The karyotype was mosaic in most of the cases of TS in the study cited above. Consistently with this, three of the four cases in the present study had other mosaic 45,X excluding 45,X/46,X,Xi and 45,X/46,XX. These results suggest that mosaic 45,X might have some correlation with schizophrenia.

Turner syndrome possess diverse complications, which showed considerable association with 45,X monosomy for cardiovascular, urinary tract diseases and epilepsy, 46,X,Xi and/or mosaic 45,X/46,X,Xi for autoimmune disease and osteoporosis, and other mosaic 45,X for schizophrenia. Further study are required to analyze which numeric and/or structural abnormalities of sex chromosomes (as well as copy number variant) are contributing to the occurrence of respective complications.

In conclusion, as women with TS had a higher prevalence of multidisciplinary complications lowering quality of life mentioned above, it is important to keep these findings in mind during the management and work closely with specialists in relevant fields.

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Disclosure

The authors have no potential conflict of interest to declare.

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