Immunological Profile and Autoimmunity in Turner Syndrome

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Keywords

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Abstract

Turner syndrome (TS), characterized by the partial or complete absence of an X-chromosome, provides a unique insight into the role of the X-chromosome and the immune system. While women have a 10-fold higher incidence of autoimmune disease (AD) compared with men, the risk in women with TS is thought to be further doubled. TS is associated with a propensity for a wide variety of ADs that increase in incidence across the life span. Isochromosome Xq as well as isolated Xp deletion karyotypes may predispose to higher rates of AD in TS suggesting the impact of X-chromosome gene dosage. It is likely, however, that epigenetic changes across the genome and the hormonal milieu may also have a profound impact on the immune profile in TS. This review explores the immune phenotype and the spectrum of ADs in TS. Genotype-phenotype correlations are presented with a brief overview of the genetic and hormonal underpinnings.

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Introduction

The X-chromosome houses the largest number of immune-related genes in the human genome [1]. It has long been known that several X-linked primary immune deficiencies are common in males due to the presence of a single X-chromosome [1]. The presence of two X-chromosomes and skewed inactivation of one of those chromosomes are thought to be protective in females, who generally have a stronger immune response to diverse pathogens. However, the hyperresponsiveness of the immune system in females results in a predisposition towards autoimmune disease (AD) [2]. Although not conclusively proven, several theories implicate the X-chromosome for the 10-fold increase in AD in females including disturbances in random X-inactivation, reactivation of genes in an inactivated X-chromosome, and loss of an X-chromosome with haploinsufficiency. In fact, women with some ADs have been shown to have a higher circulating proportion of cells with monosomy X [2]. Turner syndrome (TS), a rare genetic disorder characterized by the absence of whole or part of an X-chromosome in a phenotypic female [3], provides a unique opportunity to study the contribution of X-chromosome gene ex-

Table 1. Immune cell subsets in TS

Study	TS patients (age range, years), <i>n</i>	Lymphocyte subpopulations		Immunoglobulins		
		T cells	B cells	IgG	IgM	IgA
Jensen et al. [6]	15 (8–37)	–	–	Lower	Lower	Higher
Cacciari et al. [7]	20 (8.5–19)	Lower*, \$	Lower*	Lower	Lower trend [#]	Lower trend [#]
Lorini et al. [8]	29 (2.2–18.4)	Normal [^]	Normal [^]	Low (48%)	Low (41%)	Low (3%) High (24%)
Stenberg et al. [9]	15 (5–17)	Normal ^{&}	Normal	Low (20%) High (13%)	High (6%)	Normal
Rongen-Westerlaken et al. [10]	14 (8–19)	Normal ^{&, \$}	Normal	Normal	Normal	Normal
Su et al. [11]	20 (8–62)	Normal ^{&, ^}	Normal	–	–	–
Fan et al. [12]	13 (14–33)	Abnormal ^{&, @}	Normal	–	–	–
Lee et al. [13]	24 (17–36)	Abnormal ^{&, *, @}	Normal			

TS, Turner syndrome; T cells, Tregs. * Functional deficit. ^ No functional deficit. # Not statistically significant. & Low CD4+/CD8+ ratio. \$ Increased CD16+ Natural Killer (NK) cells. @ Increased FOXP3+ Tregs.

pression on the immune phenotype. Interestingly, women with TS have a 2–3 fold higher incidence of AD [4], but the immune landscape and triggers for AD in TS are incompletely understood. A comprehensive review of the immune profile and spectrum of AD in TS is presented here.

Brief Overview of the Immune System

The immune system is comprised of innate immune defenses of the host, and the ability to mount an antigen-specific adaptive immune response that is learned, committed to memory, and can be reactivated with specific antigen triggers. The adaptive immune system is broadly classified into cell-mediated and humoral immunity. Cell-mediated immunity functions through T-lymphocytes that mature in the thymus. Major T-cell subsets include helper cells that express cluster of differentiation 4 (CD4+), cytotoxic cells (CD8+), and immunosuppressive regulatory T cells (Tregs). Humoral immunity is orchestrated by B-lymphocytes that mature in the bone marrow and produce several classes of immunoglobulins or antibodies. The large repertoire of T- and B-cell receptors is facilitated by somatic rearrangement of germline gene elements that enables the formation of millions of antigen-

specific receptors each conferring specificity to a unique antigen [5]. The ability of the host immune system to recognize self-antigens and avoid tissue damage constitutes self-tolerance. Breakdown of self-tolerance contributes to development of AD [5].

Immune Cell Subsets in Turner Syndrome

The earliest reports demonstrated differences in immunoglobulin subclasses with lower IgG, IgM, and variable IgA in TS compared with age-matched male and female controls as shown in Table 1[6–9]. Additionally, B- and T-lymphocyte subpopulations were found to be low with reduced mitogen responsiveness in TS [7] in some studies but not others [8]. The authors concluded that these findings did not translate to clinical health impairment but speculated that it may result in immunological senescence with advancing age [7]. Hence, the clinical relevance of these findings remained uncertain. In 2004, lymphocyte subpopulations were studied in 15 Swedish girls with TS and showed lymphocytes, granulocytes, and monocytes within the age-specific reference ranges, but the ratio of CD4+/CD8+ T-lymphocytes was lower than expected [9]. Dividing the girls into 2 groups based on their risk of recurrent otitis media did not reveal any dif-

Fig. 1. Standardized incidence ratio of AD in TS by karyotype (based on data reported from the Danish Registry [22]). TS, Turner syndrome; AD, autoimmune disease.

ferences in immune profile between the groups that could explain the higher risk of otitis media [9]. A similar finding of low CD4+/CD8+ ratio was observed earlier in 14 girls with TS who were investigated for the effect of growth hormone therapy. While growth hormone did not alter immune function significantly, the investigators confirmed minor derangements in Treg subsets with a lower CD4+/CD8+ ratio [10]. Consistent with these reports, another study from the USA also confirmed low CD4+/CD8+ ratio primarily due to higher CD8+ cells and showed no differences in the number of Tregs in women with TS and AD compared with women with TS without AD. Furthermore, Tregs were functionally effective and suppressed cytotoxic CD8+ cells compared with non-TS controls [11]. Subsequent reports have confirmed these observations of lower CD4+/CD8+ Treg ratio and normal Treg number in other ethnic populations as well [4, 12]. Treatment with estrogen also did not affect the frequency of the lymphocyte subsets [12]. A study from South Korea showed that despite normal numbers, and Tregs did not effectively suppress autologous effector Treg proliferation in vitro, suggesting a functional defect [13]. There are also reports in the literature of a handful of TS patients meeting criteria for common variable immunodeficiency characterized by recurrent sino-pulmonary infections, low CD4+ counts and low immunoglobulins [14–16], and selective Treg deficiency [17] and IgA deficiency [18]. The occurrence of Kawasaki disease, an

immune-mediated acute febrile inflammatory vasculitis, is also documented in patients with TS [19, 20].

Overall, despite selected immune cell subsets being slightly lower in number (Table 1) and a lower CD4+/CD8+ ratio in several patients with TS, these changes do not constitute primary immunodeficiency and a predisposition to frequent infections has not been observed clinically in patients with TS, with the exception of recurrent and chronic otitis media. Hence, the functional significance of these observations in the immunological phenotype in TS is unclear. In a recent report of 114 consecutive adults with TS followed in an adult TS clinic, 42% were reported to have low antibody titers to Hemophilus influenza B, 23% had low antipneumococcal antibody titers, and 14% had low anti-tetanus titers. After immunization, 20% of these patients continued to demonstrate a lack of protective antibody titers [21]. The clinical implications of these data remain uncertain and require further investigation.

A possible confounding factor in relation to immunological defects observed in TS is a history of thymectomy in patients with TS who undergo major cardiac procedures during infancy. While thymectomy has the potential to reduce Treg diversity due to the central role of the thymus in Treg development, the clinical implications of the removal of the thymus in infancy are yet to be determined.

Table 2. Spectrum of AD in TS

AD	Prevalence, %	Genotype-phenotype correlations	Recommendations outlined in 2016 consensus guidelines [3]
Type 1 diabetes	0.5–6.4 [22, 39]	Karyotypes other than 45,X and isochromosome Xq had higher risk	Confirmation of diabetes diagnosis should prompt diabetes autoantibody screening and evaluation by specialist
Autoimmune hypothyroidism	15–30 [29, 32, 34]	45,X, isochromosome Xq and isolated Xp deletion display a higher risk	Screen at diagnosis and annually from early childhood through life span
Graves hyperthyroidism	0.6–2.6 [22, 32]	None	None
Celiac disease	2.2–8.1 [54]	Isolated Xp deletion increases risk	Screen by measurement of transglutaminase antibodies every 2 years in childhood starting at age 2–3 years and if symptoms in adulthood
IBD	2.6–3 [45]	Isochromosome Xq is associated with 12-fold higher risk of Crohns disease	Symptoms of unexplained weight loss, abdominal pain, diarrhea, or gastrointestinal bleeding should prompt screening
Vitiligo	2.7 [41, 45]		None
Halo nevus	18 [41]	More frequent in ring X karyotype	None
Psoriasis	3–17 [22, 40]		None
Juvenile rheumatoid arthritis	0.5–2 [22, 43]	Polyarticular JRA is associated with 45,X	None

TS, Turner syndrome; IBD, inflammatory bowel disease; AD, autoimmune disease.

Autoimmunity in Turner Syndrome

In contrast to immunodeficiency, a 2–3 fold increase in the risk of autoimmunity has been better characterized clinically in individuals with TS. Comprehensive data derived from the Danish TS registry that included 798 women with TS, enrolled between 1980 and 2004, showed a standardized incidence ratio (SIR) of 3.9 for male-predominant AD compared with 1.7 for female-predominant AD (Fig. 1) [22]. The most common male-predominant AD observed in TS is type 1 diabetes (4-fold increase); the occurrence of other male-predominant ADs in TS is rare but occurs at much higher rates than expected and includes amyotrophic lateral sclerosis, ankylosing spondylitis, reactive arthritis, and Dupuytren's contracture [22]. Female-predominant ADs observed in TS include Hashimoto's thyroiditis (almost 15-fold increase), Graves' disease, celiac disease, ulcerative colitis, Crohn's disease, juvenile rheumatoid arthritis, Sjogren's disease, sarcoidosis, and psoriasis, as well as rare diseases like polyarteritis nodosa, rheumatic fever, and immune thrombocytopenic purpura [22]. Primary biliary cirrhosis, myasthenia gravis, and membranoproliferative glomerulonephritis have also been reported [23–25]. There are no reports of increase in

frequency of autoimmune adrenal antibodies or autoimmune polyglandular syndromes I and II in TS, although one record-linkage study showed a higher risk of Addison's disease [26, 27]. There are a few reports of systemic lupus erythematosus in TS, but the overall prevalence is thought to be lower than in females with 46,XX karyotype and also lower than the incidence of systemic lupus erythematosus in Klinefelter's syndrome (47,XXY), suggesting a possible dose effect of the X-chromosome [28]. The spectrum of AD in TS is presented in Table 2.

Autoimmune Thyroid Disease

Autoimmune thyroiditis is the most prevalent AD in TS with a 40% incidence of antithyroid antibodies in women with TS (range 13–55%) [29]. The prevalence of overt hypothyroidism increases with age and has been reported to be as high as 25–30% in adult women with TS [29–31]. A recent meta-analysis of 18 cross-sectional studies estimated an overall prevalence of 39% for autoimmune thyroid disease, with 12.7% overt hypothyroidism and 2.6% hyperthyroidism [32]. Autoimmune hyperthyroidism (Graves disease) has a similar clinical course and response to treatment in TS as in females without TS but presents at a slightly later age [33, 34]. It may be pre-

ceded by hypothyroidism more often in patients with TS and is frequently associated with other autoimmune disorders [35, 36]. The clinical and biochemical severity of autoimmune hypothyroidism in TS appears to be milder but with a higher risk of progression from subclinical to overt hypothyroidism with age [31, 33, 36, 37]. Hence, current guidelines recommend screening for hypothyroidism at diagnosis with a TSH and a free T4 beginning in early childhood and annually thereafter, but routine measurement of thyroid antibodies is not recommended as it is unlikely to alter clinical management [3].

Celiac Disease

There are early reports of an association of celiac disease with TS [38]. In the Swedish National Registry, the incidence of celiac disease increased with age during childhood: odds ratio of celiac disease in TS ranged from 2.16 at age 5 years to 5.5 at age 10 years [39]. Hence, routine screening for celiac disease is recommended starting in early childhood [3]. Positive serology may be confirmed with endoscopy and intestinal biopsy.

Inflammatory Bowel Disease

Increased frequency of inflammatory bowel disease has been described in TS with Crohn's disease reported more commonly than ulcerative colitis, presenting at a younger age, affecting the colon, with increased disease severity [40, 41] (Table 2).

Diabetes

Incidence of both autoimmune type 1 diabetes [22, 27] and type 2 diabetes associated with obesity and insulin resistance is increased in TS [42]. Glucose abnormalities without overt diabetes have also been reported in patients with TS [42].

Skin and Rheumatic Diseases

Autoimmune skin diseases common in TS include alopecia areata, psoriasis and vitiligo, and Halo Nevus, a melanocytic nevus with a surrounding zone of depigmentation (Table 2) [40, 43, 44]. Autoimmune joint diseases are also observed frequently in TS, particularly juvenile idiopathic arthritis which has 6-fold increase in prevalence in TS [45]. Polyarticular disease is earlier in onset, progressively deforming and more common in monosomy X as opposed to other karyotypes in TS where a seropositive oligoarticular disease is noted with positive anti-nuclear antibodies and a more benign course [45, 46].

In summary, AD presents a sizeable health burden for patients with TS and clinicians should remain vigilant for

the development of AD. Early detection and appropriate management of AD may help improve the quality of life of patients with TS.

Mechanisms for Immune Dysregulation in Turner Syndrome

An increased propensity for AD with particular karyotypes of TS indicates that gene dosage on the X-chromosome is an important contributor to the immune phenotype. The 46,X, isochromosome Xq karyotype with 3 copies of the long arm Xq has been shown conclusively to be associated with an increased risk of AD [47]. In the Danish Registry [22], patients with isochromosome Xq were found to have a SIR of 3 for all ADs compared with 2.1 for monosomy X. While the SIR was 17 for autoimmune hypothyroidism compared with monosomy X (20.5), the SIR for ulcerative colitis was 11.6 compared with 2.3 for monosomy X [22]. More than half the cases of Crohn's disease in TS have occurred in association with the isochromosome Xq karyotype [48]. Women with TS and isochromosome Xq also have a higher proportion (83%) with positive antithyroid antibodies compared with other karyotypes (33%) and a higher risk of progression to overt hypothyroidism (37.5 vs. 14% for monosomy X vs. others, 6%) [29, 34]. Both cell-mediated and humoral responses likely contribute to autoimmune thyroid disease in TS. Polymorphisms in *FOXP3* and a higher ratio of Th17 to Tregs affecting immune tolerance have been reported to be associated with thyroid autoimmunity [49], but their role in TS is not confirmed. Type 2 diabetes, while not regarded to have an autoimmune etiology, was also shown to be increased in isochromosome Xq karyotype (40%) versus monosomy X (17%) [42]. Gene expression profiling in 5 individuals each with 45,X versus 46,X, isochromosome Xq found overexpression of genes affecting pancreatic beta cell development in the latter, and also increased transcripts and peripheral blood concentrations of anti-glutamic acid decarboxylase antibodies, insulin-like growth factor-2 (IGF-2), and C-reactive protein suggestive of a pro-inflammatory state in isochromosome Xq [42]. Recently, an isolated deletion of the short arm, Xp has similarly been shown to be associated with increased prevalence of autoimmune thyroid disease and celiac disease in a cohort of 286 women with TS and a median age of 18 years [50]. There is speculation that the parent of origin of the normal X-chromosome may also play a role in autoimmunity, especially with male-predominant AD in individuals with a maternally derived X-chromosome.

But these data are not conclusive, and no differences in the prevalence of autoimmune thyroid disease has been noted in individuals with a maternally versus paternally inherited X-chromosome in TS [34]. Additionally, an increase in pro-inflammatory cytokines interleukin (IL)-6, transforming growth factor (TGF) β 1 and lower anti-inflammatory cytokines TGF β 2, and IL-10 has been demonstrated, but these changes did not correlate with the presence of AD [34].

Several gene loci critical for immune function are located on the X-chromosome including *PAR 1*, *TLR7* (Xp22), *FOXP3* (Xp11), *XIC* (Xq13), *CD40LG* (Xq24), and *MECP2* (Xq28) [1]. The *CD40L* gene maps to Xq26 and encodes a key molecule modulating the adaptive T- and B-cell immune response. Lower expression of *CD40L* and the gene *TLR7*, which is involved in innate immunity, have been demonstrated in patients with TS compared with normal females [51]. Loss of the *FOXP3* (Xp11) gene, a key player in Treg development, is associated with loss of immune tolerance [4]. Cook et al. [52] recently showed that ubiquitously transcribed tetratricopeptide repeat on the X-chromosome (*UTX*) is one of the 10 genes with the largest decrease in expression in TS and is the only one among them that escapes X-inactivation. *UTX* encodes for a histone demethylase which promotes T follicular helper cells which then aid in the clearance of chronic viral infections, raising the possibility of its role in chronic otitis media in TS and provides putative evidence of epigenetic dysfunction in immune cells in patients with TS [52, 53]. Indeed, genomewide methylation profiles studied in TS show a diffuse hypomethylation of the entire genome and not just the X-chromosome with altered gene expression in autosomes as well [54, 55]. Analyzing the transcriptome of fibroblasts in 45,X compared with 46,XX, Rajpathak et al. [56] reported that 14% of differentially expressed genes with more than 2-fold change are involved in adhesion, immune responses, apoptosis, and cell death. Similarly, differentially expressed genes in peripheral blood lymphocytes of 45,X compared with 46,XX are not limited to the X-chromosome but are abundant in autosomes as well and are predominantly enriched in pathways involving immune processes and cytokine generation [57]. X-linked microRNA may also have a function in immune regulation, but their role in TS is unknown [1].

Specific polymorphisms in the major histocompatibility complex class II proteins encoded by the human leukocyte antigen (HLA) region located on chromosome 6 are associated with multiple autoimmune conditions. Noting the lack of differences in frequency of susceptible

HLA alleles in patients with TS compared with controls in their cohort, Larizza et al. [48] postulated that a missing paralogue of the major histocompatibility complex located on the long arm of the X-chromosome may impact an effective adaptive immune response and maintenance of self-tolerance over the life span of individuals with TS. ADs that develop in patients with TS were consistent with the presence of specific susceptibility alleles, such as HLA-Cw6 with vitiligo and halo nevus and HLA-DRB1*0301 with autoimmune thyroid disease [44, 58]. In a Brazilian TS population, AD risk was associated with a single nucleotide polymorphism in the *PTPN22* gene (C1858T) which may affect Treg receptor signaling [59]. The slightly increased prevalence of AD in the families of patients with chromosomal aneuploidies such as Down syndrome, TS, and Klinefelter's syndrome has also led to a conjecture that the immune dysregulation may predispose to nondisjunction during gametogenesis [59].

There is also definitive evidence that both estrogen and androgens essay a role in modulation of immune function [60]. Estrogen receptors are widely expressed in immune cells. While the exact molecular mechanisms are still being elucidated, estrogen has been shown to improve humoral immune response by promoting B-cell differentiation and immunoglobulin production. Estrogen also regulates cytokine production, Treg activation, and differentiation but suppresses Treg proliferation. Estrogen levels were shown to be protective for Treg mediated ADs such as psoriasis, multiple sclerosis, and rheumatoid arthritis [60, 61]. A recent study suggested a weak positive correlation between the age at estradiol exposure in TS and age at diagnosis of AD [62] although the majority of patients presented with AD prior to initiation of estrogen in this study. Previous studies also demonstrated a trend toward slightly higher estrogen exposure among TS patients with autoimmune thyroiditis, but not those with celiac disease or inflammatory bowel disease. However, these differences were not statistically significant [34]. Androgen levels were inversely correlated with ADs in TS [34]. It is highly likely that primary ovarian insufficiency and hormonal replacement in TS or the lack of thereof have consequences on immune function.

Conclusion

Immune dysregulation in TS is not just a consequence of the copy number of X-chromosome related genes, but likely stems from a multitude of epigenetic changes across the genome influenced by HLA-alleles, the karyotype,

and hormonal changes throughout the age spectrum. Further, environmental factors, infections, and accelerated immune senescence may play a role in determining the clinical manifestations of immune dysregulation and ADs in TS. The presence of a pro-inflammatory state provides a potential explanation for the increased morbidity and mortality from ADs, as well as the incidence of type 2 diabetes and cardiovascular disease observed in patients with TS. Large-scale studies across the life span, accounting for differences in karyotype and hormone replacement will shed more light on the topic and need to be pursued in the future. An improved understanding of the determinants of immune regulation in TS would not only improve clinical care and quality of life for patients with TS but also have the potential to contribute to the understanding of sexual dimorphism in immune regulation.

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Conflict of Interest Statement

The author has no conflicts of interest to declare.

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Author Contributions

I confirm that I am the sole author completing the conception, design, drafting, and revision of this work and approve the final version submitted. It is not under consideration of publication elsewhere.

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