A Clinical and Molecular Cytogenetic Study of Filipino Patients with Williams Syndrome

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ABSTRACT

Objective. To study the clinical spectrum of Filipino patients with Williams Syndrome and to confirm the gene deletion by FISH analysis.

Methods. From June 2005 to September 2008, patients who were seen at the Genetics clinic of the UP-PGH and who met the clinical criteria for Williams Syndrome were analyzed for the 7q11.23 deletion through karyotyping and FISH studies. A detailed history and a thorough dysmorphologic examination were performed. Relevant investigations included two-dimensional echocardiography, renal ultrasonography, ophthalmologic examination, developmental assessment and serum calcium determination.

Result. Eight patients were included in the study. The mean age at first diagnosis was 8.5 years. All cases were sporadic. The chromosomal analysis was normal for all patients and in the FISH analysis, a 7q11.23 deletion was detected in 100% of cases. Distinctive facial features, cardiac abnormalities and developmental delay were present in all patients. The typical behavior of overfriendliness was observed in the majority of cases. Hypercalcemia was documented in only one case and no renal anomalies were detected.

Conclusion. The craniofacial features were similar among patients but there is a broad spectrum of severity of clinical features in cardiovascular abnormalities, personality, behavior traits and mental capacity.

Key Words: Williams Syndrome, fluorescence in situ hybridization (FISH), elastin gene (ELN), supravalvular aortic stenosis (SVAS)

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Introduction

Williams Syndrome (WS) is a well-recognized genetic disorder that is noteworthy for its variable manifestations involving the cardiovascular, endocrine, ocular, and central nervous systems. It is also called Williams–Beuren Syndrome after Dr. JCP Williams and Dr. AJ Beuren who in the early 60's described children with distinctive craniofacial features, cardiovascular abnormalities, mental retardation, growth deficiency, and a unique cognitive profile and personality trait. The incidence ranges from 1 in 20,000 to 50,000 live births worldwide.[1] There are no published cases of WS in the Philippines, hence the local incidence is not known.

Although several cases of parent-to-child transmission have already been reported, most of the cases of WS result from a sporadic gene deletion. This defect is believed to have arisen by unequal recombination during meiosis leading to hemizygosity of chromosome 7 band q11.23 which contains the gene for ELN and as many as 30 other genes.[2] Among affected individuals, the size of the deletion can vary from small mutations to deletions greater than 1.5 megabases encompassing several genes within the 7q11.23 region. About 8 of these genes have an observed relationship to the WS phenotype, while in the remaining majority, the impact of the deletion is still unknown.[3] The cardiovascular and connective tissue problems that are commonly seen in patients with WS are attributed to the deletion of the ELN gene.

WS can be diagnosed based on clinical criteria but confirmation can be done by molecular cytogenetic techniques. The most widely used method is fluorescence *in situ* hybridization (FISH) that makes use of locus-specific, fluorescently labeled DNA probes and can identify submicroscopic gene deletions in more than 99% of patients with WS. At the Institute of Human Genetics, National Institutes of Health (IHG-NIH), this test is available on a research basis for a limited number of affected patients.

The objective of the study is to present the clinical spectrum of patients whose clinical diagnosis of WS was confirmed by FISH analysis.

Methods

Patients

Patients with a clinical diagnosis of WS who were seen at the Genetics clinic of the University of the Philippines, Philippine General Hospital (UP-PGH) from June 2005 to June 2008 were included in the study. Demographic data were obtained. A detailed history was taken and information on the patients regarding perinatal conditions and developmental milestones during infancy and early childhood were provided by their parents. Data from the past medical records, when available, were obtained retrospectively. A thorough dysmorphologic examination was performed and the growth parameters were plotted on the WS growth charts. A WS diagnostic scoring system published by the American Academy of Pediatrics (AAP) was used to support the clinical diagnosis of WS. This scoring system is divided into six items: growth, behavior and development, facial features, cardiovascular problems, connective tissue abnormality and calcium studies. There is a corresponding point for each item and if the total points are 3 or more, a FISH study should be considered (Appendix).

Relevant investigations included two–dimensional echocardiography, renal ultrasonography, ophthalmologic examination, developmental assessment and serum calcium determinations.

Cytogenetic Investigations

Standard cytogenetic analysis was done to detect numerical or structural abnormalities of the chromosomes. Two to three milliliter of peripheral blood was collected from each patient for chromosomal analysis. Metaphase chromosomes were obtained from whole blood cultures and chromosome spreads were processed for G-band staining using trypsin and Giemsa stains. At least fifteen metaphases from each patient were analyzed.

In the FISH analysis, a sample from the patient was cultured as in standard cytogenetic analysis, and a locus-specific identifier WS Region Probe (VYSIS) was added to the sample. This probe covered approximately 180 kb of the WBSCR (Williams Beuren Syndrome Critical Region) deleted in WS including the ELN gene, the L1MK1 gene, and the D7S613 locus. This probe also contained a control probe for the 7q31 region containing the D7S486 and D7S522 loci. The hybridization mixture containing the WS region probe (VYSIS) with the D7S486 and D7S522 probes were placed on denatured chromosome slides for an overnight in situ hybridization at 37^0C in a moist chamber. After washing and staining, the slides were observed for fluorescence signals on the chromosomes using a fluorescence microscope equipped with appropriate fluorescence filter sets. If the WBSCR was deleted, only one signal would be visible when viewed under a fluorescent microscope, whereas two signals would be visible in an unaffected person indicating that both copies of the WBSCR were present. An informed consent regarding chromosomal and FISH (fluorescence in situ hybridization) analysis was obtained from all parents.

Results

The demographic and clinical data of the patients are shown in Table 1. From the total sample, six patients were male and two patients were female (sex ratio 3:1); mean age was 8.5 years (range 19 months–19 years). The mean maternal age was 27 years while the mean paternal age was 31.6 years. Seven of the patients were born full term. In 5 cases, the birth weight was within normal range while in the other 3, the weight at birth was small for age. All cases had short stature with a characteristic pattern of postnatal growth deficiency. Six patients were diagnosed after 4 years of age while in two cases the diagnosis was made before two years of age. All cases were sporadic based on the negative family history for related features. In 5 cases, the initial diagnosis was made in a genetics clinic, while in 3 other cases, a previous clinical diagnosis of WS had been given by a pediatric cardiologist, a developmental pediatrician and a general pediatrician.

The main clinical features and diagnostic findings of the 8 patients with WS are listed in Table 2 with photographs of selected individuals in Figure 1. Cases 1 and 4 exhibited facial features that were coarser than those in the younger age group. (Figure 1b) Case 3 did not come back for follow-up, hence the cardiac evaluation was not completed. An intelligence quotient (IQ) was evaluated in only two cases but mental retardation was evident in all cases. The mean diagnostic score was 8 (range 5 to 11). Standard cytogenetic analysis showed neither chromosomal aneuploidy nor structural abnormalities but the metaphase fluorescence in situ hybridization showed microdeletion of the WS critical region at loci 7q11.23 in all cases (Figure 2).

Discussion

There have been no reported cases of Williams Syndrome (WS) in the Philippines, hence the local incidence is not known.

Although routine karyotyping can detect gross deletions, duplications or translocations in chromosomes, microdeletions are not detected by routine G-banding techniques. Fluorescence in situ hybridization (FISH) can identify microdeletions and 99% of WS are diagnosed in this manner;[3] in this series of Filipino WS patients, FISH studies confirmed the diagnosis in 100% of the cases.

Before the introduction of FISH as the definitive diagnosis for WS, patients were diagnosed based on clinical criteria alone using the diagnostic scoring system.[4] However, like many syndromes, WS shows variable phenotypic manifestations making the diagnosis difficult especially in the neonatal period. This was evident in most of our

Table 1. Patient Demographic and Clinical Data

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Age (years)	19	1 7/12	1 9/12	15 4/12	8 3/12	9 5/12	4 11/12	7 5/12
Sex	M	M	M	F	M	M	F	M
Weight	>p95	<p5	<p5	<p5	>p95	<p5	p10	<p5
Short stature	+	+	+	+	+	+	+	+
First Symptom / Sign	Facial dysmorphism	Cardiac murmur/ feeding problems	Jerking movement	Cardiac murmur	Inguinal hernia	Motor delay/ cardiac murmur	Cardiac murmur	Inguinal hernia
Age at first symptom/sign	At birth	1 month	3 weeks	1 month	1 month	1 year	1 month	3 months
Feeding problems & poor weight gain during infancy	+	+	+	-	+	+	+	-
Frequent respiratory infections	+	+	-	+	+	+	+	+
Parental consanguinity	-	-	-	-	-	-	-	-
Sporadic	+	+	+	+	+	+	+	+

Table 2. Main Clinical Features and Diagnostic Findings

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8
Typical facial features	+	+	+	+	+	+	+	+
Hypertension	+	-	-	-	-	-	-	-
Hyperacusis	+	+	+	-	+	+	+	+
Hoarseness	+	-	-	+	+	+	+	+
Joint/skin laxity	-	+	+	+	-	+	+	+
Inguinal hernia	-	-	-	-	+	-	-	+
Skeletal Anomalies	Hallux valgus, 5th finger clinodactyly	Prominent calcaneus bones	Brachydactyly	Thoracolumbar levoscoliosis & lumbar dextroscoliosis	-	5th finger clinodactyly, pes planus	5th finger clinodactyly	-
Ophthalmologic findings	Esotropia, Hyperopia w/ astigmatism	Esotropia DVM	Esotropia NLDO, bilateral	Esotropia	Normal	Esotropia Hyperopia w/ astigmatism	Esotropia Refractive Accommodation	Esotropia
Developmental assessment	Moderate MR*	GDD	GDD	MR*	MR*	MR*	GDD	MR*
Overfriendliness	+	-	+	-	+	+	+	+
Loquacious personality	+	-	+	-	+	+	+	+
Attention deficit disorders	+	+	-	+	-	+	+	-
Temper tantrums	+	+	+	+	+	+	+	+
2D ECHO result	AI, MR	SVAS, RPAS, COA mild	NA	MVP, MR	PPAS	MR, TR, AI	Subvalvar AS	Valvar AS
Renal ultrasound	Normal	Normal	Normal	Normal	Normal	Normal	Normal	Normal
Calcium level	Normal	Elevated	Normal	Normal	Normal	Normal	Normal	Normal
Diagnostic score	7	9	5	6	11	7	9	11
Chromosomal analysis	46,XY	46,XY	46,XY	46,XY	46,XY	46,XY	46,XY	46,XY
FISH (7q11.23 deletion)	+	+	+	+	+	+	+	+

+ Present; - Absent; DVM Delayed Visual Pathway Movement; NLDO Nasolacrimal duct Obstruction; MR Mental retardation; GDD Global Developmental Delay; AI Aortic Insufficiency; MR Mitral Regurgitation; SVAS Supravalvular Aortic Stenosis; RPAS Right Pulmonary Arterial Stenosis; COA Coarctation of the Aorta; NA Not available; MVP Mitral Valve Prolapse; PPAS Peripheral Pulmonary Arterial Stenosis; TR Tricuspid Regurgitation; AS Aortic Stenosis*

patients; five patients had an observed manifestation like cardiac murmur, inguinal hernia, jerking movements and developmental delay in as early as the neonatal period but the diagnosis was made years, if not months, later. Case 1 demonstrated facial dysmorphism at birth and was already given a diagnosis of WS at age 5 years but due to unavailability of the FISH test, confirmation of the diagnosis took 14 years. Case 2 was initially worked up for a congenital infection because of the cardiac abnormalities and mental retardation and it was not until 18 months later that a diagnosis of WS was considered. In case 4, a diagnosis of Kawasaki disease at age one month was made but 15 years later WS was confirmed. Overall, the mean age of diagnosis is 7.26 years unlike in most literatures where the average age of diagnosis cited is between 4.1 to 6.4 years.[5-9]

The distinctive facial dysmorphisms in the patients were evident making the diagnosis of WS straightforward in the majority of cases. These distinctive facial features included a broad forehead, prominent earlobes, periorbital fullness, a depressed nasal bridge with bulbous nasal tip, malar hypoplasia, long philtrum, full lips, wide mouth with widely-spaced teeth and a long neck. However, many of these facial features were not apparent at birth and infancy and became recognizable only by age one year and onwards. In the older age group (cases 1 and 4), the facial features changed over time and became coarser. Such facial characteristics become more pronounced as the child ages with some children developing premature aging and grey hair.[1,6,9]

Strabismus, particularly esotropia, was a consistent finding but it was not persistent in most instances. Two of the cases displayed strabismus which resolved even without corrective surgery. None of our patients had stellate iris. Of the ophthalmologic features of WS, stellate iris is the most common occurring in 70 to 74% of cases.[1,4,9] Although stellate iris is not pathognomonic for WS and can be found as a normal variation in the general population, it is of diagnostic importance in children suspected of having WS.[10] Perhaps it is because stellate iris is not a known feature of many other recognizable syndromes.

Many of the phenotypes of the WS are attributed to the hemizygosity of the ELN gene which is perhaps the single most important genetic deletion in WS because of its effect on the connective tissues of the body including those in the cardiovascular system.[3,7,9,11] In this light, there is a need to assess cardiac function in all patients with WS whether or not they are symptomatic.

Supravalvular aortic stenosis (SVAS), the most common cardiac defect reported among patients with WS,[6-8,12] serves as an important clue to the diagnosis and is the deciding factor for performing FISH studies in patients suspected to have WS.[4] Despite all of our patients having valvular problems, only one had SVAS. This particular patient had right pulmonary arterial stenosis and mild aortic coarctation at the same time but did not warrant surgical intervention. Instead, an annual cardiologic evaluation with an echocardiographic monitoring was indicated on the premise that SVAS may progress especially in the first five years of life, unlike pulmonary arterial stenosis which improves over time.[11,12]

Kawasaki disease (KD) in a WS patient is absent in literature. Its presence in Case 4 at one month of age is puzzling. Although KD occurs in approximately 80% of children under 5 years old including neonates, the presence of this illness is often more difficult to suspect and confirm at a very young age because of the subtleties of manifestations.[13] Coronary artery aneurysms and stenosis are the most common echocardiographic abnormalities in KD disease but this can also be encountered in patients with WS although infrequent.[11] Similarly, mitral regurgitation which can manifest in the acute phase of KD[13] can also be a cardiovascular feature of WS with increasing frequency observed in many studies.[11] The patient's echocardiographic result at one month of age was not available for comparison with the recent echocardiographic findings which showed mitral valve prolapse and mitral regurgitation without coronary artery abnormalities. Kawasaki disease and WS share phenotypic features of the cardiovascular system and can cause dilemmas to physicians and delay in the diagnosis. Whether KD occurs in isolation or part of WS is something that should be looked into in the future.

Hypertension which occurs in around one third of WS patients is clinically important and may manifest as early as infancy. However, it is more common in the older children (>15 years old) and adults.[8,11,12] Hypertension was observed in only one of our cases but the other children need to be monitored periodically because of the possible development of hypertension at a later age. The hypertension in Case 1 was first noticed at age 14 years. The baseline renal work up was normal and renal stenosis as a possible cause was excluded. In literature, only a small number of WS patients have an unconcealed etiology for the hypertension, majority are still idiopathic.[11]

There are few reports of frequent respiratory infection among patients with WS. De Souza et al observed respiratory problems in most of the patients they studied.[6] Similarly, seven of our patients manifested frequent respiratory infection particularly asthma, bronchitis, primary complex and pneumonia. An established links to respiratory infections are cardiomegaly and hypertension because of the propensity to develop heart failure with subsequent pulmonary involvement. Half of our patients were documented to have cardiomegaly and one had hypertension. Although cardiovascular abnormalities could possibly contribute to these pulmonary infections, the exact causes are still undetermined and further investigations are needed to explain such medical problem.

Other features that can be attributed to the ELN gene deletion also include hoarseness, inguinal and/or umbilical hernia, and joint laxity. Hoarseness was clearly evident in the older children in this study but the language delay in the two cases that were below 2 years old made hoarseness hard to ascertain; even with crying, hoarseness was not appreciated. Umbilical and inguinal hernias occur in 50% and 40% of WS patients, respectively.[4] The inguinal hernia manifested very early (1 month and 3 months of age) in two of our cases and required early surgical intervention. Hernias can be early features of WS and may give clue to the diagnosis especially in the neonatal or infancy period.

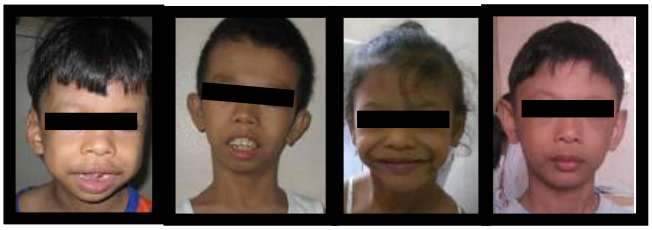

Figure 1a. Photographs of cases 2, 5, 6 & 7 (at ages 3, 9, 5 and 7 years, respectively). Typical facial features include broad forehead, periorbital fullness, prominent earlobes, short nose with bulbous tip, malar flattening, long philtrum, full lips, widely-spaced teeth, small jaw and long neck.

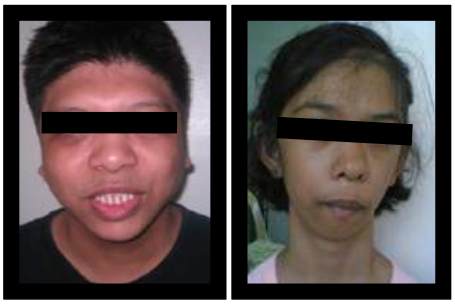

Figure 1b. Photographs of cases 1 & 4 (at ages 21 and 15 years, respectively) showing coarse facial features and premature aging**.**

Orthopedic problems are frequently described in WS with hyperextensible joints as the most common finding (90%) and scoliosis occurring in only about 17 to 20% of cases.[9,14] Only one of our patients showed significant skeletal involvement, a non-progressive thoracolumbar levoscoliosis from the 6th thoracic to the 1st lumbar vertebras and a lumbar dextroscoliosis from the 1st lumbar to the 4th lumbar vertebras. Less frequent features include fifth finger clinodactyly, hypoplastic nails, pes planus and hallux valgus which were all observed in the patients in this study.

A less common feature yet seen in many different case series involve abnormality in calcium levels which can be elevated in about 15% of patients with WS.[9] In all except one of our patients, hypercalcemia was documented although 3 others had symptoms related to hypercalcemia, i.e. irritability, jitteriness, feeding intolerance and constipation during early infancy. Unfortunately, no serum calcium determination was done. Hypercalcemia can occur at any age in WS patients, hence serum calcium should be checked at least once during infancy, early and late childhood and adolescence or when clinically indicated.[4]

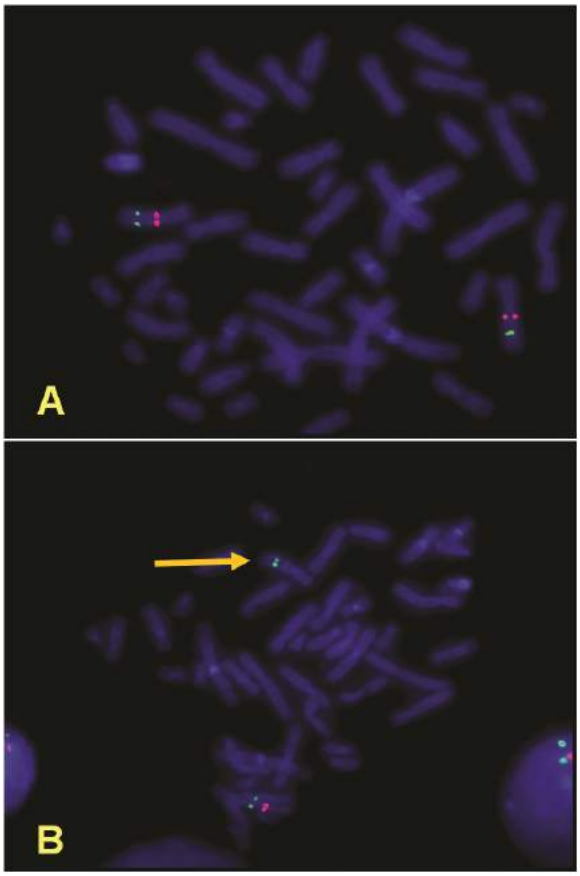

Figure 2. A FISH probe study from an unaffected person (**A**) and from one of the patients with WS (**B**) showing red signals specific for the WS critical region at loci 7q11.23 and green signals specific for control loci at 7q31. In an unaffected person (**A**), the 2 red signals on each chromosome 7 indicates presence of both copies of the WS critical region while in a patient with WS (**B**), absence of the red signals in one of the chromosome number 7 (yellow arrow) indicates microdeletion of the WS critical region.

The neurologic profile of patients with WS is vast. Normal intelligence which can be observed in 5% of WS patients[4] was not observed in this study. A universal finding was delay in achieving the motor and language milestones. On the average, the patients were able to walk at 23 months and talked at 39 months (3.2 years). The mental retardation was most severe in case 2 who at the present age of 4 years still cannot talk and has a developmental quotient

comparable to a 12-month old child. Using the Wechsler Intelligence Scale for Children-Revised (WISC-R) test, the intelligence quotient (IQ) was evaluated in Case 1 which showed moderate mental retardation with IQ points ranging from 41 to 48. In Case 4, the psychometric test using Vineland Scales (Adaptive Behavior Functioning) showed only mild mental retardation. The cognitive abilities of WS patients are unique. Although most individuals have mental handicap of various degrees, a decline in the IQ points is not something that can be expected with age.[15] In fact, some individuals acquire skills with appropriate therapy and enrichment programs. Frequently, these patients have a large stock of words compared to children of similar mental age and some exhibit potential talent for music.[16] Several intervention strategies stemmed from this affinity for language and music and gave way to annual music camp with drama workshops on the sides to utilize the language talents in these patients.

The typical behavior of overfriendliness, which can be observed in as high as 97% of cases, was noted in 6 of our patients. In one case, the hypersocial behavior caused alarm to the parents, especially with respect to interaction with strangers. In spite of this overfriendliness, emotional disturbances such as temper outbursts were also observed in four of the children. In addition, five children exhibited attention deficit for most tasks which is reported to also occur in 73% of cases.[9]

Hyperacusis (hypersensitivity to sound) particularly to loud and sudden voices, car ignition, certain television commercials and dripping water was observed in almost all of the cases. In one of the cases, hyperacusis was still apparent even with a play audiometry result of hearing loss in both ears (mild to moderate on the left, and moderate to severe on the right).

In summary, an evaluation for WS is worth doing in a child who presents with facial dysmorphism, cardiac abnormality and developmental delay. A thorough history and physical examination including assessment of growth are initial screening tools but a molecular cytogenetic study such as FISH is useful in confirming the clinical diagnosis. In instances where cardiovascular abnormalities are present, closed follow up and blood pressure monitoring should be advocated to prevent medical complications.

Conclusion

The craniofacial features of Filipino among patients with WS were similar but there is a broad spectrum of severity of clinical features in cardiovascular abnormalities, personality, behavior traits and mental capacity. A delay in diagnosis stemmed from uncertainties in the phenotypic manifestations which were observed to overlap with other disorders. FISH analysis confirmed the diagnosis of WS in all of the cases.

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Appendix

Scored Points*

Growth (Past or Present Evidence of) *If 3 of 5 items are checked, score 1 point* _____

[ ] Post-term birth > 41 wk gestation
[ ] Failure to thrive/height and weight < 5th percentile
[ ] Vomiting or gastroesophageal reflux
[ ] Prolonged colic > 4 m irritability
[ ] Chronic constipation

Behavior and Development *If 3 of 6 items are checked, score 1 point* _____

[ ] Overly friendly personality
[ ] Hypersensitivity to sound
[ ] Anxiety
[ ] Developmental delay or mental retardation
[ ] Visuospatial problems
[ ] Delayed speech acquisition, followed by excessive talking

Facial Features *If 8 of 17 items are checked, score 3 points* _____

[ ] Bitemporal narrowing
[ ] Epicanthal folds or flat nasal bridge
[ ] Strabismus (present or past)
[ ] Short nose or anteversion of nares
[ ] Full cheeks
[ ] Long philtrum
[ ] Small, widely spaced teeth
[ ] Wide mouth
[ ] Prominent ear lobes
[ ] Broad brow
[ ] Periorbital fullness
[ ] Stellate lacy iris pattern
[ ] Bulbous or full nasal tip
[ ] Malar hypoplasia (flat cheek bones)
[ ] Full prominent lips
[ ] Malocclusion
[ ] Small jaw

Cardiovascular Problems (by Echocardiography) (a) *If 1 of 2 items are checked, score 5 points* _____

[ ] SVAS†
[ ] Peripheral pulmonary artery stenosis

Cardiovascular Problems (b) *If 1 of 3 items are checked, score 1 point* _____

[ ] Other congenital heart disease
[ ] Cardiac murmur
[ ] Hypertension

Connective Tissue Abnormality *If 2 of 6 items are checked, score 2 points* _____

[ ] Hoarse voice
[ ] Inguinal hernia
[ ] Bowel or bladder diverticula
[ ] Long neck or sloped shoulders
[ ] Joint limitation or laxity
[ ] Rectal prolapse

Calcium Studies *If 1 of 2 items are checked, score 2 points* _____

[ ] Hypercalcemia
[ ] Hypercalciuria

Total Points: _____

* If the score is < 3, a diagnosis of Williams syndrome is unlikely. If the score is ≥ 3, FISH studies should be considered. (Mean score for Williams syndrome was 9 [standard deviation = 2.86]. The scoring system is based on a study of 107 persons with Williams syndrome [confirmed by FISH] evaluated by Colleen A. Morris, MD; Frank Greenberg, MD; Paige Kaplan, MD; Martin Levinson, MD; and Barbara Pober, MD; with data analysis by Carolyn B. Mervis, PhD and Byron F. Robinson, MA; presented at the 1994 Williams Syndrome Association Convention; July 31, 1994; San Diego, CA.)

† If supravalvar aortic stenosis (SVAS) is present, referral to a geneticist and FISH studies are recommended.