

# Lifelong medical challenges and immunogenetics of Turner syndrome

Won Kyoung Cho, MD, PhD

Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

Turner syndrome (TS) is a female phenotypic condition characterized by one or more typical clinical features and the partial or complete absence of a second X chromosome as determined by karyotype analysis. TS, among the most common chromosomal abnormalities, has an estimated prevalence of approximately 1 in 2,500 live-born females, with ethnic and racial differences. TS encompasses a wide array of medical challenges, including cardiovascular, endocrine, autoimmune, and mental health issues, as well as a heightened cancer risk. The somatic stigmata of TS are thought to arise from haploinsufficiency of the X chromosomes. This review explores the lifelong medical challenges and immunogenetics of individuals with TS and aimed to investigate strategies for preventing and managing TS while considering the implications of immunogenetics.

**Key words:** Turner syndrome, Immunogenetics, X chromosome

## Key message

- This summary emphasizes the importance of the early diagnosis of Turner syndrome (TS) and presents a multidisciplinary approach to its prevention and management, highlighting the need for customized care.
- Advancements in immunogenetic research may improve our understanding of TS and improve its outcomes.
- TS encompasses a wide array of medical challenges, including cardiovascular, endocrine, autoimmune, and mental health issues, as well as a heightened cancer risk.

## Introduction

Identified in 1938 by Henry Turner, Turner syndrome (TS) is a phenotypic female condition that features one or more typical clinical features and a partial or complete absence of a second X chromosome as determined by karyotype

analysis.<sup>1,2)</sup> TS, among the most common chromosomal abnormalities, has an estimated prevalence of approximately 1 in 2,500 live-born females, with ethnic and racial differences.<sup>3)</sup> Recent data from a Danish nationwide cytogenetic registry indicated an increasing incidence of TS in female live births, suggesting a prevalence of 1 in 1,700 live-born females.<sup>4)</sup> We recently determined the prevalence of TS to be 7.84 per 100,000 in South Korean women.<sup>5)</sup>

Prenatal karyotype confirmation by chorionic villous sampling or amniocentesis is generally performed using ultrasonography to identify nuchal translucency in the first trimester, the presence of advanced maternal age, or abnormal triple or quadruple maternal serum screening results ( $\alpha$ -fetoprotein, human chorionic gonadotropin, inhibin A, and unconjugated estriol).<sup>6)</sup> Postnatal karyotype confirmation should include a minimum of 30 counted cells unless mosaicism is documented within the first 20 cells.<sup>7)</sup> TS karyotypes present a spectrum of variations, including complete X monosomy, mosaicism, and structural anomalies such as isochromosome or ring formation of the X chromosome. Approximately 40%–50% of individuals with TS have monosomy X, whereas 5%–10% possess a duplication (isochromosome) of the long arm of one X chromosome. The majority of other cases demonstrate mosaicism for 45,X along with one or more additional cell lineages.<sup>7)</sup> The Cincinnati International TS Meeting recommended against considering a diagnosis of TS in females with one X chromosome and a deletion distal to Xq24 on the other X chromosome as well as in women older than 50 years with <5% 45,X mosaicism.<sup>8)</sup>

TS is characterized by distinctive physical traits (webbed neck, low hairline, low-set ears, hand and foot lymphedema, and cubitus valgus). Short stature and primary ovarian insufficiency are the 2 most important characteristics of TS.<sup>5)</sup> Cardiovascular complications are also significant, notably congenital anomalies such as bicuspid aortic valves (BAVs) and coarctation of the aorta (CoA). Endocrine disorders,

Corresponding author: Won Kyoung Cho, MD, PhD. Department of Pediatrics, St. Vincent's Hospital, College of Medicine, The Catholic University of Korea, Jungbudaero(Ji-dong), Paldal-gu, Suwon 16247, Korea

✉ Email: [wendy626@catholic.ac.kr](mailto:wendy626@catholic.ac.kr), <https://orcid.org/0000-0003-0918-0565>

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particularly Hashimoto thyroiditis (HT), diabetes, and dyslipidemia, are also frequent concerns. Skeletal abnormalities such as scoliosis and osteoporosis further complicate the health landscape of patients with TS.<sup>9</sup> Hearing loss and ear infections are also common, necessitating regular auditory assessments.<sup>10</sup> Mental health is another crucial aspect, as individuals with TS are more susceptible to anxiety, depression, and social adjustment challenges.<sup>11</sup> The life expectancy of women with TS is shorter than that of healthy women.<sup>12</sup> In South Korea, the prevalence of cancer (specifically thyroid cancer) and the risk of mortality from all causes are higher in affected versus healthy females.<sup>5</sup> Individuals with TS face various medical challenges throughout their lives.

The observed somatic stigmata of TS are thought to arise from haploinsufficiency of the X chromosomes. The X chromosome harbors approximately 1,000 genes, including numerous immune-related genes encoding receptors, associated proteins, and regulators, compared with the Y chromosome, which has a comparatively smaller number of genes (approximately 100).<sup>13</sup> Although females possess 2 X chromosomes, the allelic dosage balance between females and males is maintained through X chromosome inactivation (XCI), which randomly silences one of the 2 X chromosomes in females.<sup>14</sup> However, approximately 15%–20% of genes linked to the X chromosome escape XCI.<sup>15</sup> In normal female individuals, both genes are typically well expressed in the pseudoautosomal regions of the X chromosome. In patients with TS, the expressions of the XCI escape genes as well as those in the pseudo-autosomal regions of X chromosome are reduced.<sup>16</sup> These genetic underpinnings, which are characterized by the partial or complete loss of an X chromosome in TS, can result in a spectrum of clinical features attributed to the diminished expression of genes that normally escape XCI. Research indicates that deletions of the small distal short arm (Xp-) of the X chromosome, including the *SHOX* gene, are associated with short stature and various skeletal anomalies.<sup>17</sup> Deletion of the long arm distal to Xq24 is associated with primary or secondary amenorrhea.<sup>8</sup> This review explores the lifelong medical challenges and immunogenetics of individuals with TS and aimed to investigate strategies to prevent and manage TS while considering the implications of immunogenetics.

## Autoimmune diseases among patients with TS

Autoimmune diseases are a significant health concern among patients with TS. HT affects 23%–34% of individuals with TS, and research indicates that antithyroperoxidase antibodies are detectable in 45% of patients with TS, with one-third of them being symptomatic for hypothyroidism.<sup>18–20</sup>

Patients with TS had a relative risk (RR) of 11.6 for type 1 diabetes and an RR of 4.4 for type 2 diabetes, demonstrating a significant health burden. The prevalence of type 2 diabetes was particularly elevated in certain karyotypes: 18% among those with 45,X and up to 43% among those with isochromosome Xq. While extensive reports have highlighted the correlation between diverse genotypes and phenotypes in TS, there exists a counter-perspective suggesting that the clinical presentation of TS may not be directly tied to karyotype variations.<sup>8,21</sup>

Considering the increasing susceptibility to hypothyroidism and diabetes among patients with TS, the Cincinnati Group recommends regular health screenings for hypothyroidism at diagnosis and annually through measurements of (free) T4 and thyroid stimulating hormone starting in early childhood and continuing throughout life. Additionally, they advocated annual glycosylated hemoglobin tests, with or without fasting plasma glucose, beginning at 10 years of age to monitor for diabetes starting in adolescence.<sup>8,19,22</sup> Patients with TS are also susceptible to autoimmune diseases such as celiac disease, systemic lupus erythematosus (SLE), Sjögren syndrome (SS), Crohn disease, and ulcerative colitis.<sup>19,23–27</sup> In addition to diabetes and thyroiditis, it is necessary to consider the potential development of other autoimmune conditions in necessary.

Autoimmune diseases in TS present a complex array of conditions that might be influenced not only by the associations of numerous immune-related genes located on the X chromosome, but also by the absence of XCI skewing, escape, and immunogenetics.<sup>20</sup> Monosomy of X chromosome, a genetic deficit that manifests as inherited or acquired anomalies in the structure or number of X chromosomes, may precipitate autoimmunity. For instance, some studies suggest that the long arm of the X chromosome hosts an MHC locus, and its loss in TS may lead to a deficiency in immune regulation.<sup>28</sup> Furthermore, other researchers have suggested that increasing susceptibility to autoimmune diseases of TS is related to uncommon X chromosome abnormalities that might play a role in these diseases and could pinpoint the location of the gene(s) responsible for the X chromosome dose effect observed in SLE and SS.<sup>25</sup> Patients with TS who have isochromosome Xq exhibit lower levels of immunoglobulin G and a reduced percentage of CD4 cells than healthy girls, supporting the idea that immunological differences may contribute to their susceptibility to autoimmune diseases.<sup>29</sup>

Epigenetic regulation of the X chromosome is also believed to contribute to susceptibility to autoimmune diseases.<sup>30</sup> Variations in the X chromosome count can lead to epigenetic changes such as DNA methylation alterations, which are thought to play a role in genetic expression.<sup>31</sup> Viuff et al.<sup>32</sup> revealed that the number of X chromosomes affects gene regulation, noting that individuals with TS monosomy

show decreased gene expression and lower methylation levels of genes such as *XIST*, *JPX*, *KDM6A*, *AKAP17A*, *CD99*, *DHRX*, *EIF2S3*, *GTPBP6*, *PP2R3B*, *PUDP*, *SLC25A6*, *TSIX*, *ZBED1*, and *ZFX* than healthy females. Conversely, individuals with an extra X chromosome (47,XXY) exhibited increased gene expression and methylation. These results suggest that variations in X chromosome count could influence genetic expression and methylation patterns, potentially affecting phenotypic outcomes and disease manifestations in sex chromosome aneuploidies. In TS cases, copy number variations (CNVs) were detected by a microarray analysis of clinical variations observed in TS. Studies of 36 participants revealed CNV in 22.2% of cases. Significant CNV were found in several patients with a single X chromosome, showing gains and losses in specific X chromosomal genes, and suggesting that CNV may affect clinical variations in TS.<sup>33</sup> The complex interplay of genetic and epigenetic modifications affecting gene expression of the remaining X chromosome in TS may explain the wide range of TS phenotypes.<sup>31</sup>

### Short stature among patients with TS

A short stature is a hallmark of TS, and growth hormone (GH) therapy enhances the final adult height. Individuals with TS have a significantly lower mean plasma 24-hour GH level than healthy but short girls.<sup>34</sup> The lack of alignment of GH secretion levels and growth implies that monitoring GH secretion may not be crucial for managing growth.<sup>35</sup> Substantial evidence supports the idea that GH therapy significantly enhances the final adult height of individuals with TS. GH therapy was approved for girls with TS in the United States, Europe, and Japan in 1996 and in South Korea in 1998.<sup>36</sup> GH therapy efficacy is influenced by factors such as therapeutic duration, GH dose, initial height standard deviation score, parental height, and initiation timing.<sup>37,38</sup> Variations in the *GHR* gene may also affect the response of individuals with TS to GH therapy.<sup>39</sup> The recommended approach is to start GH therapy for patients with TS early, at around 4–6 years of age and preferably before 12–13 years of age, especially when there is evidence of growth failure, such as having a height <50th percentile for >6 months.<sup>8</sup> GH therapy is typically suggested even in patients with TS as young as 2 years of age when their height drops to <5th percentile.<sup>6</sup> This early initiation is crucial because it can lead to greater improvements in final adult height.<sup>40</sup>

GH treatment in TS typically involves doses higher than those used for managing standard GH deficiency, starting at 0.33 mg/kg/wk (1 IU/kg/wk) and increasing to 0.46 mg/kg/wk (1.4 IU/kg/wk) when aiming to optimize adult height, particularly if the growth potential is significantly

affected.<sup>41</sup> Reducing GH treatment doses is recommended if insulin-like growth factor-1 levels exceed +2.5 standard deviations over at least 6 months, ensuring that dosage adjustments align with individual growth responses and hormone levels.<sup>42</sup> Some studies have indicated a possible association between GH therapy in TS and an increased aortic diameter, increasing the risk of aortic dilation.<sup>19</sup> However, after adjusting for factors such as age, height, weight, and cardiac anomalies, GH therapy had no independent effect on the aortic diameter.<sup>43,44</sup> The long-term effects of GH therapy on the heart and arteries of patients with TS are not fully understood and will require careful monitoring and personalized approaches, especially considering the potential cardiovascular effects.

### Cardiovascular health among patients with TS

Approximately half of all individuals with TS present with congenital heart defects, including CoA, BAV, and partial anomalous pulmonary venous return.<sup>45</sup> Despite normal fetal echocardiography results, infants with TS should receive a comprehensive assessment from a pediatric cardiologist and undergo further imaging of the potential for BAV and CoA to remain undetected during fetal echocardiography.<sup>46</sup> If a baseline echocardiogram fails to conclusively exclude congenital structural abnormalities such as CoA or partial anomalous pulmonary venous return, magnetic resonance imaging (MRI) can be used.<sup>46</sup> The Cincinnati guidelines for TS suggest tailored cardiac monitoring based on age and risk level, which are determined by the CoA, BAV, hypertension (HTN), and TS-specific z score of the aorta.

Among children up to 16 years of age, those who are at low risk require transthoracic echocardiography (TTE) or cardiac MRI every 5 years, while those at high risk for specific heart conditions require checks every 6–12 months. Adults >16 years without risk factors should undergo surveillance every 5–10 years, while those at high risk with an aortic size index (ASI) > 2.3 cm/m<sup>2</sup> are advised to receive more frequent assessments every 6–12 months.<sup>8</sup> The American Heart Association recommends that infants up to 15-year-olds with moderate risk factors such as CoA, BAV, or HTN should undergo repeat examinations, including TTE or Cardiac magnetic resonance (CMR), at intervals of 6–24 months.<sup>47</sup>

A nationwide Danish study found that women with TS were 3.5 times more likely to develop coronary heart disease and had a 2.2-fold increased risk of cerebrovascular disease than the general female population.<sup>48</sup> The incidence of aortic dissection in patients with TS is estimated to be 36 per 100,000 TS years, which is 6 times higher than the 6 per 100,000 incidence rate in the general population.<sup>49</sup> In patients with

TS, aortic dilation, a potential early stage leading to aneurysm, represents a significant concern, affecting 15%–30% of girls.<sup>50,51</sup> In TS, the occurrence of dissecting aortic aneurysms is often linked to additional risk factors, such as BAV, other aortic valve anomalies, CoA, and HTN.<sup>38,52</sup> In the literature review, aortic dissection in TS patients occurred at an average age of 30.7 years, much earlier than that in the general female population (68 years). Among the cases evaluated for systemic HTN and congenital heart disease, 15% had only HTN, 30% had only congenital heart disease (CHS), 34% had both, and 11% had neither condition.<sup>53</sup> These results suggest that, even without traditional risk factors, vasculopathy inherent to TS may predispose individuals to aortic dissection, indicating that TS itself might serve as an independent risk factor for this condition.<sup>38,53</sup> The risk of aortic dissection is not solely determined by aortic size. It's recommended to use a body surface area-adjusted ASI >2 cm/m<sup>2</sup> for close follow-up and referral if ASI is <0.5 cm/m<sup>2</sup> irrespective of stature.<sup>54</sup> Opinions suggest that the cardiovascular health concerns related to TS might be highly influenced by individual genetic profiles. Patients with TS and monosomy X are particularly monitored for cardiovascular health as they may exhibit a higher likelihood of aortic dissection than individuals with other karyotypes of TS.<sup>19</sup> One study reported a higher incidence of congenital heart disease in TS patients with monosomy X, but the likelihood of developing aortic dilation was similar across all TS karyotypes.<sup>55</sup>

Managing the cardiovascular health of patients with TS requires a tailored approach that considers patient age, health, and genetic specifics. For young individuals with TS, priority is given to monitoring congenital heart defects, whereas adults should focus more on preventing and managing HTN and aortic disorders. Lifestyle modifications such as maintaining a healthy weight and engaging in regular exercise are crucial; however, there is a notable lack of focus on physical activity among individuals with TS. Research indicates that they tend to participate less in physical activity than the healthy population.<sup>56</sup> However, competitive sports are contraindicated when specific criteria are related to aortic enlargement, including an aortic sinus of Valsalva or ascending aorta with a body size-adjusted z score >2, evidence of increasing z score on subsequent aortic imaging, or a single z score >3.<sup>38</sup> The necessity for individualized management strategies for TS becomes evident immediately after its diagnosis and persists throughout the patient's lifespan.<sup>57</sup>

## Hypogonadism and reproductive issues among patients with TS

Nearly 95% of patients with TS experience premature ovarian insufficiency characterized by menstrual disrup-

tions such as amenorrhea or notably short cycles lasting more than 4 months with follicle-stimulating hormone levels >25 mIU/mL. Particularly for patients with TS and 45,X/46,XX mosaicism, approximately 30% of these individuals experience natural-onset puberty, with 10%–20% experiencing spontaneous menstruation. Ovarian function typically declines after a few years, leading to halted puberty and the emergence of primary or secondary amenorrhea.<sup>42</sup> Natural pregnancies occur in an estimated 7% of individuals with TS, especially among those with 45,X/46,XX mosaicism.<sup>58</sup>

There are many age-specific guidelines for estrogen therapy for TS.<sup>42</sup> Hormone replacement therapy (HRT) is pivotal for managing primary ovarian failure, which is prevalent in patients with TS. To replace lost estrogen in TS, various pharmaceutical formulations, such as oral tablets, transdermal patches, and topical gels, can be administered.<sup>59</sup> The use of a percutaneous route to induce puberty reduces first-pass hepatic metabolism and is less likely to cause coagulation than the use of an oral route.<sup>59–61</sup> HRT initiation should be customized to each patient's clinical and genetic profile. Low-dose estrogen therapy should be initiated at ages 10–11 years if spontaneous puberty is lacking and the follicle-stimulating hormone level is elevated to simulate natural puberty and promote bone health.<sup>9,38</sup> While some groups recommend beginning this therapy at 11–12 years of age,<sup>8,42</sup> others suggest a starting age of 12–13 years.<sup>38</sup> Additionally, the routine addition of extremely low doses of estrogen in the prepubertal years is advised to enhance growth.<sup>8</sup> The pubertal induction process in TS typically spans 2–2.5 years. Once menarche is achieved, the regimen is supplemented with progesterone, and the treatment is transitioned to a cyclical pattern that closely mimics natural menstrual cycles.<sup>62</sup> In adults with TS who are >30 years old, use of the lowest dose of estrogen that provides full protection against osteoporosis is recommended. Postmenopausal considerations for estrogen use are similar to those for other postmenopausal women.

Infertility is prevalent in TS, and fertility and family planning are becoming increasingly important concerns. Advances in assisted reproductive technologies are expanding pregnancy options for individuals with TS. The use of cryopreserved ovarian tissue and immature oocytes harvested before childhood ovarian regression is promising.<sup>8</sup> However, pregnancies among patients with TS carry high risks, including a 2% chance of maternal death from aortic dissection along with complications such as severe hypertensive disorders and increased fetal morbidity, mortality, and chromosomal abnormality rates.<sup>63</sup> Women with TS are at a threefold increased risk of mortality, a figure that becomes even more pronounced during pregnancy.<sup>64</sup> The American Society for Reproductive Medicine advises



against pregnancy in the presence of any cardiac defects identified on MRI, especially at an ASI > 2 cm/m<sup>2</sup>.<sup>65</sup> The French Joint Practice Committee stated that pregnancy is contraindicated in the presence of any past or current aortic disease, uncontrolled HTN, or portal HTN with esophageal varices.<sup>66</sup> Thus, providers must be familiar with the risks and recommendations of caring for women with TS of reproductive age.

## Bone health of patients with TS

The skeletal health of patients with TS frequently involves distinctive traits such as a wide, short neck; broad chest; square torso; cubitus valgus; finger malformations, particularly short fourth and fifth metacarpals; delayed bone maturation; and kyphosis, scoliosis, and osteopenia.<sup>67</sup> Individuals with TS have a low bone mineral density (BMD) and are at high risk of fracture starting at a young age.<sup>9</sup> Osteopenia and osteoporosis are prevalent among individuals with TS, especially those with ovarian failure, affecting about 45%, and early-onset menopause is common.<sup>68</sup> There is an approximately 25% increase in fracture risk, most of which cases are correlated with medium- or high-impact trauma.<sup>69</sup> Nguyen et al.<sup>70</sup> showed that nearly one-third of patients with TS experienced fractures and delayed HRT as key risk factors along with intrinsic bone abnormalities and comorbidities such as vitamin D deficiency, emphasizing the need for early pubertal induction and the use of HRT to optimize BMD. A meta-analysis revealed that HRT significantly increases BMD and reduces the risk of fractures.<sup>71</sup> A nationwide study in the United States reported that patients with TS who are <45 years of age had similar fracture rates to those of controls, whereas those >45 years of age faced a higher risk of fractures that was possibly exacerbated by balance impairments.<sup>72</sup>

While dual X-ray absorptiometry is crucial to the effective bone health management among patients with TS, caution should be exercised because of their inherent tendency to underestimate the bone density in people of short stature. Thus, bone size-independent methods such as quantitative computed tomography (QCT) or volumetric transformation of dual X-ray absorptiometry data should be used for individuals shorter than 150 cm.<sup>69</sup> In patients with TS, peripheral QCT also offers a more precise measure of bone quality, including geometry and microarchitecture.<sup>73</sup> Screening for vitamin D deficiency should be performed at 9–11 years of age and every 2–3 years thereafter. Starting HRT early, around ages 11–12 years, and promptly titrating to the adult dose after 2 years is key to preventing osteoporosis among individuals with TS.<sup>8,9</sup> Physical activities that promote bone strength coupled with nutritional advice

to improve bone health can significantly affect a patient's well-being.<sup>8</sup>

## Cancer and mortality risks among patients with TS

Regarding the cancer and mortality risks associated with TS, focus is increasing on the heightened risk of certain types of cancers and a shortened life expectancy. Based on national data, we reported an increased all-cause mortality risk among South Korean women with TS (hazard ratio, 3.36)<sup>5</sup> as well as a higher cancer risk among patients with TS than age-matched controls, particularly for thyroid cancer, with a hazard ratio of 2.78.<sup>5</sup> Upon analyzing data for 3,439 women diagnosed with TS in 1959–2002, a British study found that the mortality rate among patients is 3 times higher than that among the general population.<sup>22</sup> In a nationwide Danish study, the risk of premature death increased threefold, while the life expectancy was reduced by at least a decade.<sup>48</sup> A British national study highlighted an elevated risk of central nervous system tumors, especially meningioma and childhood brain tumors, bladder and urethral cancers, and eye cancers, in patients with TS. Conversely, in patients with TS aged 15–44 years, the risk of breast cancer was lower, whereas those of cutaneous melanoma and corpus uteri cancer were higher.<sup>12</sup> A nationwide Danish study found that, while the overall cancer risk was not elevated among individuals with TS, the risks of skin cancer and benign skin neoplasms were increased twofold, while that of breast cancer was lower.<sup>74</sup> Two other European studies that surveyed the prevalence of different types of neoplasia among patients with TS reported an increased risk of skin neoplasm/cancers and central nervous system tumors, while thyroid cancer occurred in only one of 87 women with TS.<sup>75,76</sup>

There is also concern regarding ovarian gonadoblastoma in TS patients with overt or cryptic Y chromosomes. A Korean study conducted in 2017 revealed that 12.9% (16 of 124) of patients with TS had Y chromosomes by karyotyping or Y chromosome material by polymerase chain reaction; of them, 18.8% (3 of 16) were diagnosed with gonadoblastoma.<sup>77</sup> The presence of Y chromosome material, a possible risk factor for gonadoblastoma, has been suggested in mosaic TS with Y chromosomes. One study reported a 33.3% (4 of 12 patients) prevalence of gonadoblastoma in a series of gonadectomized patients with TS with Y-chromosome markers (SRY and Y-centromeric DYZ3 repeats). Given this substantial risk, prophylactic laparoscopic gonadectomy is currently recommended as a preemptive measure.<sup>78</sup> The presence of Y chromosome material in TS was tested by DNA studies, including polymerase chain reaction or FISH

using a Y-centromeric probe. However, routine testing for SRY or Y chromosome material is not clinically warranted at present.<sup>8)</sup> To manage cancer and mortality risks in TS, regular health screenings such as mammography and thyroid screening might be necessary. Early intervention strategies, such as prophylactic surgery, can be considered for patients with TS harboring Y chromosomes. Regular monitoring and consultation with specialists are vital for the early detection and effective management of these risks.

## Mental health aspects of TS

Mental health in TS is a complex area associated with distinct neurocognitive and psychosocial challenges, including deficits in visuospatial abilities, memory, motor skills, and attention, that affect individuals with TS across all races and socioeconomic backgrounds.<sup>79)</sup> These challenges are typically influenced by the physical manifestations of TS, including shorter stature, distinct facial features, and delayed feminization compared to peers. These physical aspects, combined with difficulties with social cognition and appropriate responses, are speculated to intensify the social challenges faced by patients with TS, further complicating their interactions and integration within social environments.<sup>80)</sup> Intelligence quotient variability has been observed in TS, and many individuals face specific cognitive challenges, particularly in terms of spatial awareness and nonverbal memory, that affect their academic and social functioning. Academic challenges, especially in mathematics and reading, were noted.<sup>8)</sup> Various assessments used to evaluate the neurocognitive, academic, social, and psychological phenotypes of TS include the Wechsler Adult Intelligence Scale and the Wide Range Achievement Test.<sup>8)</sup>

The impact of hearing loss on TS extends beyond physical challenges and potentially contributes to psychological issues. A hearing impairment can exacerbate an individual's mental health conditions, as it may hinder effective communication and social interactions. This barrier can lead to increased feelings of isolation and frustration, potentially aggravating mental health disorders such as anxiety, depression, and even schizophrenia. The interplay between hearing impairment and cognitive challenges, particularly spatial awareness and nonverbal memory, can further strain social function and academic performance.<sup>10,81,82)</sup> One study reported that 91% of adolescents with TS had middle-ear disease and 9% (2 children) had sensorineural hearing loss.<sup>10)</sup> The annual hearing screening program initiated in Glasgow for girls with TS revealed that 69% experienced some form of ear disease over a 3-year period due to a range of conditions, including cholesteatoma, tympanic membrane issues, and varying degrees of hearing loss. This finding implies that

regular hearing screenings are beneficial for patients with TS and feasible for healthcare providers to implement.<sup>82)</sup>

The management of mental health in patients with TS emphasizes the importance of early detection, tailored interventions, ongoing education, and holistic support to ensure well-being.<sup>42)</sup> Ensuring timely puberty is advised to support patients' psychosocial and psychosexual development.<sup>8)</sup> Ross et al.<sup>79)</sup> reported that estrogen replacement therapy can improve motor function, executive function, and memory. One report assessed the psychological impact of GH therapy in girls with TS and found a notable decrease in both internalizing and externalizing behavioral problems after GH treatment, with the TS group showing fewer behavioral problems.<sup>83)</sup> Supportive psychotherapy delivered individually or in group settings is also beneficial. Additionally, specific training in social and communication interventions tailored to individual learning needs can significantly improve students' academic performance and self-esteem.<sup>79)</sup> Paying special attention to social skills and emotional intelligence through structured programs can enhance the social interactions and relationship-building capabilities of individuals with TS.

## Conclusion

TS encompasses a wide array of medical challenges, including cardiovascular, endocrine, autoimmune, and mental health, as well as a heightened cancer risk. This review emphasized the importance of early diagnosis and a multidisciplinary approach to preventing and managing TS that highlights the need to provide customized care. Advancements in immunogenetic research may improve our understanding and management of TS, improving the outcomes of affected individuals. Several reputable websites provide comprehensive information about preventing and managing TS for those seeking in-depth knowledge and support, including the TS Society ([www.turnersyndrome-society.org](http://www.turnersyndrome-society.org)), TS Foundation ([www.turnersyndrome-foundation.org](http://www.turnersyndrome-foundation.org)), and National Organization for Rare Disorders ([www.rarediseases.org](http://www.rarediseases.org)). Genetic counseling provided by a geneticist or genetic counselor is essential before and after any prenatal diagnostic procedure for TS.

## Footnotes

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## ORCID

Won Kyoung Cho  <https://orcid.org/0000-0003-0918-0565>

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