

## STATE OF THE ART ARTICLE

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# Congenital Cardiovascular Disease in Turner Syndrome

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### ABSTRACT

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Turner syndrome (TS), or monosomy X, occurs in ~1/2000 live born females. Intelligence is normal and short stature is the most obvious and consistent feature of the syndrome. Congenital cardiovascular disease affects ~50% of individuals and is the major cause of premature mortality in adults. Unfortunately, this most important aspect of the syndrome has received little attention outside of pediatric medicine, and adult cardiological follow-up is seriously lacking. This review describes the spectrum of cardiovascular defects with particular attention to identifying risk factors for aortic dissection/rupture. X-chromosome genetic pathways implicated in Turner cardiovascular disease, including premature coronary artery disease, are discussed. Recent guidelines for diagnosis and treatment of girls and women with TS are reviewed.

**Key Words.** Adult Congenital Heart Disease; Aortic Dissection; Aortic Valve; Hyperlipidemia; Hypertension; Sex Chromosomes

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Monosomy X, or Turner syndrome (TS) is the only monosomy compatible with life and is characterized by short stature, premature ovarian failure and congenital cardiovascular defects in a phenotypic female. The majority of 45,X gestations end in spontaneous abortion because of defects in cardiovascular development. However, approximately 1/2000 live born females is missing all or significant parts of the second X sex chromosome.<sup>1</sup> The diagnosis of TS requires key clinical features including short stature as well as the abnormal karyotype. A normal statured woman with early menopause and a few 45,X cells on her peripheral karyotype does not meet the criteria for TS (45,X lymphocytes increase with aging and up to 5% are found in normal women >60 years). Further details on the phenotypic and karyotypic features of the TS diagnosis have been recently reviewed.<sup>2</sup> This article will describe the spectrum of cardiovascular anomalies, identify diagnostic difficulties in defining aortic dilatation and risk for dissection in small women and review possible genetic mechanisms whereby haploinsufficiency for a sex chromosome impairs cardiovascular system development. This material is of particular

importance medically because cardiac care for adults with TS is seriously deficient or non-existent<sup>3</sup> and scientifically because the potential identification of X-linked genes involved in cardiovascular development and coronary artery disease (CAD) may be just around the corner.

### Development of 45,X Fetuses

Most 45,X gestations end in fetal demise.<sup>4</sup> Almost all these fetuses have cystic nuchal hygromas<sup>5</sup> because of distended, blind-ended jugular lymphatics. Central lymphatic obstruction is apparent in fetuses with TS as early as 10–12 weeks. In surviving fetuses, the lymphatics mature and hygromas resolve, leaving webbing of the neck postnatally (Figure 1). Most 45,X fetuses detected because of the presence of cystic hygroma have severe cardiovascular defects, including left heart hypoplasia, aortic hypoplasia, interruption or coarctation.<sup>5–7</sup> Interestingly, there is a statistically significant association between neck webbing, indicative of fetal lymphedema, and the presence of bicuspid aortic valve (BAV) and aortic coarctation in surviving females with TS.<sup>8</sup> Because of this



**Figure 1.** Fetal cystic hygroma and postnatal webbing of the neck in Turner syndrome. The fetal sonogram shows bilateral nuchal hygromas (arrows, left panel) caused by extreme dilatation of blind-ended jugular lymphatics. Resolution of the lymphatic obstruction during the second half of gestation leaves redundant nuchal skin folds called pterygium colli, seen here in a girl with aortic coarctation and bicuspid aortic valve.

association, it has been hypothesized that fetal lymphedema contributes to the cardiovascular defects in TS. Distended lymphatics are thought to impair venous return and/or compress the developing outflow tract, resulting in specific left-sided defects including hypoplastic left heart, BAV and aortic coarctation because of low flow, and specific right-sided defects such as persistent left superior vena cava (LSVC), anomalous pulmonary venous return and dilated right atrium, because of back-pressure from obstruction to forward flow.<sup>9</sup> This hypothesis includes the constellation of congenital cardiovascular defects most commonly found in TS. However, while dilated lymphatics may be found in the vicinity of developing aorta, no correlation between this observation and aortic defects is apparent.<sup>6,7,9</sup> Moreover, this theory does not account for individuals that have neck webbing but no heart defects (after comprehensive screening) as well as patients with cardiovascular defects but no neck webbing or other evidence of lymphedema.<sup>8</sup> Thus it seems possible that haploinsufficiency for the same X-linked gene or genes produces impaired lymphatic development in some patients, defective cardiovascular development in others, and both defects in yet other patients, with the exact phenotype and survivability dependent on diverse genetic backgrounds.

Miyabara et al. suggested that cardiovascular defects in TS were due to a primary neural crest defect impacting the portion of the aorta derived from the fourth branchial arch,<sup>7</sup> similar to the DiGeorge syndrome. However, the main cardiac

defects in DiGeorge are tetralogy of Fallot and truncus arteriosus, and these patients have major immunodeficiency and prominent parathyroid defects—not seen in TS. A recent study reported a general reduction in cardiac size in TS fetuses and suggested that impaired myocardial growth is a primary feature of cardiovascular disease in TS.<sup>5</sup> This work, however, did not account for the generalized growth retardation in TS fetuses. Heart size was actually proportionate to arm and leg length in the TS fetuses, suggesting that the small heart size was simply reflecting the diminutive fetal size in these gestations (to some extent masked by excess tissue weight secondary to massive edema). Moreover, absent congenital anatomic defects, cardiac size is normal, i.e., proportionate to body size, in live born individuals with TS.<sup>10,11</sup>

### Cardiovascular Defects in TS

The spectrum of congenital defects reported in recent screening studies is summarized in Table 1. This table includes only individuals that survived the postnatal period, excluding those that died perinatally from hypoplastic left heart, estimated at 10% of live born 45,X patients.<sup>12</sup>

The first four studies in Table 1 had cardiac diagnoses based on transthoracic echocardiography and surgical reports. The National Institutes of Health (NIH) prospective study has studied 250 subjects with clinical exam, electrocardiograph (ECG), transthoracic echocardiography, and cardiac magnetic resonance angiography (MRA). In this study of over 250 patients, the aortic valve was adequately visualized in 99% using combined transthoracic echocardiography and magnetic resonance imaging (MRI). In the final analysis, 30% of subjects had a BAV, with the great majority resulting from fusion of right and left coronary leaflets.<sup>15</sup>

The higher frequency of BAV found in the NIH study could be explained by a number of factors. Difficulty in visualizing aortic valves with transthoracic echocardiography is common, especially in those with BAVs.<sup>17,18</sup> In the NIH study, consistent with prior studies, the majority of aortic valves not captured by echocardiography were abnormal. If these earlier studies had a substantial number of inadequately imaged cases, there would be a bias in reporting normal valves. In general, the previous TS studies were not particularly focused on the AV and did not describe how a BAV was defined or how many cases could not be adequately visualized. Finally, the NIH S study has

**Table 1.** Congenital Cardiovascular Defects in Turner Syndrome

	BAV	Coarc	ASD/VSD	PAPVC	LSVC	ETA	Any
Gotzsche <sup>10</sup>	14%	10%	0	1%	NR	NR	26%
Sybert <sup>13</sup>	14%	14%	5%	1%	NR	NR	
Mazzanti <sup>11</sup>	12%	7%	1%	5%	NR	NR	23%
Volkl <sup>14</sup>	18%	18%	8%	5%	NR	NR	30%
NIH	30%*	12%†	1%*	13%†	13%†	49%†	50%

Each study included in this table had at least 100 subjects.

\*Based on 250 subjects studied with transthoracic echocardiography and MRA.<sup>15</sup>

†Based on 100 subjects studied with MRA.<sup>16</sup>

BAV, bicuspid aortic valve; Coarc, aortic coarctation; ASD/VSD, atrial or ventricular septal defects; PAPVC, partial anomalous venous connection; LSVC, left superior vena cava; ETA, elongated transverse arch of the aorta; NR, not reported; MRA, magnetic resonance angiography; NIH, National Institutes of Health.

inclusion criterion specifying that at least 70% of cells on a 50-cell peripheral karyotype have loss of all or part of the second sex chromosome. Some previous studies included subjects with high-grade mosaicism for normal cells, e.g., 45X(50%)/46,XX(50%). These patients are typically less expressive of most phenotypic features of the syndrome, including BAV.

In contrast to the BAV, aortic coarctation is usually diagnosed on clinical grounds as opposed to screening. However, many cases are not detected until later childhood or teen years, and a few clinically unsuspected cases are routinely detected on MRA screening.<sup>16,19–21</sup> One recent study reported the *new onset* of aortic coarctation in adult women with TS followed over several years with serial MRI.<sup>21</sup> This seems contrary to the usual view of the embryonic origin of aortic coarctation, and requires confirmation in larger longitudinal, radiologically rigorous studies. MRA using gadolinium produces clear visualization of the entire aortic arch, allowing recognition of clinically silent anomalies such as elongation of the transverse aortic arch with prominent kinking past the site of the ductus insertion (elongated transverse arch of the aorta [ETA])<sup>16</sup> in almost 50% of patients with TS (Figure 2). This distinctive anatomy, sometimes termed pseudocoarctation, is embryologically similar to coarctation, and may be associated with aortic dissection.<sup>22</sup> Longitudinal studies are necessary to determine whether the presence of ETA predicts aortic complications such as dilatation or dissection or progression to overt coarctation.

Partial anomalous pulmonary venous connection (PAPVC) and persistent LSVC are each found in ~13% of adults by MRA (Figure 2)<sup>16</sup> and by anatomical study of fetal cases.<sup>7</sup> BAV and PAPVC have the highest relative risk (3603- and 1293-fold, respectively) compared with the general population.<sup>14</sup> PAPVC appears to be clinically significant in about 50% of cases but may not become symptom-

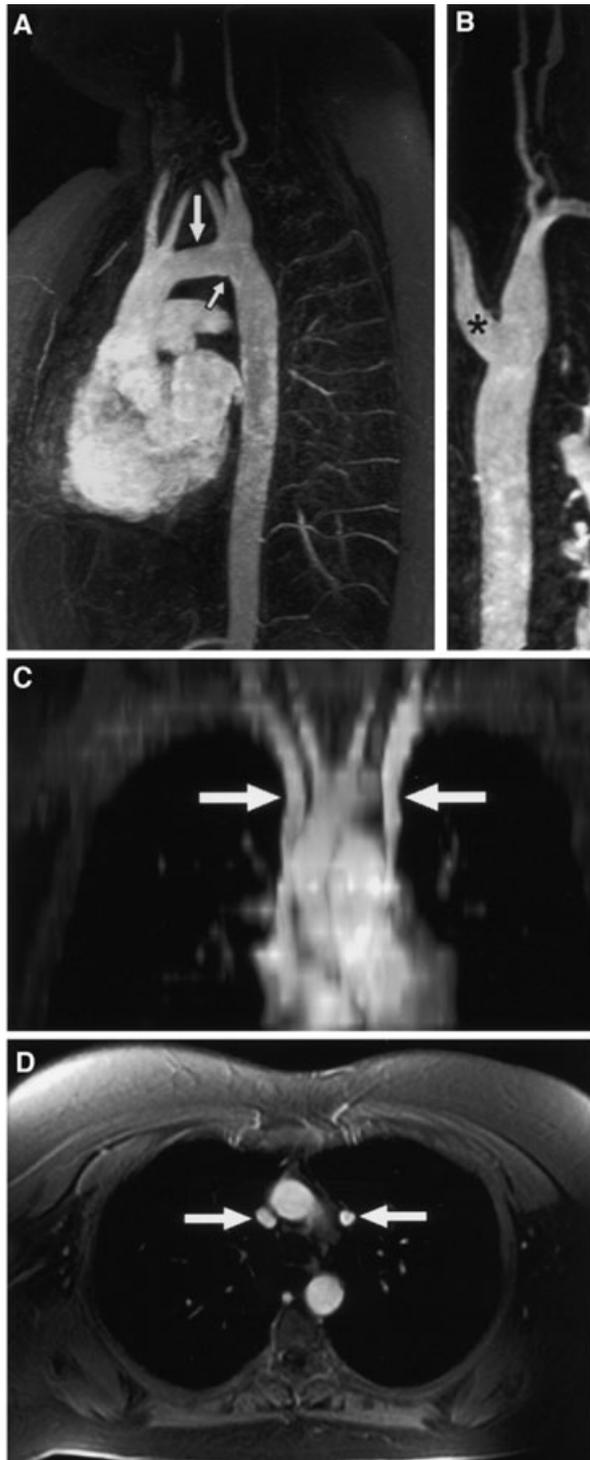
atic until teenage or adult years.<sup>23–25</sup> The ECG may be abnormal in patients with even minor degrees of PAPVC.<sup>26,27</sup> A persistent LSVC is not normally a problem, but may become one if encountered unexpectedly during surgery or attempts at central venous or right heart catheterization. MRA is excellent for detection of these venous anomalies, adding to its value in diagnosing aortic and aortic valve abnormalities and making MRA the preferred screening tool for detection of congenital cardiovascular disease in TS.<sup>2</sup>

Atrial or ventricular septal defects are not so common in TS and usually do not require surgical correction. Mitral or pulmonic valve involvement is also exceptional and may not be more frequent than in the general population.

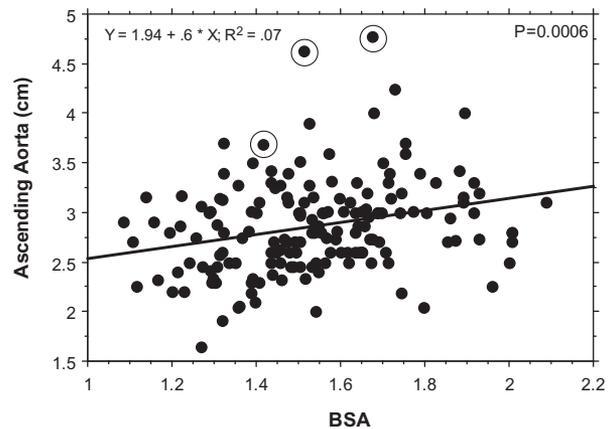
## Aortic Dilatation and Dissection

### Defining Aortic Dilatation

Ascending aortic dilatation has been reported in 15–30% of girls and women with TS.<sup>20,28</sup> The prevalence is partly determined by how “dilatation” is defined. Aortic diameter is determined by age and body size<sup>29</sup> and females with TS are very petite compared with age-matched controls. Hence, comparing TS patients to reference populations of the same age without controlling for important size differences may significantly underestimate aortic dilatation. If in fact the ascending aorta is the same size in a 4’6” woman as in 46,XX age-matched women of 5’6”, it is almost certainly dilated. One approach to normalization for body size differences is to use body surface area (BSA) or height normalized diameters in comparison with age-matched female controls. Another uses ascending/descending aortic diameter ratios (obtained by MRI or computerized tomography [CT]) to normalize the ascending aorta to each patient’s presumed body size appropriate, internal standard of the descending aorta. This latter



**Figure 2.** Multiple vascular anomalies in a woman with Turner syndrome. Magnetic resonance angiography reveals an elongated transverse arch of the aorta (ETA, panel A), aberrant origin of the r. subclavian artery (B) and persistent l. vena cava (C and D).<sup>16</sup> The large arrow in A indicates the ETA extent and the smaller arrow the kink in the descending aorta, sometimes called “pseudocoarctation.” The r. and l. superior vena cavae are indicated by arrows in coronal (C) and transverse views (D). Modified from the study by Ho et al.<sup>16</sup>



**Figure 3.** Correlation between ascending aortic diameter and body surface area in women with TS. The encircled points represent patients that experienced aortic dissection.<sup>30</sup> BSA, body surface area.

strategy assumes that dilatation affects only the ascending aorta, and that the descending aorta is normal, which may not be true in TS. The first study investigating the ascending/descending diameter ratio determined that 33% of a group ~100 TS adults had significant aortic dilatation defined by a ratio  $>1.5$ .<sup>20</sup>

We compared women with TS to age-matched control women using MRI to measure ascending and descending aortic diameters at the level of the right pulmonary artery.<sup>30</sup> Comparing height, body mass index, and BSA, we found the latter correlated most closely with aortic diameter (Figure 3), and therefore normalized aortic diameters to BSA for both TS and control groups. The ascending aortic diameter/BSA is termed the aortic size index (ASI). Despite their smaller stature, actual ascending aortic diameters were similar in TS and control groups, while descending aortic diameters were appropriately smaller in the TS group (Table 2). The 95th percentile for actual ascending aortic diameter in our group of healthy controls was 3.4 cm, very similar to normal female volunteers in a previous MRI study.<sup>20</sup> The 95th percentile for ASI in controls was  $\sim 2.0$  cm/m<sup>2</sup> and for ascending to descending ratio was 1.5 (also similar to reference<sup>20</sup>). Remarkably, almost 10% of women with TS exceeded the 95th percentile for absolute ascending diameter; 25% exceeded the 95th percentile for ASI, and  $\sim 34\%$  exceeded the 95th percentile for ascending to descending ratio.

**Table 2.** Body Size and Aortic Diameters

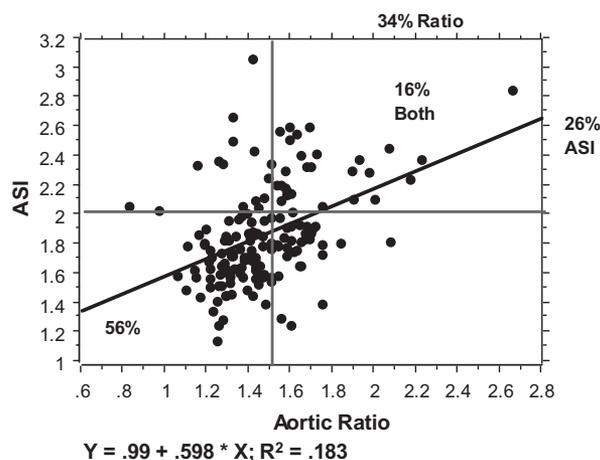
	TS (166)	Control (37)	95% Control	P*	% Dilated
Age (years)	36.2 ± 0.9	37.5 ± 2		0.7	
Height (cm)	147 ± 1	164 ± 1		<0.0001	
AD (cm)	2.86 ± 0.4	2.91 ± 0.06	3.40	0.6	10%
DD (cm)	1.94 ± 0.03	2.18 ± 0.05		0.0003	
AD/DD	1.49 ± 0.02	1.34 ± 0.02	1.50	0.002	47%
AD/BSA (cm/m <sup>2</sup> )	1.89 ± 0.03	1.70 ± 0.02	1.95	0.003	32%
TAV only	TS (131)				
Age	36.5 ± 1	37.5 ± 2		0.6	
AD	2.77 ± 0.04	2.91 ± 0.06	3.40	0.1	7%
AD/DD	1.45 ± 0.02	1.34 ± 0.02	1.50	0.003	43%
AD/BSA (cm/m <sup>2</sup> )	1.83 ± 0.03	1.70 ± 0.02	1.95	0.03	30%

The diameters of the ascending (AD) and descending aorta (DD) were measured on axial T1-weighted images at the level of the right pulmonary artery, perpendicular to the long axis of the ascending aorta.<sup>30</sup>

\*"95% Control" is the 95th percentile value for the control group above which is deemed "dilated."

\*TS vs. Control compared by ANOVA followed by *t*-tests.

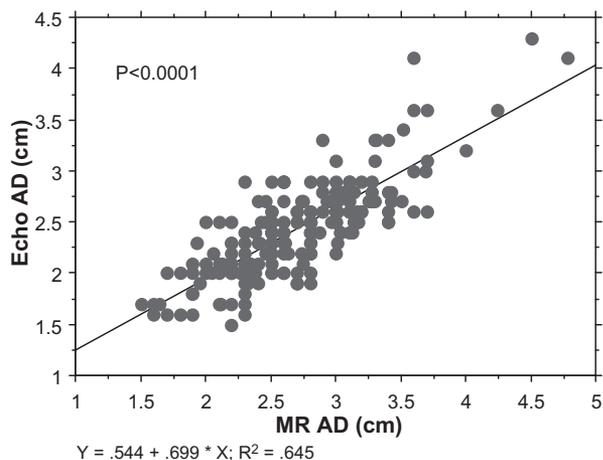
TS, Turner syndrome; BSA, body surface area; TAV, tricuspid aortic valve.



**Figure 4.** Aortic size index (ASI) vs. ascending/descending ratio measures of aortic dilatation in adults with Turner syndrome. The 95th centile for aortic ratio for normal women is indicated by the vertical line at 1.5, and the corresponding 95th centile for ASI is marked by the horizontal line at 2.0. The percentages of the population deemed abnormal (or normal) by the different diagnostic criteria are indicated within or beside the graph frame. For example, 16% of the study population had a dilated ascending aorta by both ASI and aortic ratio, while 34% were dilated according to the aortic ratio upper limit of 1.5. Fifty-six percent were normal by both measures.

Only 16% of study subjects had aortic dilatation by both ASI and ascending to descending ratio. The discriminatory characteristics of the two measures are illustrated in Figure 4.

It is difficult to use Roman nomograms, which plot BSA vs. aortic diameter at the sinuses of Valsalva and sinotubular junction,<sup>29</sup> to identify aortic root dilatation in adults with TS. Some are too small to fit on the adult charts, but since aortic diameter is dependent on age as well as body size,



**Figure 5.** Correlation between ascending aortic diameter (AD) measured by echocardiography and magnetic resonance imaging (MRI). The echo measures AD approximately 1 cm above the sinotubular junction and the MRI at the level of the origin of the right pulmonary artery.

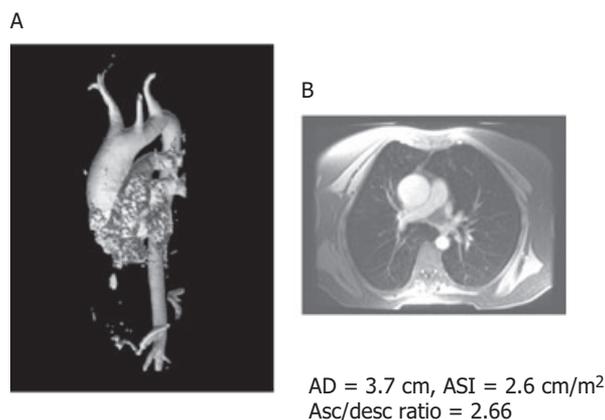
it is not appropriate to plot them on pediatric charts. Moreover, the 95% CI for aortic diameters for adults >40 years are very wide encompassing data for both (tall) men and women and thus are insensitive to dilatation in very small women. Finally, the most significant dilatation may occur at the ascending aorta rather than the sinuses or sinotubular junction.<sup>31</sup> Therefore, we recommend using the ASI based on ascending aorta diameter and BSA as described above. There is a very close correlation between diameters measured by MR and echo at this site (Figure 5), so echocardiographic evaluation and follow up is adequate if the ascending aorta is well visualized.

The high prevalence of ascending aortic dilatation in TS is not explained by the high prevalence

of BAV. As seen in the Table 2, when all BAV subjects were excluded, the prevalence of aortic dilatation was similar in the TAV group. Aortic distensibility is reduced in TS,<sup>32,33</sup> and other large vessels including brachial and carotid arteries appear to have increased diameters,<sup>32,34</sup> suggesting a general vasculopathy. In some surgical reports, cystic medial necrosis and vascular friability have been reported.<sup>13,35,36</sup> Although these are very limited observations, the reduced vascular compliance and increased dilatation and friability suggest similarity to the vasculopathy found Marfan syndrome. Other signs of connective tissue disorder, such as joint laxity or lens dislocation, however, have not been found in TS.

#### Aortic Dissection in TS

In recent years, there have been reports of a high rate of aortic dissections in TS, including patients without known predisposing factors such as BAV or hypertension.<sup>37–39</sup> The dissections usually begin in the ascending aorta, with a few case reports of type B dissections in patients with aortic coarctation post surgical or endovascular intervention. The age of presentation for spontaneous dissections ranges from 25 to 60 years.<sup>30,37</sup> Unfortunately, a young woman presenting with chest or back pain rarely prompts consideration of aortic dissection since the usual dissection patient is a hypertensive male in his 60s. Hence, the diagnosis is not made in a timely manner for many women with TS, and most cases are fatal. Twenty-five percent of the women with dissection in a Danish study were normotensive without BAV or coarctation and thus apparently had zero risk factors for aortic dissection apart from the diagnosis of TS.<sup>37</sup> Sybert reviewed 45 TS cases of aortic dissection published through 1997<sup>13</sup>. Ages ranged from 4 to 64 years and ~10% had neither BAV nor coarctation nor hypertension (the pediatric cases were all postsurgical with rupture or dissection related to the surgery). Thus it seems that 10–25% of patients may have no apparent risk factor for aortic dissection other than TS. Moreover, while BAV and hypertension are major risk factors, dissection related to these pathologies occurs much later in life in the general population. It was not known if dilatation of the ascending aorta preceded/predicted aortic dissection in TS. Thresholds of 5.5 cm for the general population and 5 cm for those with Marfan syndrome are used to guide “prophylactic” intervention to replace or stabilize the aneurysmal segment. Under this “one size fits all” prescription, however, women have a higher



**Figure 6.** Dilatation of the ascending aorta shown by magnetic resonance angiography. (A) Axial “bright blood” post-Gadolinium spoiled gradient echo image obtained at the level of the pulmonary artery origin. (B) Three-dimensional reconstruction of aortic arch. AD, aortic diameter; ASI, aortic size index; asc/desc, ascending/descending.

likelihood of dissection and death<sup>40,41</sup> and it has been suggested that intervention at a smaller diameter such as 4.5 cm would save more female lives.<sup>41</sup> As noted above, given the very small size of many women with TS, they might have significant aortic dilatation at diameters considered in the normal range.

We recently reported the first prospective measure of the incidence of aortic dissection in TS and proposed new guidelines for identifying high risk patients.<sup>30</sup> We evaluated aortic diameters and other parameters in a large group of asymptomatic, unselected women with TS and followed these women followed for an average of 3 years. We recorded three cases of aortic dissection among 158 patients during this time. This translates to an incidence of ~618 cases per 100 000 TS years, compared with ~6 per 100 000 non-TS women years.<sup>42</sup>

The women who dissected were in their 40s and had aortic diameters ranging from 3.7 to 4.8 cm. They were under cardiologist care in their home area, but at less than 5 cm were not considered candidates for prophylactic intervention. These women all had elongated transverse arches and ASI > 2.5 cm/m<sup>2</sup>. AD/DD ratios were variable (1.42, 1.69, 2.66). The MRA study of one of these patients is shown in Figure 6. In summary, 25% of the women with absolute ascending aortic diameter >3.5 cm and 33% of the women with ASI > 2.5 cm/m<sup>2</sup> experienced aortic dissection within ~3 years of follow-up. Only 3% of the women with AD/DD ratio >1.5 experienced aortic

dissection and thus it appears that the ascending to descending aortic ratio may not be very helpful in predicting aortic complications.

Thus, for screening purposes, the ASI 95th percentile upper limit of 2 cm/m<sup>2</sup> for the ascending aorta determined by MRI, CT or cardiac echo is a reasonable benchmark. This measure takes into account the considerable size variation of these patients and identifies about 30% of women with TS that require close monitoring (Box 1). Patients with a mildly dilated aorta require serial evaluations at 6–12 months depending on size of aorta and rate of growth. Use of CT or MR is most preferred, but transthoracic echocardiography may be used if imaging quality is adequate. It is critical that accurate measurements of the aorta be made and compared with prior studies at the same site. If a woman with TS has an ASI  $\geq 2.5$  cm/m<sup>2</sup>, she should have evaluation for prophylactic intervention. If the aortic valve is abnormal, or if other vascular anomalies are present such as coarctation or ETA, and/or if the patient has hypertension, she is likely at heightened risk for aortic complications. If aortic valve surgery is imminent in a TS patient with a dilated aorta, one needs to consider whether the proximal aorta should be replaced at the time of valve replacement. Clearly, further study is needed to determine if beta blocker or renin angiotensin system blockade may prevent or retard aortic dilatation in patients with TS and if prophylactic surgery may reduce the incidence of aortic dissection and rupture. The use of ascending to descending aortic ratio to screen for dilatation is not recommended.

#### Box 1

Normative	Aortic Size Index (ASI)	Clinical Concern
95th centile female controls	>2.0 cm/m <sup>2</sup>	Close monitoring
99th centile female controls	$\geq 2.5$ cm/m <sup>2</sup>	Evaluate for intervention

ASI = ascending aortic diameter at the pulmonary artery origin/body surface area.

#### Potential Genetic Etiologies

The cause(s) of congenital cardiovascular defects in TS are unknown at this time. This review will discuss X-linked genes implicated in cardiovascular development and their potential relevance to TS, and various theories on pathogenetic mechanism for congenital heart defects in TS that have been advanced in the past. As we know from the study of classical genetics, males are uniquely susceptible to

a number of diseases caused by abnormalities of X-chromosome (X-linked) genes. This is because they are monosomic for an X-chromosome and thus have 100% exposure to the defective allele, in contrast to females that have two X-chromosomes and assuming random X-inactivation, are exposed to just 50% (and often a higher gradient since the defective X may lead to skewed inactivation, or selection against abnormal cells). Congenital cardiovascular defects are in general more common in males than females, including BAV and aortic coarctation.<sup>43</sup> Females with only a single X-chromosome are at also at risk for X-linked recessive disorders.

Several syndromes including congenital heart defects are attributed to X-linked genes. Filamin A is a cytoskeletal protein involved in actin cross-linking and interacting with a multiplicity of cellular scaffold and signaling molecules. Mutations of the gene encoding filamin A (FLNA) have been linked to a diversity of syndromes involving the central nervous system, skeletal and cardiovascular systems. One type of filamin A mutation causes X-linked myxomatous valvular dystrophy (XMVD).<sup>44</sup> It is not known how mutation of the gene leads to valve degeneration, but because filamin cross links appear to modulate transforming growth factor (TGF)- $\beta$  activity and interaction with Smad proteins, it has been speculated that one potential mechanism underlying cardiac valvular dystrophy could involve disrupted interaction of Smads with filamin A and inhibition of endothelial–mesenchymal transformation via perturbation of TGF- $\beta$  signaling.<sup>45</sup>

The phenotype of XMVD, mainly involving mitral valve degeneration, does not really fit with the TS congenital defect profile, where aortic defects are more prevalent. In fact, mitral defects are not at all common in TS. However, another type of FLNA mutation results in a seizure disorder related to defective neuronal migration, or perinodular heterotopia (PH), which has been associated with aortic aneurysm in some female patients. Live born males with PH are rare but can exhibit severe, usually lethal, vascular malformations. Given the identification of TGF- $\beta$  receptor mutations in some aneurysm syndromes, and the association of Smads with filamin A, the TGF- $\beta$  pathway is an attractive candidate for inducing both valvular and vascular malformations. The dosage of filamin A and TGF- $\beta$  activity may require precise regulation.<sup>45</sup>

The other X-linked genes listed in Table 3 do not seem strong candidates for the TS

**Table 3.** X-linked Genes and Congenital Cardiovascular Disease

Gene	Disease	Protein Function	X locus	Cardiac Phenotype
Filamin A	Myxomatous valvular dystrophy	Cytoskeleton, interacts TGF	Xq28	Mitral and aortic valve degeneration
LAMP2	Danon	Lyzosomal membrane	Xq24	HCM
Tafazzin, TAZ, G4.4	Barth	Phospholipid/glycerol transferase	Xq28	Ventricular hypertrophy
Dystrophin (DMD)	DMD, BMD	Sarcolemmal membrane protein	Xp21.2	DCM
Emerin (EMD)	EDMD	Nuc. membrane, interacts w/lamin	Xq28	Conduction defects, sudden death
XK, Kell bg	McLeod	Membrane transport	Xp11.4	DCM
ZIC3		Transcription factor	Xq26.2	TGA, situs inv

TGF, transforming growth factor; EDMD, Emery-Dreifuss muscular dystrophies; DMD and BMD, Duchenne and Becker muscular dystrophies; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; TGA, transposition of the great arteries.

cardiovascular defects. Most (i.e., Duchenne, Becker and Emery-Dreifuss muscular dystrophies [EDMD] and Barth and Danon syndromes) are associated with prominent myopathies as well as heart defects, as noted in the table. McLeod syndrome features generalized seizures, neuromuscular weakness and atrophy, and heart involvement mainly manifesting with atrial fibrillation, malignant arrhythmias, and dilated cardiomyopathy. Rarely, individuals with EDMD syndrome, which is due to defects in emerin, a nuclear envelope protein that binds lamin A, may present with sudden death, apparently because of complete heart block, with subclinical myopathy and cardiomyopathy—with atrial fibrillation reported for female “carriers.”<sup>46</sup> Finally, mutations in ZIC3, a zinc finger transcription factor, are associated with nonsyndromic transposition of the great arteries or situs inversus, clearly not typical of the TS phenotype.

There are other X-linked genes that might contribute to the TS cardiovascular defects, based on what is known about their function, e.g., vascular endothelial growth factor (VEGF)-D (Xp22.1). A recent novel hypothesis has proposed that VEGF and/or its receptors/signaling pathways may be involved in multiple aspects of TS.<sup>47</sup> This peptide is implicated in lymphogenesis, angiogenesis and regulation of vascular permeability. This theory suggests that distended jugular sacs cause a strong overexpression of VEGF which enters the circulation, increasing vascular permeability resulting in fetal edema and hydrops. VEGF excess is also suggested to promote fibrosis of developing heart valves and prevent normal cardiac septation.<sup>47</sup> There are, however, no human disorders traced to defects in the VEGF-D gene, also known as “fos-induced growth factor.”

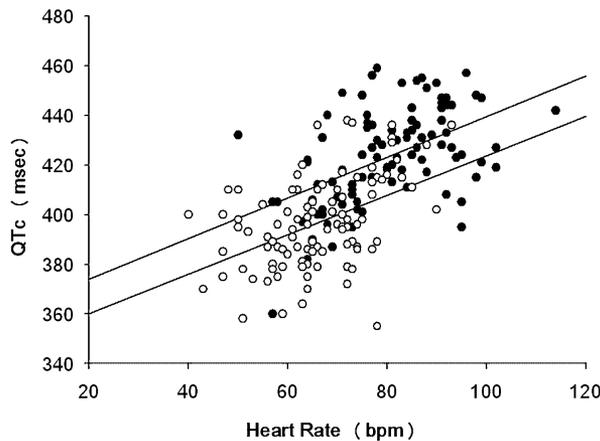
There is a conceptual problem with the proposition that X-linked genes without Y-homologs contribute to congenital defects in TS. That is, if

the increased prevalence of BAV in TS were due to exposure of a recessive mutation in FLNA or another X-linked gene, one would expect a frequency of a few percent, as seen in the male population, not 30%, as we see among females with TS. It seems more likely that bi-allelic expression of one or more pseudoautosomal genes located on both X and Y chromosomes is essential for normal cardiovascular development in both sexes. There are at least 20 such genes or putative genes that are expressed from both sex chromosomes and do not undergo inactivation on the supposedly inactive X. Thus far, we know the function of just one of these genes—*SHOX*—which is required in two copies in both sexes for normal skeletal development and longitudinal bone growth.<sup>48</sup>

As noted in the section on fetal development, there is a significant association between fetal lymphedema and congenital cardiovascular defects in TS, interpreted by Dr Clarke as indicative of a causal relation between the lymphedema and impaired cardiovascular development.<sup>9</sup> An alternative explanation for this association could be that haploinsufficiency for an X-chromosome gene causes central fetal lymphedema and aortic heart defects independent of each other. Haploinsufficiency for an autosomal gene (*FOXC2*;16q) causes lymphedema and occasional cardiac defects in the Lymphedema–Distichiasis syndrome.<sup>49</sup> However, targeted deletion of this gene in mice results in abnormal aortic arch development without lymphedema,<sup>50</sup> suggesting that the heart defects and lymphedema may be independent effects of haploinsufficiency for *FOXC2*. Clearly, the jury is still out on the etiology of congenital cardiovascular defects in TS.

### Electrophysiology and Autonomic Nervous System

Females with TS have a high prevalence of electrocardiographic conduction and repolarization



**Figure 7.** Heart rate and QTc length in women with TS (solid circles) and age-matched control women (open circles). Women with TS have longer QTc interval compared to controls for every heart rate (ANCOVA: F-value for heart rate 59.16,  $p < 0.0001$ ; F-value for TS versus control 29.12;  $p < 0.0001$ ) QTc, rate-corrected QT interval.

abnormalities. Right axis deviation, T wave abnormalities, accelerated AV conduction and rate-corrected QT interval (QTc) prolongation are significantly more common in girls and women with TS than normal, age-matched controls.<sup>26,27,51</sup> Right axis deviation may be associated with underlying PAPVC or LSVC, but the other findings appear independent of anatomic defects. The QTc prolongation is not due to the typically higher heart rate in both girls and women with TS.<sup>26,27</sup> The same effect is seen comparing groups using a QT adjusted as a linear function of the R-R interval<sup>52</sup> and comparing QTc in heart rate-matched groups. Moreover, plotting QTc vs. heart rate for TS and control groups demonstrates a higher QTc at every heart rate with the regression line shifted upward for the TS group (Figure 7).<sup>26</sup> The abnormal ECG may be a non-specific association of congenital cardiovascular disease. Patients with Marfan syndrome are also noted to have abnormal ECG with prolonged QT and possibly increased risk for arrhythmic sudden death.<sup>53,54</sup>

The tendency for QTc prolongation and resting tachycardia beginning *in utero*<sup>55,56</sup>—along with reduced heart rate variability in adults,<sup>57</sup> suggest that there may be an intrinsic defect in autonomic regulation of the cardiovascular system in TS. One study documented a relatively higher heart rate and systolic BP in young women with TS compared with age-matched controls, and a higher level of resting norepinephrine in TS.<sup>58</sup> This study also found a compromised response to sym-

thetic stimulation in the TS group, and concluded that there is a deregulation of the sympathetic nervous system in TS. The prevalence of hypertension is increased in girls and women with TS, independent of the presence of cardiovascular or renal defects.<sup>59</sup> The etiology is unknown, but is associated with overactivation of the sympathetic and renin-angiotensin systems (our unpublished data). Interestingly, several relevant genes encoding proteins implicated in homeostasis of these systems are found on the X-chromosome, i.e., ACE2, AT2, MAO-A, and -B.

### Growth Hormone and the Cardiovascular System in TS

Many girls with TS are now treated with recombinant human growth hormone (GH) to increase adult stature.<sup>2</sup> The doses used are usually supra-physiological and treatment duration may exceed 5 years. As GH excess caused by GH producing tumors produces cardiac hypertrophy and eventually cardiomyopathy,<sup>60</sup> there was concern about potential adverse effects on cardiovascular development in girls with TS. We investigated this issue by comparing left ventricular and aortic dimensions in treated vs. untreated groups.<sup>61,62</sup> The average duration of GH treatment was approximately 5 years and average height differential between treated and untreated groups was about 10 cm. Both ascending and descending aortic diameters were increased in GH-treated girls, but this increase was entirely explained by their increase in height, with no evidence for adverse effects of GH treatment on the cardiovascular system. Likewise, after adjusting for their larger body size, there were no significant differences in cardiac dimensions in the two groups. The fractional shortening, a one-dimensional index of LV function, was also similar in the two groups. Our data confirm previous echocardiography studies reporting normal left ventricular morphology and function in GH-treated girls with TS using dosage groups or normative data comparisons.<sup>63,64</sup> A recent MRI study reported that aortic compliance was greater in TS girls formerly treated with a higher vs. lower dose of GH, suggesting a beneficial effect of GH on aortic wall properties.<sup>33</sup> These findings are reassuring that pharmacological GH treatment does not adversely impact cardiovascular development in girls with TS. More follow-up is clearly necessary to be certain that there are no long-term adverse effects on the cardiovascular system.

### Premature CAD and Genomic Imprinting

Epidemiological data from the UK and Denmark indicate that premature mortality is primarily related to cardiovascular disease in women with TS.<sup>65,66</sup> The latter study reports increased mortality attributed to CAD, in addition to complications from congenital defects. Major CAD risk factors, including hypertension, diabetes, and dyslipidemia, are all increased in prevalence in girls as well as women with TS.<sup>67-73</sup> The fact that the great majority of women with TS have premature ovarian failure complicates the evaluation of CAD risk factors, as lipid metabolism and blood pressure may be affected by the presence, absence or type of estrogen exposure. Clinical studies that controlled for sex steroid milieu, however, showed that women with (45,X) TS have a distinctly more atherogenic lipid profile than women with karyotypically normal (46,XX) premature ovarian failure.<sup>73,74</sup> As exposure to sex steroids was the same in these two female groups, the more atherogenic lipids in TS were attributed to the absence of a second X-chromosome.

A disparity in X-chromosome gene expression may influence gender-specific differences in body composition, lipid metabolism, and CAD through the mechanism of genomic imprinting. Genomic imprinting involves the selective expression of certain genes determined by their parental origin, often associated with DNA methylation of imprinted, or silenced, alleles.<sup>75</sup> Genomic imprinting of X-linked genes could result in different gene expression in males and females, as normal women are mosaic for maternally and paternally inherited active X-chromosomes ( $X^M$  and  $X^P$ ), while men are monosomic for  $X^M$ . Genes imprinted on  $X^M$  would still be expressed in normal females from ~50% of cells in which the  $X^P$  is active, but not expressed at all in males. Men typically have a selective accumulation of visceral fat, which is associated with an atherogenic lipid profile and increased CAD risk, compared with women.<sup>76</sup> As (46,XY) males are also monosomic for an X-chromosome, and have a more atherogenic lipid profile and have ~twofold increased risk for CAD death at all ages compared with females, we hypothesized that monosomy for the  $X^M$  chromosome may promote abdominal (male-pattern or android) adiposity with adverse effects on lipid metabolism and CAD risk.<sup>77</sup>

To determine whether imprinting of X-linked genes is associated with visceral adiposity and CAD risk, we compared regional fat distribution and plasma lipids and in women with TS based on

**Table 4.** X-Chromosome Parental Origin and Metabolic Profile

	$X^M$	$X^P$	<i>P</i>
Age (years)/SD	30.7/11	26.7/12	0.1
Body mass index (kg/m <sup>2</sup> )/SD	27.6/7.5	25.2/6.2	0.2
Total body fat by DXA (%)/SD	37.1/7.6	36.3/8.1	0.550
Total abdominal fat (mL)/SD	78.3/49.0	57.7/36.0	0.010
Visceral abdominal fat (mL)/SD	24.8/19.4	13.9/8.0	0.0005
Triglycerides (mg/dL)/SD	131/62	100/50	0.02
LDL-cholesterol (mg/dL)/SD	137/41	113/44	0.005

Adapted from the study by Van et al.<sup>77</sup>  
DXA, dual X-ray absorptiometry; LDL, low density lipoprotein.

their  $X^M$  vs.  $X^P$  status.<sup>77</sup> Table 4 displays the results of this comparison. Both groups had ovarian failure and were off HRT for 2 weeks at the time of study. Body mass and the percentage of *total* body mass composed of fat determined by DXA were similar in the two groups. Total abdominal fat measured by CT was increased by 34% in  $X^M$  vs.  $X^P$ , and visceral fat was remarkably increased by 71% in the  $X^M$  group ( $P = 0.0005$ ).

Both groups have TS and both have premature ovarian failure, so the only apparent variable is the parental origin of the single X-chromosome, supporting the view that monosomy for  $X^M$  predisposes to selective accumulation of visceral fat and dyslipidemia, independent of sex steroid effects. This could be explained by the imprinting or silencing of maternally transmitted X-linked gene(s) that prevent visceral fat accumulation or of paternally genes that promote visceral fat accumulation and dyslipidemia. These findings if confirmed would suggest that the increased risk for CAD reported for women with TS is because ~70% of these women are monosomic for  $X^M$  and, in addition, have important implications with regard to gender differences in CAD.

### Practice Guidelines

#### Screening

A recent consensus conference has issued general guidelines for diagnosis and care of girls and women with TS.<sup>2</sup> These guidelines emphasized the paramount importance of cardiovascular concerns. All newly diagnosed individuals, regardless of age at diagnosis, need a baseline evaluation by a cardiologist familiar with congenital heart disease. The presence of neck webbing is a strong indicator of congenital cardiac defects.<sup>8</sup> Infants with TS require comprehensive evaluation by a pediatric cardiologists and imaging studies, even if a fetal echocardiogram was “normal.” Echocar-

diography is usually effective in infants and children, but may be limited in some adults because of abnormal thoracic shape or obesity. It is essential that aortic valve leaflets be clearly visualized to exclude significant abnormalities. If echocardiography is not successful, cardiac MRI or CT should visualize the aortic valve well and provide additional important information about smaller arteries as well as the distal aortic arch and descending aorta. All individuals with TS should undergo cardiac magnetic resonance imaging at an age when the study may be performed without sedation. This should be performed at a center with appropriate technical expertise to screen for abnormalities of the aortic arch and descending aorta. If a younger child needs further imaging on clinical grounds, MR is an excellent choice even if sedation is necessary.

Girls and women with TS need careful screening for hypertension and electrocardiographic abnormalities in addition to anatomic anomalies. Blood pressure should be monitored on a regular basis and treated vigorously in all patients with TS. Given the frequent presence of relative tachycardia and risk for aortic aneurysm in patients with TS, treatment with beta-adrenergic and/or angiotensin receptor blocker is recommended. If the baseline ECG reveals a significantly prolonged QTc, then medications which might further prolong the QT should be avoided.

#### Ongoing Care

Approximately 50% of females with TS appear to have no apparent cardiovascular issues after a comprehensive evaluation. For children, routine pediatric care is advised, with continued monitoring of blood pressure and reassessment of the cardiovascular system at transition to adult care. For normotensive adults with TS who have no underlying cardiovascular disease, the frequency or even the need for continued cardiovascular imaging is unclear, but it seems prudent to reevaluate aortic dimensions at 5–10-year intervals under more is known about the natural history. Adults with or without congenital defects need evaluation for CAD risk factors as described above, with early, vigorous attempts to promote a healthy lifestyle. Women with abdominal obesity will likely benefit from statin therapy.

Patients with *cardiovascular defects* need continued monitoring by a cardiologist, as mandated on a case by case basis. Ideally, adults will receive specialized care at a center specializing in adult congenital heart disease. Patients with coarctation

repair or other presumed cured congenital defects must not be discharged from cardiology when they become adults, because their risk for new or recurrent cardiovascular problems remains significant<sup>78</sup> as for all adults with congenital heart disease.<sup>79</sup> Patients with hypertension require monitoring for aortic dilatation as discussed above and summarized in Box 1.

Patients at increased risk for aortic complications because of the presence of a BAV, aortic coarctation, dilatation, and/or hypertension should be educated about this risk and the importance of compliance with medical monitoring and treatment. Patients with multiple risk factors that put them at high risk for aortic deterioration should carry medical information alerting medical personnel to the aortic disease. At the present time, it is unknown if treatment with beta adrenergic or angiotensin II receptor blockers will inhibit aortic dilatation in TS as in Marfan and related syndromes. As these treatments are usually benign and may also reduce the risk for CAD, this seems a reasonable approach to treatment. Hopefully, more evidence-based guidance may become available in the not too distant future. The question of when to recommend elective surgical intervention for treatment of aortic dilatation is more problematic, since it is unknown if TS patients will do as well as those with Marfan and similar syndromes.

#### Pregnancy

Spontaneous or assisted pregnancy in TS should be undertaken only after thorough cardiac evaluation. Alarming reports of fatal aortic dissection during pregnancy and the postpartum period have raised concern about the safety of pregnancy in TS.<sup>39</sup> If pregnancy is being considered, preconception assessment must include cardiology evaluation with MRI of the aorta. A history of surgically repaired cardiovascular defect, the presence of BAV or current evidence of aortic dilatation or systemic hypertension constitute relative contraindications to pregnancy. TS patients who do become pregnant are at increased risk for eclampsia and diabetes as well as aortic dissection, and require specialist monitoring throughout gestation and the postpartum period.

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