

Williams Syndrome-The Singapore General Hospital Experience

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Abstract

Williams syndrome first described in 1961 is generally characterised by mental deficiency, gregarious personality, unusual "elfin" facies, supraaortic stenosis and idiopathic, infantile hypercalcaemia. Patients with Williams syndrome show a hemizygous submicroscopic deletion of 7q11.23 detectable by fluorescent in-situ hybridisation (FISH). The deleted portion of the chromosome corresponds to the Elastin gene.

We report 3 girls with characteristics of Williams syndrome in whom the diagnosis was confirmed by demonstration of the hemizygous deletion of 7q11.23 in the karyotype by FISH. These patients, aged 6, 7 and 10 years, showed the characteristic facies and gregarious personalities. Some developmental delay with mild mental deficiency and dysmorphic facies were prominent features in the initial presentation. Cardiac lesions found in these patients were small patent ductus arteriosus which closed, pulmonary valvular stenosis and mitral valve prolapse associated with mitral regurgitation respectively. Hypercalcaemia was not documented in these patients. Learning difficulty was a major issue and all patients required special schooling. Chromosome analyses done on peripheral blood were found to be normal in all patients. FISH using the Elastin Williams Syndrome Chromosome Region (WSCR) probes (Oncor®) showed the hemizygous deletion of 7q11.23. Diagnosis of Williams syndrome can now be confidently confirmed with the help of FISH.

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Introduction

Cytogenetic abnormalities are increasingly found to be the causes of many described syndromes. This is made possible with the advancement of technology in the field of cytogenetics.¹ High resolution banding techniques have contributed to better visualisation of the karyotype and fluorescent in-situ hybridisation (FISH), a relatively new technique in the field of cytogenetics, is utilised to complement microscopic examination such that submicroscopic deletions are "seen" in the karyotype. All these advances have led to better understanding of the chromosomal basis of many well-known syndromes like the Prader-Willi-Angelman syndrome (deletion 15q11-13), Miller Dieker syndrome (deletion 17p13.3) DiGeorge syndrome (deletion 22q11) and Williams syndrome (deletion 7q21). The discovery of

these chromosomal abnormalities has led to the molecular understanding of the pathophysiological processes that brought about the constellation of the signs and symptoms found in these syndromes. In addition, they also opened up new and exciting areas in genetics that remain to be explored; the classic example of Prader-Willi-Angelman syndrome and the theory of genomic imprinting.*

Williams syndrome was described in 1961 in 4 patients with supraaortic stenosis, unusual facies and mental deficiency.³ The vast phenotypic variability of this syndrome had, however, led to the description of various aspects of this syndrome as two separate entities: supraaortic stenosis⁴ and infantile hypercalcaemia.⁵ Black and Bonham-Carter⁶ pointed out the similarity of the two syndromes, and suggested

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that the two disorders were in fact the same. Various cardiac abnormalities were described in this syndrome; besides supraventricular aortic stenosis, peripheral pulmonary stenosis, pulmonary valvular stenosis, mitral incompetence and coarctation of aorta were found to be associated with it.⁷

Ewart and coworkers in 1993⁸ identified hemizygosity of the Elastin locus at 7q11.23 in patients with Williams syndrome, resulting from a submicroscopic deletion which is detectable by FISH. Many reports have now confirmed the usefulness of this deletion in Williams syndrome.⁹⁻¹¹

We report our series of 3 girls with features of Williams syndrome in whom we demonstrated the submicroscopic deletion of 7q11.23 in the karyotype by FISH.

The patients were seen and followed up in the Departments of Neonatology and Paediatric Medicine, and they were also assessed by the paediatric cardiologist. When the diagnosis of Williams syndrome was clinically suspected, the patients were further ascertained by the geneticists. Lymphocytes from a peripheral blood sample of these patients were cultured using the method described by Yunis.¹² Chromosomal analysis was carried out on G-bands by trypsin using Giemsa (GTG banding) at greater than 500-band level. Metaphase spread on a slide was set aside for FISH work. Cosmid probes, Elastin Williams Syndrome Chromosome Region (WSCR) from Oncor® corresponding to the Elastin gene on chromosome 7 and control probes, D7S427 (Oncor®) corresponding to the region at 7q36 were hybridised and the signals were visualised under fluorescent microscope. Positive signals from both WSCR and D7S427 probes were indicative of absence of the deletion, whereas a positive signal from D7S427 probe only was indicative of the deletion of 7q11.23.

Case Reports

Patient 1 (Fig. 1)

SPH, a 10-year-old Chinese female was born full term with birthweight of 3300 g. She is the child of non-consanguineous parents who are normal. She has one older sibling who is normal. In 1990 she had an admission to the hospital for diarrhoea, but her dysmorphic features were not noted. Her early milestones were delayed. She was seen again in 1992 for recurrent cough, failure to thrive and mental deficiency. Her height and weight were at the third percentile for her age. The bone age was appropriate and thyroid function test was normal. Psychological assessment using Wechsler Intelligence Scale for Children-Revised¹³ showed her intelligent quotient (IQ) to be 70. Dysmorphic facies with prominent epicanthic folds, broad nasal bridge, a bulbous nose with anteverted nares, malar hypoplasia, long philtrum and thick lower lip with an open mouth

was noted in 1993. She was loquacious and had difficulties in coping with studies since kindergarten. She was also noted to have a hoarse voice. A subsequent Wechsler Intelligence Scale for Children-Revised test in 1993 showed her IQ to be 55 and she was referred for special education. Cardiac assessment done in October 1993 showed mitral valve prolapse with mild to moderate mitral regurgitation.

She was admitted for an episode of supraventricular tachycardia in August 1995 and Williams syndrome was recognised. Karyotypes with FISH studies for 7q deletion were done, and there was absence of positive signal from the WSCR(Oncor®) probe.

Patient 2 (Fig. 2)

YYY, a 7-year-old Chinese female was born at 40 weeks gestation via normal vaginal delivery with birthweight of 3390 g. Her parents are non-consanguineous. She developed cyanotic spells on crying and during feeding on day 1 of life and was found to have pulmonary stenosis. Her cyanotic spells improved and she could be discharged on day 9 of life. During outpatient review, she remained asymptomatic with adequate weight gain. A grade 3/6 ejection systolic murmur was first heard at the upper left sternal edge at the age of three months. A two-dimensional echocardiogram was repeated when she was six months old and showed only mild pulmonary valve stenosis.

YYY was referred at 2 years 4 months old to the Development Assessment Clinic for delayed motor milestones and speech. Her comprehension was limited and she communicated in single words from 2 to 3 years of age. Psychological assessment using the Bayley Scales of Infant Development¹⁴ showed generally delayed development with a mental age equivalent of 18 months when assessed at 2 years 9 months old. The peripheral blood karyotype was normal (46XX). She defaulted developmental reviews subsequently.

YYY was seen again at the age of 4 years 6 months when her parents were concerned over her inability to cope with her first year at kindergarten. She was slow in mental development with an IQ (Leiter International Performance Scale¹⁵) of 61. She was clinically suspected of having Williams syndrome at the age of 6 years 4 months. Her facial features were: short palpebral fissures, prominent epicanthic folds, broad nasal bridge, bulbous nose, anteverted nares, thick lips with an open mouth and malar hypoplasia. Her height was at the tenth percentile for age whereas her weight was at the third percentile for age. She displayed poor attention and chattered incessantly, using stereotyped clichés without any relevant context. She was recommended to attend a special school for the educationally subnormal.

Fluorescent in-situ hybridisation studies for the WSCR (Oncor®) probe confirmed the microdeletion of 7q11.23.



Fig. 1.

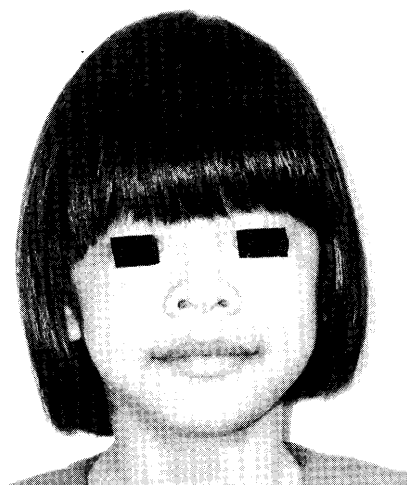


Fig. 2.



Fig. 3.

Fig. 1. Patient 1: Note the dysmorphic features-prominent epicanthic folds, broad nasal bridge, bulbous nose with anteverted nares, malar hypoplasia, long philtrum and thick lower lip.

Fig. 2. Patient 2: Soft features of facial dysmorphism noted.

Fig. 3. Patient 3: Similar facial features to Patient 1.

She had normal levels of serum calcium (2.24 mmol/l), serum phosphate (1.21 mmol/l) and serum alkaline phosphatase (156 units) when assayed at 6 years 4 months old.

Patient 3 (Fig. 3)

SYJ, a 6-year-old Chinese female was born at 40 weeks gestation via normal vaginal delivery with birth weight of 2600g. Her parents are non-consanguineous and her mother had gestational diabetes. She has one older sibling who is normal. SYJ had a cardiac murmur detected on day 4 of life and a paediatric cardiologist was consulted. A two-dimensional echocardiogram done showed a small patent ductus arteriosus with a small atrial septal defect. There were no other complications and a routine serum calcium level at day 2 of life was normal (2.23 mmol/l).

Her height and weight were at the tenth percentile for age and she grew along the percentile line. Early motor milestones were delayed. There was an admission to the hospital at the age of 11 months for an upper respiratory tract infection and dysmorphic facies was noted. Williams syndrome was suspected at that time. Her cardiac murmur had disappeared and a repeat two-dimensional echocardiogram was normal. She had a left inguinal hernia noted at the age of 3 years for which a herniotomy was done. She was also noted to have a hoarse voice.

In 1995 she started kindergarten but could not cope with her studies. She had poor attention span and was said to be stubborn. A psychological assessment showed her IQ (Wechsler Preschool and Primary Scale of Intelligence¹⁶) to be 55. She was recommended special edu-

cation but her mother was distressed at the notion. With the availability of the FISH studies, Williams syndrome was confirmed in May 1996. Further counselling was easier with proper diagnosis and she was enrolled in a special school.

All the cardinal features of these patients are summarised in Table I. Figure 4 shows the absence of WSCR signal on one homologue of chromosome 7 using FISH from the same patient.

Discussion

Williams syndrome is a contiguous gene deletion syndrome involving the Elastin gene which is located on 7q11.23. A contiguous gene deletion syndrome means that the manifestation of the syndrome is believed to be caused by a deleted or missing portion of a chromosome

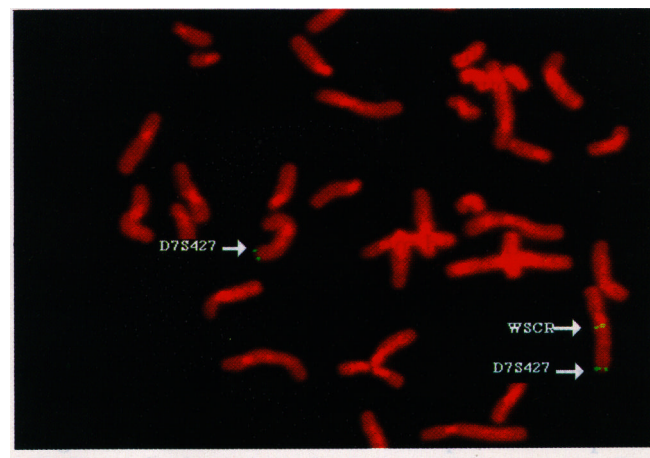


Fig. 4. Absence of WSCR signal on one homologue of chromosome 7 of Patient 1 using FISH technique.

TABLE 1: CLINICAL FEATURES OF THE THREE PATIENTS

	Patient 1 (SPH)	Patient 2 (XYY)	Patient 3 (SYJ)
Age	10 years	7 years	6 years
Sex	Female	Female	Female
Race	Chinese	Chinese	Chinese
Height at diagnosis	3rd percentile	10th percentile	10th percentile
Weight at diagnosis	3rd percentile	3rd percentile	3rd to 10th percentile
Dysmorphic features			
Broad nasal bridge	+	+	+
Hypotelorism	+	+	+
Epicanthic folds	+	+	+
Periorbital fullness	+	+	+
Small palpebral fissure	+	+	
Anteverted nares	+	+	+
Bulbous nose	+	+	+
Long philtrum	+	+	+
Thick lips/open mouth	+	+	+
Malarhypoplasia	+	+	+
Cardiac lesion	Mitral prolapse with regurgitation	Pulmonary valve stenosis	Patent ductus arteriosus (closed)
General features			
Hernia			Inguinal
Hoarse voice	+		+
Serum calcium	Not done	Normal	Normal
Behaviour			
Gregarious personality	+	+	+
Loquacious	+	+	+
Others		poor attention span	poor attention span stubborn
Intelligence quotient*	55	61	55
School failure	Yes	Yes	Yes

* Main tests used were Wechsler Intelligence Scale for Children-Revised and Wechsler Preschool and Primary Scale of Intelligence

and the absence of genetic input from the few or multiple critical genes situated next to each other on that deleted portion of the chromosome. The genes themselves may carry information that affect cellular functions in different areas that are not linked physiologically. In other words, many widely different aspects of cellular function are defective or deficient causing multisystemic manifestation of the syndrome. The only link is that the different genes leading to each of the widespread abnormalities are in the same neighbourhood in a particular region of the chromosome.¹⁷

The features of classical Williams syndrome so far described include supra-aortic stenosis, unusual elfin facies, mental deficiency with an outgoing personality and with or without idiopathic infantile hypercalcaemia.¹⁸ The facial dysmorphisms described include broad forehead, periorbital fullness, prominent

epicanthic folds, short palpebral fissures, ocular hypotelorism, anteverted nares, long philtrum, thick lips with open mouth, pointed chin, and malar hypoplasia.¹⁹ These features are not easily recognisable and at times rather non-specific. Other general features that are useful for clinical recognition are short stature, inguinal or umbilical hernia, small nails, hallux valgus and a hoarse voice.¹⁸ Short stature is seen in these patients especially in the first two years of life and is the result of prenatal growth deficiency and poor growth in early postnatal period.²⁰ A wide variety of cardiac abnormalities is found in about 75% of these patients with supra-aortic stenosis and peripheral pulmonary stenosis being the two most common anomalies seen.^{7,18} Hypercalcaemia is not a constant feature in Williams syndrome.¹⁹ These wide phenotypic manifestations of the syndrome have led to the formulation of

a tedious diagnostic index²¹ or simple scoring system⁹ to define and classify patients.

Our patients had similar soft facial dysmorphic features which could only be appreciated if they were seen collectively. It was not easy to make a syndromic diagnosis without experience. None of these patients had supravulvar aortic stenosis and their cardiac abnormalities were varied. Hypercalcaemia was not documented in any of these patients. The consistent features were a gregarious personality that was exhibited during social contact, and the mental deficit that was present in all patients. School failure was prominent despite the fact that all these patients were socially outgoing and loquacious. Their mental retardation was deceptively concealed in the early years. Recently a specific pattern of cognitive impairment has been recognised in Williams syndrome in that these patients have been shown to be deficient in visuospatial abilities.²² It will be ideal to have these three patients assessed for these cognitive deficits in the near future. An inguinal hernia that was present in Patient 3 is another soft feature in these patients. For this patient, diagnosis was suspected in 1990 but confirmation could only be done in 1995.

With the discovery of the hemizygous deletion of the Elastin gene in these patients, diagnosis of Williams syndrome is now more definitive. Clinical suspicion in loquacious children with school failure and suggestive Williams syndrome facies and features could now be tested categorically. Fluorescent in-situ hybridisation technique used to demonstrate the hemizygous deletion of the Elastin gene has been shown to correlate well with the clinical phenotype.⁹⁻¹¹ Confirmation of Williams syndrome can also be done confidently especially in patients with atypical features like in the mildly expressed form or in the first year of life in cases where possible familial segregation of this syndrome is suspected. The early diagnosis would certainly improve genetic counselling in families with the syndrome. However in the many published reports, there was a small disparity of FISH results with the clinical classification.⁹⁻¹¹ This disparity could be explained as follows: (1) the Elastin gene deletion is smaller and not detectable by the present WSCR probes; (2) mutations rather than deletions are involved at the molecular level; (3) other genetic mechanism is at play, leading to a phenocopy of Williams syndrome i.e. the phenotypic manifestation of Williams syndrome is not due to involvement of the Elastin gene locus, or (4) the patients may have been misclassified.⁹ As the test may be very readily available, there is practical need to keep category (4) at a low level through proper clinical ascertainment of these patients

preferably by experienced doctors, before proceeding to do the diagnostic test.

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