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Autoimmune Diseases in Women With Turner's Syndrome

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Objective. **In terms of number of X chromosomes, women with Turner's syndrome cytogenetically resemble men. An increased risk of autoimmune diseases has been observed among women with Turner's syndrome. This study was undertaken to investigate whether the autoimmune disease profile in women with Turner's syndrome is characterized by diseases with a female or male predominance.**

Methods. **Using the Danish Cytogenetic Central Register, the Danish National Patient Register, and the Danish Civil Registration System, we estimated relative risk of 46 different autoimmune diseases in a cohort of 798 Danish women with Turner's syndrome followed up for 12,461 person-years between 1980 and 2004. Standardized incidence ratios (SIRs) of first hospitalization for autoimmune disease and 95% confidence intervals (95% CIs) were used as measures of relative risk.**

Results. **The overall risk of autoimmune disease among women with Turner's syndrome was twice that among Danish women in general (SIR 2.1 [95% CI 1.6–2.7]). For autoimmune diseases with a female predominance, the SIR among women with Turner's syndrome was 1.7 (95% CI 1.2–2.4), whereas the SIR for autoimmune diseases with a male predominance among these women was 3.9 (95% CI 2.5–5.8). Associations were strongest for Hashimoto thyroiditis (SIR 14.6 [95% CI 6.7–27.1]), a strongly female-predominant condition, and type 1 diabetes mellitus (SIR 4.1 [95% CI 2.5–6.3]).**

Conclusion. **Women with Turner's syndrome are at excess risk of autoimmune diseases, notably autoimmune diseases characterized by male predominance.**

Autoimmune diseases predominantly affect women, but the causes of the higher risk in women remain unclear. Sex hormones, reproductive factors, fetal microchimerism, environmental factors, skewed X chromosome inactivation patterns, major defects in the sex chromosomes, and X chromosome gene dosage have all been proposed as being etiologically involved (1–3). Thus, it is of particular interest that women with Turner's syndrome, a condition characterized by complete or partial X chromosome monosomy, have been reported to be at an increased risk of autoimmune diseases, most notably autoimmune thyroid diseases and type 1 diabetes mellitus, but also ulcerative colitis, Crohn's disease, juvenile rheumatoid arthritis, psoriasis, celiac disease, and vitiligo (4–10). The higher risk of autoimmune diseases in women with Turner's syndrome has been suggested to be due in part to the haploinsufficiency of genes on the X chromosome (11). However, other features of the Turner's syndrome phenotype may also be partly responsible for the elevated risk. The proinflammatory cytokines interleukin-6 and interleukin-8 and tumor necrosis factor α seem to be up-regulated in women with Turner's syndrome (12), and autoantibody positivity is seen in a high proportion (57%) (13). Furthermore, women with Turner's syndrome often experience estrogen deficiency and require long-term estrogen replacement therapy (5,14).

Women with Turner's syndrome cytogenetically resemble men in terms of number of X chromosomes. However, no prior study has examined whether the excess autoimmune disease risk in women with Turner's syndrome is most pronounced for female-predominant autoimmune diseases or whether it is characterized by a

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Table 1. Distribution of karyotypes in Danish women with Turner's syndrome*

Karyotype group/karyotypes	Total population of women with Turner's syndrome (n = 882)	Study cohort	
		Women with Turner's syndrome (n = 798)	Person-years (n = 12,461)
X monosomy/45,X	364 (41)	339 (42)	6,142 (49)
Isochromosome Xq/45,X/46,X,i(Xq); 46,X,i(Xq) or equivalents	96 (11)	81 (10)	1,296 (10)
All others/45,X/46,XX; 45,X/46,X,del(X); 46,X,del(Xp); 45,X/46,X,t(X:X); 46,XXp−; 45,X/46,X,i(Xp); 45,X/46,X,+mar; 45,X/47,XXX; karyotypes containing Y chromosome material (45,X/46,XY; 45,X/46,X,del[Y]) and others	422 (48)	378 (47)	5,023 (40)

* Values are the number (%).

different autoimmune disease profile from that of other women. In the present study, we undertook a detailed scrutiny of a long list of diseases with an established or possible autoimmune etiology among 798 Danish women with Turner's syndrome followed up from 1980 until the end of 2004.

PATIENTS AND METHODS

Ethics approval. The study was approved by the Danish Data Protection Agency (approval no. 2006-41-7097) and by the directing board of the Danish Cytogenetic Central Register, which represents all of the hospital departments of clinical genetics in Denmark.

Cohort of women with Turner's syndrome. Women with Turner's syndrome, including individuals with cytogenetically determined karyotypes with a 45,X cell line or a structurally abnormal X chromosome, were identified from the Danish Cytogenetic Central Register. This register, which was established in 1968, prospectively collects results from all chromosome examinations in cytogenetic laboratories in Denmark (15,16). The karyotype distribution of the women studied is shown in Table 1.

Autoimmune diseases. Information about autoimmune diseases was obtained from the Danish National Patient Register, which contains data on all somatic inpatient hospital contacts in Denmark since 1977 and all outpatient hospital contacts since 1995 (17). Information concerning dates of admission and discharge, hospital department, and diagnoses is kept for every hospitalization and linked to the patient's unique personal identification number assigned to all residents in Denmark since 1968 (18). Diagnoses were classified according to the International Classification of Diseases, Eighth Revision (ICD-8) between 1977 and 1993 and according to the ICD-10 since 1994. We focused on 44 of the autoimmune diseases mentioned in *Harrison's Principles of Internal Medicine* (19,20), plus amyotrophic lateral sclerosis and Dupuytren's contracture (Table 2). Although not conventionally categorized as autoimmune, the latter 2 diseases were included on the basis of literature indicating that an autoimmune pathogenesis might be involved (21–24). For type 1 diabetes mellitus, the observation period started in 1987, because before then ICD-8 codes did not distinguish between insulin-dependent and non–insulin-dependent diabetes mellitus. We considered records of insulin-dependent diabetes mellitus as type 1 diabetes mellitus.

Statistical analysis. An incident case of a given autoimmune disease was defined as the first occurrence of the particular autoimmune disease in an individual, determined by date of first recorded inpatient or outpatient hospital admission. When studying broader disease categories, only the first occurrence of any of the component diseases was counted as incident. Sex-, age-, and period-specific national incidence rates from 1980 to 2004 for each of the 46 autoimmune diseases were calculated using demographic data from Statistics Denmark and records of first hospital contacts for the respective autoimmune diseases as defined in Table 2.

Women with Turner's syndrome were followed up for the subsequent occurrence of an autoimmune disease from the date of Turner's syndrome karyotyping or January 1, 1980 (whichever came later), and monitoring was continued until death, emigration, or end of study followup on December 31, 2004 (whichever came first). The observed numbers of autoimmune diseases were divided by the numbers expected, thereby providing standardized incidence ratios (SIRs). The expected numbers were calculated as the sum of the sex-, age-, and period-specific person-years at risk in the cohort multiplied by corresponding sex-, age-, and period-specific incidence rates of the specific autoimmune diseases. SIRs with accompanying 95% confidence intervals (95% CIs) based on Poisson likelihood ratio tests were used as the measure of relative risk.

Individuals first recorded as having any of the autoimmune diseases between 1977 and 1979 were excluded from the cohort to prevent prevalent conditions from being considered incident cases at the beginning of followup in 1980. Additionally, to ensure that women with Turner's syndrome were not diagnosed as having the chromosomal abnormality on the basis of hospital contacts for an already diagnosed autoimmune disease, women with Turner's syndrome who had had a hospital contact with an autoimmune disease prior to the date of karyotyping were excluded from the cohort.

In order to determine whether an autoimmune disease

Table 2. Autoimmune diseases, corresponding International Classification of Diseases, Eighth Revision (ICD-8) and ICD-10 codes, and their estimated female:male lifetime risk ratios in the general population, Denmark 1980–2004

Disease	ICD-8	ICD-10	Female:male ratio
Male-predominant			
Reactive arthritis	13601	M023	0.2
Dupuytren's contracture	73390	M720	0.3
Ankylosing spondylitis	71249	M45, M081	0.4
Buerger's disease	44319	I731, M311B	0.5
Kawasaki disease	44692	M303	0.6
Sympathetic ophthalmia	36602	H441B	0.7
Goodpasture's syndrome	44619	M310A	0.8
Guillain-Barré syndrome	35400	G610	0.8
Amyotrophic lateral sclerosis	34809	G122G	0.8
Henoch-Schönlein purpura	28709	D690B	0.8
Wegener's granulomatosis	44629	M313	0.9
Type 1 diabetes mellitus	249	E10	0.9
Pemphigus foliaceus	69402	L102	0.9
Female-predominant			
Sarcoidosis	135	D86	1.0
Raynaud's syndrome	44300–44309	DI730	1.1
Psoriasis	69609–69619	L40	1.1
Pemphigus vulgaris	69400	L100	1.1
Dermatitis herpetiformis	69309	L130	1.2
Ulcerative colitis	56319, 56904	K51	1.2
Rheumatic fever	390, 391	I00, I01	1.2
Polyarteritis nodosa	44609	M300	1.3
Idiopathic thrombocytopenic purpura	28710	D693	1.3
Pemphigoid	69405	L12	1.3
Myasthenia gravis	73309	G700	1.4
Crohn's disease	5630	K50	1.4
Hemolytic anemia	28390, 28391, 28392	D590, D591	1.4
Behçet's disease	13602	M352	1.5
Polymyositis/dermatomyositis	716	M33	1.5
Addison's disease	25510, 25511	E271A, E272A	1.6
Celiac disease	26900	K900	1.6
Vitiligo	70901	L80	1.6
Pernicious anemia	2810	D510A	1.7
Juvenile rheumatoid arthritis	71209	M080, M082, M083, M084, M088, M089	1.8
Multiple sclerosis	340	G35	1.8
Temporal arteritis/polymyalgia rheumatica	44630, 44631, 44639	M315, M316, M353	2.3
Rheumatoid arthritis	71219, 71229, 71239, 71259	M05, M06	2.4
Erythema nodosum	69259	L52	2.7
Localized scleroderma	70101, 70108, 70109	L940, L941, L943	3.2
Systemic sclerosis	7340	M34	3.7
Primary biliary cirrhosis	57190	K743	3.9
Localized lupus erythematosus	69549	L93	4.7
Graves' disease	2420	E050	5.1
Systemic lupus erythematosus	73419	M32	5.2
Sjögren's syndrome	73490	M350	7.5
Hashimoto thyroiditis	24503	E063	8.3
Takayasu arteritis	44691	M314	9.3

had a female or male predominance, we estimated lifetime autoimmune disease risks based on the average sex- and age-specific hospitalization rates and death rates in Denmark in the period from 1980 to 2004 (Table 2). The lifetime risk of an autoimmune disease was calculated according to life-table methods, using the formula $\int h(a) \exp(-H[a] - D[a])\, da$, where $H(a) = \int_{[0,a]} h(u)\, du$ and $D(a) = \int_{[0,a]} d(u)\, du$; $h(a)$ is the incidence rate of the relevant autoimmune disease as a function of age (a), and $d(a)$ is the death rate. The integrand of the formula expresses that one would have to be alive and disease-free, with the probability $\exp(-H[a]-D[a])$, in order to get the disease at a certain age (a) with intensity $h(a)$. The integral then summarizes all of the ways that one can get the disease in terms of the age. For each autoimmune disease, the female:male ratio of lifetime risks characterized the disease as being male-predominant (ratio <1) or female-predominant (ratio ≥ 1).

RESULTS

There were 882 women identified in the Danish Cytogenetic Central Register with cytogenetically diag-

Table 3. Standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs) for autoimmune diseases in women with Turner's syndrome, Denmark 1980–2004

Autoimmune disease	Observed	Expected	SIR (95% CI)
Male-predominant			
Reactive arthritis	1	0.1	22.1 (1.3–97.2)
Dupuytren's contracture	4	0.6	7.0 (2.2–16.2)
Ankylosing spondylitis	1	0.3	3.7 (0.2–16.4)
Amyotrophic lateral sclerosis	1	0.1	22.2 (1.3–97.7)
Type 1 diabetes mellitus	18	4.4	4.1 (2.5–6.3)
Male-predominant autoimmune diseases overall*	23	5.8	3.9 (2.5–5.8)
Female-predominant			
Sarcoidosis	3	1.0	3.1 (0.8–7.9)
Psoriasis	3	1.9	1.6 (0.4–4.2)
Ulcerative colitis	8	3.2	2.5 (1.2–4.7)
Rheumatic fever	1	0.2	6.2 (0.4–27.2)
Polyarteritis nodosa	1	0.1	14.0 (0.8–61.6)
Idiopathic thrombocytopenic purpura	2	0.3	5.9 (1.0–18.4)
Crohn's disease	3	2.0	1.5 (0.4–3.9)
Celiac disease	1	0.4	2.7 (0.2–11.7)
Juvenile rheumatoid arthritis	2	0.5	4.4 (0.7–13.6)
Multiple sclerosis	2	1.8	1.2 (0.2–3.5)
Temporal arteritis/polymyalgia rheumatica	1	0.9	1.2 (0.1–5.1)
Rheumatoid arthritis	3	3.2	0.9 (0.2–2.4)
Graves' disease	5	4.4	1.2 (0.4–2.5)
Sjögren's syndrome	1	0.5	2.2 (0.1–9.9)
Hashimoto thyroiditis	8	0.6	14.6 (6.7–27.1)
Female-predominant autoimmune diseases overall*	37	21.4	1.7 (1.2–2.4)
All autoimmune diseases*	55	26.6	2.1 (1.6–2.7)

* For broad autoimmune disease categories (i.e., male-predominant autoimmune diseases overall, female-predominant autoimmune diseases overall, and all autoimmune diseases), only the first occurrence of any of the component diseases was counted as incident. Autoimmune diseases listed in Table 2 that were not observed in women with Turner's syndrome were included in the calculation of expected numbers for these broad autoimmune disease categories.

nosed Turner's syndrome, of whom 842 had the syndrome diagnosed before January 1, 2005. Of these, 44 women with Turner's syndrome were excluded, either because they did not contribute followup time in the period 1980–2004 (n = 21), because they had a hospital contact for an autoimmune disease in the period 1977–1979 (n = 8), or because they had an autoimmune disease before the date of karyotyping (n = 15). Consequently, our study cohort consisted of 798 women with Turner's syndrome. Of these, 339 (42%) had X monosomy, 81 (10%) had isochromosome Xq (including mosaic for isochromosome Xq), and 378 (47%) had other karyotypes associated with the Turner's syndrome phenotype (Table 1). The median birth year was 1967 (range 1900–2003), and the median age at cytogenetic diagnosis of Turner's syndrome was 15 years (range 0–85).

Overall, during 12,461 person-years of followup, 55 women with Turner's syndrome had at least 1 hospital contact at which they had an autoimmune disease (Table 3). Compared with Danish women in general, women with Turner's syndrome had a doubled risk of developing any autoimmune disease (SIR 2.1 [95% CI 1.6–2.7]). For female-predominant autoimmune diseases (i.e., autoimmune diseases with a female:male ratio of ≥ 1 [n = 37]), the SIR was 1.7 (95% CI 1.2–2.4). For the group of autoimmune diseases with a male predominance (female:male ratio <1 [n = 23]), the SIR was 3.9 (95% CI 2.5–5.8) (Table 3).

The spectrum of autoimmune diseases included in the study was wide and heterogeneous. In a supplementary SIR analysis of the group of major classic autoimmune rheumatic diseases, including ankylosing spondylitis, Henoch-Schönlein purpura, Wegener's granulomatosis, polyarteritis nodosa, polymyositis/dermatomyositis, juvenile rheumatoid arthritis, temporal arteritis/polymyalgia rheumatica, rheumatoid arthritis, systemic sclerosis, systemic lupus erythematosus, and Sjögren's syndrome, the SIR was 1.4 (95% CI 0.6–2.5) (n = 8).

Women with Turner's syndrome were at significantly increased risk of certain specific autoimmune diseases, i.e., Hashimoto thyroiditis (SIR 14.6 [95% CI 6.7–27.1]) (n = 8), type 1 diabetes mellitus (SIR 4.1

Table 4. Standardized incidence ratios (SIRs) and 95% confidence intervals (95% CIs) for selected autoimmune diseases in women with Turner's syndrome by karyotype, Denmark 1980–2004

Autoimmune disease, karyotype group	Observed	Expected	SIR (95% CI)
Dupuytren's contracture			
X monosomy	2	0.2	9.1 (1.5–28.1)
Isochromosome Xq	1	0.1	19.5 (1.1–85.7)
All others	1	0.3	3.3 (0.2–14.6)
Type 1 diabetes mellitus			
X monosomy	4	1.9	2.1 (0.6–4.8)
Isochromosome Xq	1	0.4	2.3 (0.1–10.0)
All others	13	2.0	6.4 (3.5–10.5)
Ulcerative colitis			
X monosomy	3	1.5	2.0 (0.5–5.2)
Isochromosome Xq	4	0.4	11.6 (3.6–26.9)
All others	1	1.3	0.8 (0.0–3.3)
Hashimoto thyroiditis			
X monosomy	5	0.2	20.5 (7.4–44.0)
Isochromosome Xq	1	0.1	17.3 (1.0–76.1)
All others	2	0.3	8.1 (1.3–25.0)
Male-predominant autoimmune diseases overall*			
X monosomy	6	2.6	2.3 (0.9–4.7)
Isochromosome Xq	3	0.6	5.3 (1.3–13.6)
All others	14	2.7	5.2 (2.9–8.5)
Female-predominant autoimmune diseases overall*			
X monosomy	20	9.6	2.1 (1.3–3.1)
Isochromosome Xq	7	2.2	3.3 (1.4–6.3)
All others	10	9.6	1.0 (0.5–1.8)
All autoimmune diseases*			
X monosomy	25	11.9	2.1 (1.4–3.0)
Isochromosome Xq	8	2.7	3.0 (1.4–5.6)
All others	22	12.0	1.8 (1.2–2.7)

* For broad autoimmune disease categories (i.e., male-predominant autoimmune diseases overall, female-predominant autoimmune diseases overall, and all autoimmune diseases), only the first occurrence of any of the component diseases counted was as incident. Autoimmune diseases listed in Table 2 that were not observed in women with Turner's syndrome were included in the calculation of expected numbers for these broad autoimmune disease categories.

[95% CI 2.5–6.3]) (n = 18), Dupuytren's contracture (SIR 7.0 [95% CI 2.2–16.2]) (n = 4), and ulcerative colitis (SIR 2.5 [95% CI 1.2–4.7]) (n = 8). Additionally, amyotrophic lateral sclerosis (SIR 22.2) (n = 1), idiopathic thrombocytopenic purpura (SIR 5.9) (n = 2), and reactive arthritis (SIR 22.1) (n = 1) occurred in excess (Table 3), but because each of these findings was based on only 1 or 2 observed cases, the risk estimates were highly unstable. For 26 of the 46 individual autoimmune diseases studied, no cases were observed among women with Turner's syndrome during the observation period. The specific Turner's syndrome karyotypes for the 55 cohort members with 1 or more autoimmune diseases are shown in Supplementary Table 1 (available in the online version of this article at http://www3.interscience.wiley.com/journal/76509746/home).

In a supplementary analysis we excluded the 2 most common autoimmune diseases, Hashimoto thyroiditis and type 1 diabetes mellitus, from the female-predominant and male-predominant autoimmune diseases, respectively. This did not change the order of magnitude of the overall association between Turner's syndrome and female-predominant autoimmune diseases (SIR 1.5 [95% CI 1.1–2.1]) (n = 32, including 3 cases of female-predominant autoimmune diseases that occurred after a diagnosis of Hashimoto thyroiditis) or male-predominant autoimmune diseases (SIR 4.1 [95% CI 1.6–8.2]) (n = 6, including 1 case of a male-predominant autoimmune disease that occurred after a diagnosis of type 1 diabetes mellitus).

After dividing the 798 cohort members into 3 broad groups according to their Turner's syndrome karyotype, all subgroups were found to be at increased risk of developing an autoimmune disease. Specifically, 25 cases of autoimmune diseases were observed in women with the X monosomy karyotype (SIR 2.1 [95% CI 1.4–3.0]), 8 cases in women with the isochromosome Xq karyotype (SIR 3.0 [95% CI 1.4–5.6]), and 22 cases in women with all other Turner's syndrome karyotypes (SIR 1.8 [95% CI 1.2–2.7]) (Table 4). Women with X

monosomy and women with an isochromosome Xq karyotype were at 2-fold (SIR 2.1 [95% CI 1.3–3.1]) and 3-fold (SIR 3.3 [95% CI 1.4–6.3]) increased risk, respectively, of female-predominant autoimmune diseases, whereas women with all other Turner's syndrome karyotypes exhibited no unusual risk of female-predominant autoimmune diseases compared with women in general (SIR 1.0 [95% CI 0.5–1.8]). For male-predominant autoimmune diseases, women with X monosomy were at approximately doubled risk (SIR 2.3 [95% CI 0.9–4.7]), while among women with the isochromosome Xq karyotype, the SIR was 5.3 (95% CI 1.3–13.6), and among women with all other Turner's syndrome karyotypes, the SIR was 5.2 (95% CI 2.9–8.5).

Particularly strong associations were found between specific Turner's syndrome karyotypes and specific autoimmune diseases. X monosomy was highly associated with Hashimoto thyroiditis (SIR 20.5 [95% CI 7.4–44.0]), the isochromosome Xq karyotype with ulcerative colitis (SIR 11.6 [95% CI 3.6–26.9]), and the Turner's syndrome karyotype category "all others" with type 1 diabetes mellitus (SIR 6.4 [95% CI 3.5–10.5]) (Table 4).

In a robustness analysis we reexamined all the above-reported associations after inclusion of cases of autoimmune disease that occurred before the date of karyotyping, as well as diseases occurring in the period from 1977 to 1979. Using these less restrictive criteria, we obtained similar results, but 2 additional associations emerged as being statistically significant, namely, increased risks of rheumatic fever (SIR 6.7 [95% CI 1.1–20.5]) (n = 2) and juvenile rheumatoid arthritis (SIR 5.6 [95% CI 2.0–12.1]) (n = 5).

Of the 798 women with Turner's syndrome in our study cohort, 40 had a karyotype that included Y chromosome material. Six of these women (15%) had at least 1 autoimmune disease (patients 2, 15, 22, 27, 38, and 43 [Supplementary Table 1; http://www3.interscience.wiley.com/journal/76509746/home]). The overall risk of autoimmune diseases in this subgroup was increased 5-fold (SIR 5.0 [95% CI 2.0–10.2]), and the risks of female-predominant and male-predominant autoimmune diseases were increased 3-fold and 11-fold, respectively, compared with Danish women in general (SIR 3.1 [95% CI 0.8–8.1] [n = 3] and SIR 11.5 [95% CI 2.9–29.9] [n = 3], respectively).

In an additional robustness analysis we compared the rates of male-predominant autoimmune diseases in women with Turner's syndrome with the corresponding autoimmune disease rates in Danish men. Although the incidence rates of male-predominant autoimmune diseases were, by definition, higher in men than women in the general population, the overall risk of male-predominant autoimmune diseases was doubled for women with Turner's syndrome as compared with the risk in men (SIR 2.1 [95% CI 1.4–3.1]) (n = 23).

DISCUSSION

Our study confirms and expands prior evidence from smaller studies that women with Turner's syndrome are at increased risk of developing a range of autoimmune diseases. The salient observations include an overall 2-fold increased risk of autoimmune diseases, especially of the male-predominant types, for which the risk was increased ~4-fold, whereas the risk of autoimmune diseases with a female predominance was increased 1.7-fold compared with that in Danish women in general. In addition, all main karyotype groups giving rise to Turner's syndrome were associated with an overall 2–3-fold increased risk of development of autoimmune disease.

Previous studies have suggested that women with Turner's syndrome may be at increased risk of several female-predominant diseases, such as Hashimoto thyroiditis, celiac disease, Crohn's disease, ulcerative colitis, juvenile rheumatoid arthritis, and vitiligo (4,7,8,10,25–28). We were able to confirm these findings only for Hashimoto thyroiditis and ulcerative colitis. However, in order to prevent inclusion of prevalent cases and to avoid selection bias, we excluded individuals with hospital contacts for autoimmune diseases occurring before the date of karyotyping and in the period between 1977 and 1979. These stringent criteria might have yielded overly conservative estimates of the incidence of autoimmune diseases with a young age at onset, e.g., juvenile rheumatoid arthritis, in women with Turner's syndrome. When we performed the analyses with inclusion of events prior to the diagnosis of Turner's syndrome and events recorded in the period between 1977 and 1979, we also observed significantly elevated risks of rheumatic fever and juvenile rheumatoid arthritis.

Women with Turner's syndrome were at an almost 4-fold increased risk of male-predominant autoimmune diseases compared with Danish women in general. Type 1 diabetes mellitus was by far the most common of these autoimmune diseases, but the association with male-predominant autoimmune diseases remained significant after exclusion of type 1 diabetes mellitus from the analysis.

Part of the excess of male-predominant autoimmune diseases might be explained by the close simi-

larity of the chromosomal makeup of women with Turner's syndrome and men, and may reflect the hemizygosity of X-linked genes. While in women with a normal karyotype there is compensation by the normally functioning copy on the other X chromosome, a harmful allele will be unmasked in women with Turner's syndrome and in men, due to X monosomy. Thus, it is possible that susceptibility to the specific male-predominant autoimmune diseases that occurred in excess among women with Turner's syndrome, i.e., type 1 diabetes mellitus, amyotrophic lateral sclerosis, ankylosing spondylitis, reactive arthritis, and Dupuytren's contracture, is particularly dependent on genes on the X chromosome. In addition to sharing the male vulnerability to deleterious mutations or polymorphisms in X-linked genes, women with Turner's syndrome exhibit haploinsufficiency of genes in the pseudoautosomal region of the X chromosome, which, among men, has a Y chromosomal counterpart (29,30). This might explain why the risk of male-predominant autoimmune diseases in women with Turner's syndrome is not only higher than that observed in women in general, but also higher than the risk in men.

It has been proposed that the Turner's syndrome phenotype may be influenced by the parental origin of the retained X chromosome (31). It has previously been shown that women with Turner's syndrome who have some Y chromosome material have inherited the complete X chromosome from their mother (32). Approximately 5% of the women with Turner's syndrome in this cohort had a karyotype that included Y chromosome material, and this subgroup of female Turner's syndrome patients exhibited a 5-fold increased risk of autoimmune diseases. Even though this observation was based on limited numbers, it indicates that women with Turner's syndrome who have the maternal X chromosome might be at higher risk for autoimmune disease than women with Turner's syndrome in general. However, among women with X monosomy, 60–80% of the X chromosomes are also maternal in origin (31,32) and these women had only a 2-fold increased risk of autoimmune diseases in the present study. Thus, we are not able to determine whether the high risk in women with Turner's syndrome carrying Y chromosome material might be driven by the maternally inherited X chromosome, by the presence of Y chromosome material, by a combination of the two, or by other factors.

Phenotypic differences between women with Turner's syndrome are, to some extent, correlated with karyotype. X monosomy increases the risk of congenital lymphedema and cardiac abnormalities and is associated with the most severe phenotype. Isochromosome Xq has been associated with increased risk of autoimmune diseases and deafness, while women with a 45,X/46,XX mosaic karyotype have increased mean height and a greater probability of spontaneous menarche and fertility than other women with Turner's syndrome (5,14). Despite the phenotypic variation, women with Turner's syndrome in the 3 karyotype groups, i.e., the X monosomy, the isochromosome Xq, and the all-other-karyotypes group (which mainly comprised 45,X/46,XX mosaicism), were all at a 2–3-fold increased risk of autoimmune disease development. This finding is corroborated by those of a recent study that demonstrated a high prevalence of autoantibody positivity in women with Turner's syndrome but showed no general association with karyotype (13). For women with X monosomy, risks of female- and male-predominant autoimmune diseases were equally increased in the present study. However, while women with isochromosome Xq were at 3-fold risk and women with all other Turner's syndrome karyotypes were at no unusual risk of female-predominant autoimmune diseases, risk of male-predominant autoimmune diseases was increased 5-fold in both the isochromosome Xq and the all-other-karyotypes groups.

It would be reasonable to expect that an association with male-predominant autoimmune diseases would be strongest in women with Turner's syndrome of the X monosomy karyotype or of karyotypes including Y chromosome material, because these karyotypes are more similar to a male karyotype than are other Turner's syndrome mosaic cell lines. However, apart from an 11-fold increased risk of male-predominant autoimmune diseases in women with a Turner's syndrome karyotype including Y chromosome material, we observed a higher risk of male-predominant autoimmune diseases among women with mosaic cell lines than among women with X monosomy. In view of the small numbers within the subgroups, our findings require confirmation in other studies.

Studies examining the association between certain karyotypes and autoimmune thyroid disease have yielded conflicting results. Some studies (9,33), but not all (7,8), have demonstrated an increased risk of autoimmune thyroid disease among women with the isochromosome Xq karyotype. In the present study, we observed increased risks of Hashimoto thyroiditis in all 3 karyotype groups, a finding that was most robust for women with the X monosomy karyotype. Thus, our findings failed to support the notion of a specific association between Hashimoto thyroiditis and the isochro-

mosome Xq karyotype. Among women with this karyotype, we noted an 11.6-fold increased risk of ulcerative colitis. This association was based on only 4 cases; however, women with the isochromosome Xq karyotype have previously been found to be at increased risk of ulcerative colitis (10).

The present study has limitations that should be considered. To limit any influence of coding problems between type 1 and type 2 diabetes mellitus, we assessed only cases of type 1 diabetes mellitus that were recorded in or after 1987, when differentiation between the 2 types of diabetes became possible in the ICD-8. However, we cannot exclude the possibility that some patients with type 2 diabetes mellitus who required insulin treatment might have been misclassified as having type 1 diabetes mellitus. Still, because the association between Turner's syndrome and type 2 diabetes mellitus is likely to be weaker than the association with type 1 diabetes mellitus (6), the observed increased risk of type 1 diabetes mellitus among women with Turner's syndrome in our study is most likely a conservative estimate.

We only had information on autoimmune diseases that involved hospital contacts, so women whose autoimmune diseases were diagnosed and treated only by private practitioners were not captured in the study. Also, we note that women with Turner's syndrome may be at risk of a number of medical problems other than autoimmune diseases and are therefore more likely than other women to be in contact with health professionals (14). Thus, milder diseases might potentially be recognized at an earlier stage in women with Turner's syndrome than for women in general. We cannot exclude the possibility that such earlier ascertainment of autoimmune diseases in women with Turner's syndrome might have led to a slight overestimation of the risk, particularly for less severe autoimmune diseases that do not always require treatment in hospital settings.

Information about autoimmune diseases was extracted from the nationwide Danish National Patient Register, a database that was originally established for administrative purposes but is widely used for research purposes (17). Diagnoses such as inflammatory bowel disease, type 1 diabetes, and rheumatoid arthritis have been evaluated systematically and found to be usable for epidemiologic studies (34–36), but most autoimmune disease diagnoses have not been subjected to systematic validation. However, it is unlikely that the regular contact with health professionals mentioned above and the lack of formalized validation of autoimmune diseases in the Danish National Patient Register would have affected the registration of diseases with a female or male predominance differently.

Some of the sex ratios calculated for the autoimmune diseases in this study differ from other published data. For instance, in this study the female:male ratios for primary biliary cirrhosis and systemic lupus erythematosus were 3.9 and 5.2, respectively, while sex ratios of ~9 have been reported for these diseases elsewhere (1,37). Even though published autoimmune disease sex ratios are known to vary (2) the sex ratios presented in this study were based on population-based hospital data and therefore probably represent accurate estimates.

There is broad consensus that women with Turner's syndrome may be at increased risk of autoimmune diseases as compared with other women. Our results corroborate this view and reveal that, in addition to having a markedly elevated risk of Hashimoto thyroiditis, women with Turner's syndrome, for reasons that are as yet unclear, appear to be especially at risk of developing autoimmune diseases that are normally characterized by male predominance.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Mr. Jørgensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Jørgensen, Rostgaard, Bache, Biggar, Nielsen, Tommerup, Frisch.

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