High Levels of Education and Employment Among Women with Turner Syndrome

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Abstract

Background: Turner Syndrome (TS) is due to X chromosome monosomy and affects ~1 per 2500 females at birth. The major features are short stature and primary ovarian failure. Short stature and monosomy for a maternal X chromosome have been implicated in impaired functionality in adult life; however, data on adult outcomes in TS are limited. In this study we evaluated the influence of adult height and parental origin of the single X chromosome on education, employment, and marital outcomes among women with TS.

Methods: This was a cross-sectional study of 240 women (25–67 years old) with TS participating in an intramural National Institutes of Health (NIH) study. Parental origin of the single X chromosome was determined by genotyping proband and parental genomic DNA. Information on education, employment, and family status was self reported. Normative data was obtained from the U.S. Bureaus of Census and Labor and Statistics.

Results: Seventy percent of the TS group had a baccalaureate degree or higher, compared with 30% of U.S. women ($p < 0.0001$). Eighty percent of the TS group was employed compared with 70% of the U.S. female population. Approximately 50% of the TS group had ever married, compared with 78% of the general female population ($p < 0.0001$). Height and parental origin of the single normal X chromosome had no association with education, employment, or marital status.

Conclusion: Women with TS currently achieve education and employment levels higher than the female U.S. population but are less likely to marry. Neither adult height nor parental origin of the single X chromosome influenced outcomes in education, employment, or marriage.

Introduction

TURNER SYNDROME (TS) AFFECTS APPROXIMATELY 1 in 2500 live-born females and results from total or partial monosomy for an X chromosome.^{1–2} The principal features are short stature, premature ovarian failure, cardiac and renal malformations, and hearing impairment.³ There has been substantial progress in medical care for girls and women with TS over the last few decades, including improved recognition of and care for short stature, estrogen and thyroid deficiency, and hearing loss.⁴ Although full-scale intelligence quotient (IQ) is usually normal, individuals with TS may have difficulties with math and visual-spatial abilities associated with haploinsufficiency for sex chromosome genes.⁵

In addition, psychosocial difficulties consistent with autism spectrum disorder are reportedly increased among girls with TS, possibly related to monosomy for a maternally derived X chromosome.⁶ Skuse et al. hypothesized that male-biased vulnerability to autism and related disorders of social cognition is due to genomic imprinting of unknown X-linked

gene(s).⁷ According to this theory, a gene or genes that enhance neurodevelopment of social skills may be selectively expressed from paternally transmitted X chromosomes and suppressed (imprinted) on maternally transmitted X chromosomes. Since males are always monosomic for a maternally derived X chromosome (X^M), such a mechanism could contribute to the well-described differences in male versus female social cognition, and to excess risk for autism spectrum disorders in males. Girls with TS have increased likelihood for attention deficit hyperactivity disorder (ADHD) diagnoses, apparently not influenced by the parental origin of the single normal X chromosome.⁸

These cognitive and behavioral observations on TS were derived from research studies stimulated by interest in the role of sex chromosomes in sex-based differences in cognition, social behavior, and vulnerability to psychological disorders such as autism and ADHD. It is not clear that girls and women with TS actually have clinically significant learning or psychosocial problems. Several small clinical follow-up studies from the 1980s reported poor psychosocial adjustments

among adults with TS, including impaired self-esteem, social isolation, and stigmatization and lower occupational status.^{9–11} However, large natural history cohort studies showed that psychiatric diagnoses exclusive of depression were not increased in women with TS compared with the general female population and that history of depression was similar to that reported for women with karyotypically normal premature ovarian insufficiency (POI).¹² In addition, scores for self-esteem, shyness, and social anxiety were identical in TS and POI groups,¹³ suggesting many of the reputed genetic psychosocial defects in TS were actually related to the social impact of infertility.

In the present study, we compared education levels, employment, marriage, and parenting in a current cohort of women participating in the National Institute of Child Health and Human Development (NICHD) Turner Syndrome study to current census data for the U.S. female population. In addition, we addressed the potential effects of parental origin of the single normal X chromosome, adult height, and age of diagnosis with TS on these outcomes.

Materials and Methods

Study subjects

This study includes women with TS aged 25 years and older participating in an intramural NICHD prospective study (00-CH-0219), at the National Institutes of Health (NIH) Clinical Research Center in Bethesda, Maryland during 2001–2010. The study was approved by the NICHD Institutional Review Board, and all patients signed an informed consent prior to participating. Criterion for entry into the TS study is a 50-cell karyotype by G-banding with >70% of cells showing absence or abnormality of the second sex chromosome. The lower age limit of 25 years was specified for this outcomes analysis because younger individuals are commonly in transitional situations.

Measurements

Height and weight were measured on an SR scale (SR Scales, Tonawanda, NY) with a height rod. Karyotype was determined by G-banding on 50 peripheral white blood cells for all participants. Fluorescence *in situ* hybridization using X- and Y-specific α satellite DNA probes was employed to characterize marker and ring chromosomes. Parental origin of the single normal X chromosome was determined by genotyping the patient and her parents' genomic DNA using a panel of eight highly polymorphic microsatellite markers dispersed along the X chromosome as previously described.^{14–15}

Outcomes Survey

Data on estrogen and GH treatment, education, employment, marriage, and parenting were collected by written survey and personal interview during admission to the NIH Clinical Research Center. Educational attainment was characterized by number of years of formal education and by highest degree attained: high school or less, a college baccalaureate or master's degree, or an advanced degree (MD, DO, Pharm D, JD, PhD). Civil status was characterized as ever married or never married. Parenting status was categorized as none, adopted, spontaneous pregnancy, or oocyte donation with *in vitro* fertilization (IVF).

The social outcomes for TS women were compared with data for the 25 years and older female U.S. population obtained from the U.S. Census Bureau and the Bureau of Labor and Statistics, accessed in June 2012. Information on educational level and marital status was also obtained from the U.S. Census Bureau (www.census.gov/hhes/socdemo/education/data/cps/2011/tables.html).

Data on employment and occupational choices for the general female population was provided by the U.S. Bureau of Labor and Statistics (www.bls.gov/cps/cpsaat03.htm).

Statistical analysis

Continuous variables are presented as means and standard deviation or median and range, and nominal variables as number and percentage. Associations were analyzed using linear regression, or chi square test. We used analysis of variance (ANOVA) *t*-test to compare continuous variables, and *z*-test for proportions to compare the Turner outcome data to the general female population. In analyses where the models had two or more independent variables, we used generalized linear method with normal distribution for continuous dependent variables or binomial distribution for nominal dependent variables. We defined $p < 0.05$ as statistically significant. Bonferroni correction for multiple comparisons was applied where appropriate. Analyses were performed with Stat View for Windows, version 5.0.1 (SAS Institute, Cary, NC).

Results

Study population demographics

There were 261 women over the age of 24 that enrolled in the NIH Turner syndrome study from 2001 to 2010. Of these, 4 were excluded because their karyotype did not meet inclusion criteria. Information on social outcomes was incomplete for 17 women who were therefore excluded from this outcomes analysis. Thus, 240 participants with a median age of 38.5 years, range 25–67 years, were included in the final analysis. The age distribution was skewed toward young adult years, with fewer than 15% of participants over age 50 (Fig. 1A). Our population was 90% Caucasian, with the rest being distributed between African Americans (4%), Hispanics (4%), Asian (1%), and other (1%). The karyotype distribution for this group was 45,X (57%); 46,XiXq or 46,XiXq/45,X (22%); 46,XdelXp or 45X/46,XdelXp (6%); 45X/46,XdelXq (4%); 45,X/46,XX (6%); 45X/46Xr(X) (5%).

The average age at diagnosis of TS was 12.3 ± 8.9 years (distribution shown in Fig. 1B). Participants younger than 40 years ($n = 135$) had been diagnosed significantly earlier in life (at age 10.4 ± 8.9 years) compared to those older than 40 years ($n = 105$; age at diagnosis 14.7 ± 8.4 years; $p = 0.0002$). Study participants came from 45 of the 50 states. Texas contributed the most participants, but Maryland and Utah were the most highly represented states per capita.

Education level

The average total years of formal education for the TS study population was 15.4 ± 2.4 years. Table 1 summarizes the educational attainment of the TS and age-matched U.S. female population. Seventy percent of women with TS had a college baccalaureate degree or higher, compared with 30% in the

FIG. 1. Age at time of study (A) and age at diagnosis of Turner syndrome (TS) (B). (A) shows the number of women in each age group at time of study. The youngest women eligible for this study were 25 years old. There were only two participants 65 and over. (B) shows age at the time of diagnosis with TS. There are prominent peaks at birth and the pubertal years. The age of diagnosis of TS was 10.4 ± 8.4 years for women younger than 40 compared with 14.7 ± 8.9 years for women older than 40 years of age ($p = 0.0002$).

TABLE 1. EDUCATIONAL ATTAINMENT IN 240 WOMEN WITH TURNER SYNDROME COMPARED TO THE AGE-MATCHED U.S. FEMALE POPULATION

Highest education/degree	Turner syndrome [n (%)]	U.S. female population %*	p†
Less than high school	3 (1.2%)	15%	<0.001
High school	69 (28.8%)	55%	<0.001
Bachelor's/Master's	153 (63.8%)	27%	0.001
Advanced	15 (6.2%)	3%	=0.007

High school category is defined as completion of grades 1–12; Bachelor's/Master's category includes women with a typical 4-year baccalaureate degree or with a Master's degree or Bachelor's degree with additional education (e.g., nursing); Advanced category is defined as an advanced degree in medicine (MD; DO), pharmacy (Pharm D), research (PhD), or law (JD).

*United States Census Bureau, 2009; available from <http://www.census.gov/hhes/socdemo/education>

†Comparison by z-test for proportion. Significance level for p set at <0.0125 after Bonferroni correction.

general U.S. female population. Multiple logistic regression analysis did not show association of current age, age of diagnosis, or adult height with achieved education level.

Employment and occupational choice

The TS group was employed at a rate of 80.4%, compared with 70% in the general female population ($p = 0.001$). Generalized linear model did not show association of age, age of TS diagnosis, and height with employment status. Type of occupation of those employed was characterized according to the Bureau of Labor and Statistics Occupation Field Description (Table 2).

Women with TS were significantly more likely to enter healthcare ($p < 0.0001$), legal, community, and social services occupations ($p < 0.0001$), and less likely to enter office and administrative support ($p < 0.0001$), and food preparation and serving related ($p = 0.001$) occupations. In the general female population, the category with the highest employment was office and administrative support occupations (Table 2).

Among the 20% non-employed in our TS group, about half were not seeking employment due to family responsibilities, medical disability, or "in training" status. About half, or 10% of the total group, would qualify as unemployed, similar to the rate for single women in the general population (Bureau of Labor and Statistics, www.bls.gov/opub/ee/2012/cps/annual.htm#charunem).

TABLE 2. OCCUPATIONAL CHOICES IN WOMEN WITH TURNER SYNDROME

Occupation field description	Turner syndrome (%)	U.S. women (%)*
Management	4.2	8.6
Business and financial operations	4.2	5.3
Computer and mathematical	2.9	1.2
Architecture and engineering	0	0.6
Life, physical, and social science	2.9	1
Community and social services	10†	2.2
Legal	4.2†	1.3
Education, training, and library	14.6	10
Arts, design, entertainment, sports and media	4.7	2
Healthcare practitioners and technical	17.5†	9
Healthcare support	11.7†	4.5
Protective service	2.9	1
Food preparation and serving related	0.8†	5.9
Building and grounds cleaning and maintenance	0	3.5
Personal care and service	1.2	6
Sales and related	6.4	11
Office and administrative support	9.4†	20
Farming and construction‡	0.8	0.94
Production	1.2	3.6
Transportation and material moving	0.8	1.8

Percentage of TS study participants in various occupations compared with age-matched women in the general U.S. population.

*Source: U.S. Bureau of Labor and Statistics; available from <http://www.bls.gov/cps/tables.htm>

†Significant difference with US female population. Significance level $p < 0.0025$ after Bonferroni correction.

‡Encompasses the categories of farming, fishing, and forestry; construction and extraction; and installation, maintenance, and repair.

TABLE 3. PARENTAL ORIGIN OF X CHROMOSOME AND EDUCATIONAL, EMPLOYMENT, AND MARITAL STATUS

<i>X chromosome origin (n)</i>	<i>Age* ± SD (years)</i>	<i>≥ Baccalaureate† (%)</i>	<i>Employed† (%)</i>	<i>Ever married† (%)</i>
X^P (45)	37 ± 8	78	82	40
X^M (116)	38 ± 9	67	83	45
<i>p</i>	0.45	0.23	0.94	0.60

*Comparison by ANOVA or †chi-squared test derived from generalized linear model with binomial distribution; X-chromosome origin, age, and height entered as independent variables.

SD, standard deviation.

Family status

Forty-six percent of the women in our TS group were previously or currently married compared to 78% of the general female population ($p < 0.0001$). In a generalized linear model age was positively ($p = 0.01$) and height negatively associated with marital status ($p = 0.03$) while age at diagnosis and years of education were not. Fourteen percent of the TS cohort had children; 10% had adopted children and 4% had spontaneous or assisted pregnancies. Age was positively associated with parenting ($p = 0.005$) but age of diagnosis, height, and years of education were not.

Genetic factors

We compared years of education and employment status in groups with predominant 45,X karyotypes ($n = 137$) versus groups with karyotypes that contained isoXq chromosome ($n = 52$) and those with a ring X chromosome ($n = 11$). Levels of education and employment were very similar in these three karyotype groups (data not shown).

DNA for determining the parental source of the X chromosome was available for 161 study participants. We compared the various outcome measures for subjects whose single normal X chromosome was derived from the mother (X^M) to those whose X chromosome was derived from the father (X^P). Parent of origin of the X chromosome is not associated with educational attainment, employment, or civil status (Table 3).

History of growth hormone treatment

Eighty-five study subjects were aged 25–35 and had thus been candidates to receive growth hormone (GH) treatment to improve adult height during the 1980s–1990s. A past history of GH therapy was not related to level of education, employment status, and marriage rate (Table 4).

Discussion

Over the past 50 years, there has been an extraordinary level of research interest in the cognitive and psychosocial aspects of TS. One recent review lists 45 studies involving IQ and additional cognitive testing on girls and women with TS

published between 1962 and 2007.¹⁶ Many of these reports on cognitive deficits in TS suggest a potential for significant impairment of everyday functioning. Our study, however, demonstrates high levels of educational achievement and gainful employment among women with TS. These measures of success in adult life were not related to adult height, suggesting that stature is not a major determinant of success in school or entry into the working world for women with TS. Academic and employment achievements were similar in women monosomic for X^M and those monosomic for X^P , indicating that X chromosome genomic imprinting is unlikely to contribute to cognitive and behavioral traits impacting such achievements. Indeed, the current high levels of education and employment demonstrated by women with TS seem to be fundamentally inconsistent with an increased prevalence of clinically significant learning disability, ADHD, or autism spectrum disorder. These diagnoses are correlated with poor educational and employment outcomes among adults,^{17–18} The difference in educational and employment levels among the general U.S. female population and the women with TS in this study may reflect the lower rates of having children and marriage in this population. Given that caring for children and maintaining a relationship require a great amount of time, women with TS may have more time to invest in educational and employment aspirations.

The women participating in this NIH natural history study were volunteers from all across the United States. It might be speculated that women choosing to participate in a research protocol represent a more mildly affected or higher performing group compared with the Turner population as a whole. However, inclusion in this study requires that greater than 70% of cells on a 50-cell karyotype demonstrate absence of the second sex chromosome, which is more rigorous than all prior studies, which typically include substantial numbers of individuals with mosaicism for normal cell lines. In fact, only 6% of the current group had evidence of a 46,XX cell line, and the proportion of cells with the normal karyotype was in all cases less than 14%. The ratio of X^M versus X^P individuals of ~2–3 to 1 in the current study is identical to that found in previous studies.^{15,19} Moreover, this same cohort participated in studies demonstrating that the specific cognitive issues first

TABLE 4. HISTORY OF GROWTH HORMONE TREATMENT AND EDUCATION, EMPLOYMENT AND MARITAL STATUS

<i>Growth hormone treatment (n)</i>	<i>Age* ± SD (years)</i>	<i>Height* ± SD (cm)</i>	<i>≥ Baccalaureate† (%)</i>	<i>Employed† (%)</i>	<i>Married† (%)</i>
Not treated (53)	31 ± 3	148.5 ± 7.7	66	77	30
Treated (32)	29 ± 2	151 ± 6.9	73	70	26
<i>p</i>	0.0016	0.14	0.58	0.51	0.67

*Analysis by ANOVA or †chi-squared test derived from generalized linear model with binomial distribution; growth hormone treatment, age, and height entered as independent variables.

identified in girls with TS were also present in adults with TS,^{20–21} so they clearly have the neurocognitive phenotype. Finally, a recent epidemiology study that interrogated national registry data for all Danish citizens reports that 65% of women with TS (not research volunteers) had a baccalaureate and similar levels of employment compared with the general Danish population.²² These observations, taken together, support the view that these present observations are indeed representative of women with TS in general.

The present study found that women with TS currently are less frequently married than are women in the general U.S. population, and that only a small minority had children. These data are consistent with the recent Danish study.²² This cannot be viewed primarily as social cognition issue, since most women with TS have infertility associated with premature ovarian insufficiency and one of the major factors promoting the institution of marriage, until recently, was the production and protection of children. Among women with TS in this cohort, the likelihood of marriage increased progressively with age.

In summary, although girls and women with TS have distinctive cognitive differences related to arithmetic, visuospatial, and social skills, this study suggests that majority function well as adults. This observation is all the more impressive given that most adults with TS have multiple medical problems in addition to premature ovarian failure. Moreover, it is important to remember that society continues to discriminate against people that are different, and that being short, or infertile, or looking different impose quite a social burden on individuals. It is possible that women with TS self-select for occupations where height is not a big consideration (i.e., healthcare or teaching). Our demonstration of very similar academic, employment, and relationship outcomes in groups of women monosomic for X^M and X^P suggests that genomic imprinting of X-linked genes has little to do with functioning in school or socially. Moreover, the current evidence disputes the notion of clinically significant autism spectrum disorders in TS. A recent review of all available cognitive and psychological testing studies suggests that there may be “TS-specific social cognitive profile” that is not similar to autism spectrum or nonverbal learning disorders.¹⁶ We would like to add to that concept the positive observation that many individuals with TS display excellent coping skills, including perseverance in the face of adversity and equability of temperament.

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Disclosure Statement

No competing financial interests exist.

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