Williams syndrome : The experience in a pediatric hospital

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Rome

Bambino Gesù
OSPEDALE PEDIATRICO

- FACIAL ANOMALIES
- DEVELOPMENTAL DELAY
- CONGENITAL HEART DEFECT
- STRABISMUS
- HERNIAE
- HYPERTENSION
- GROWTH DEFICIENCY

Multidisciplinary medical team

- NEUROPSYCHIATRY
- CARDIOLOGY
- OPHTHALMOLOGY
- SURGERY
- NEPHROLOGY
- ENDOCRINOLOGY

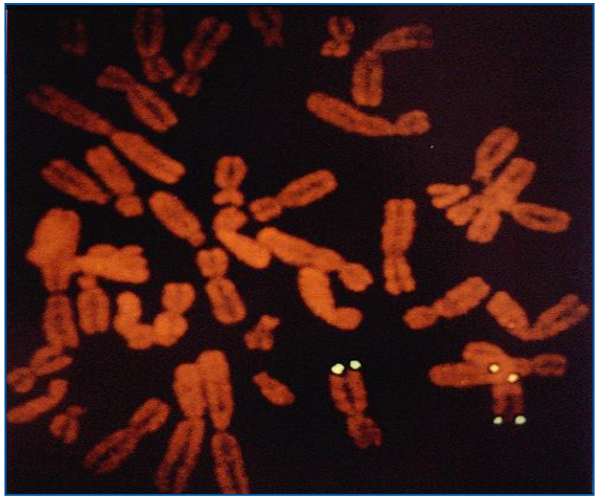
.....

- THE DIAGNOSIS
- CLINICAL MANAGEMENT
- GENETIC COUNSELING

THE DIAGNOSIS

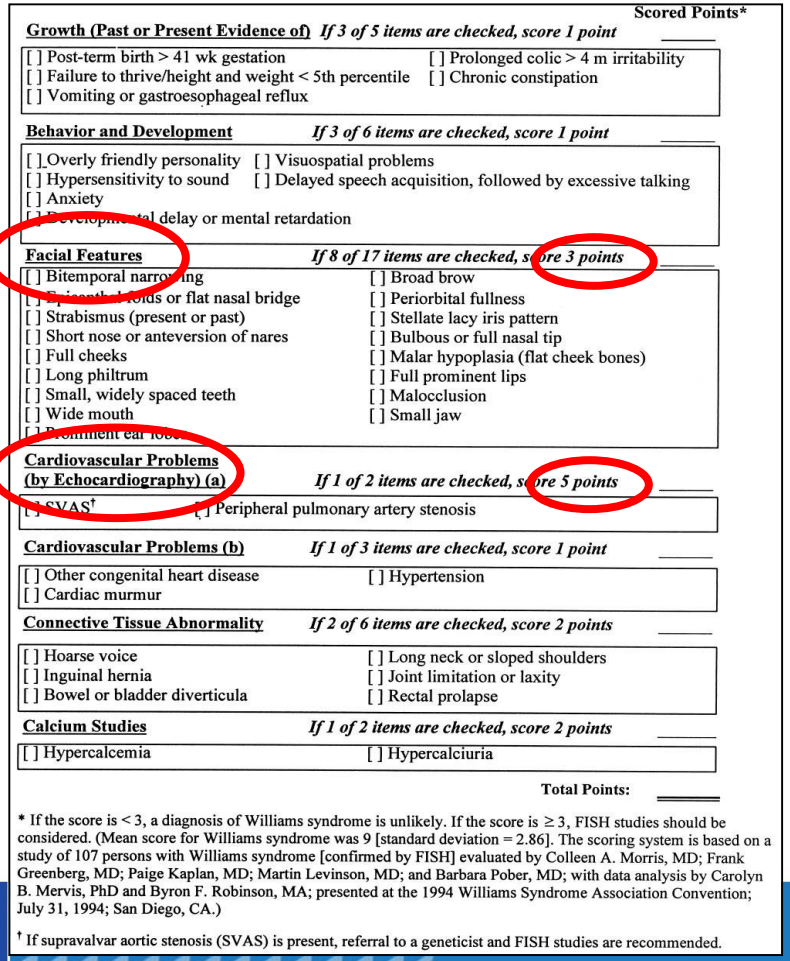
Before the availability of a diagnostic test, the average age of diagnosis was 6.4 years

Colleen A.Morris, 2001



THE DIAGNOSTIC SUSPECT IN THE FIRST YEAR OF AGE

- Gastroenterology: Feeding difficulties
- Neurology: Developmental delay
- Surgery: Inguinal hernia
- Cardiology: Congenital heart defect



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.

THE DIAGNOSIS

PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

Score > 3

Suspect of of Williams syndrome

AMERICAN ACADEMY OF PEDIATRICS
Committee on Genetics

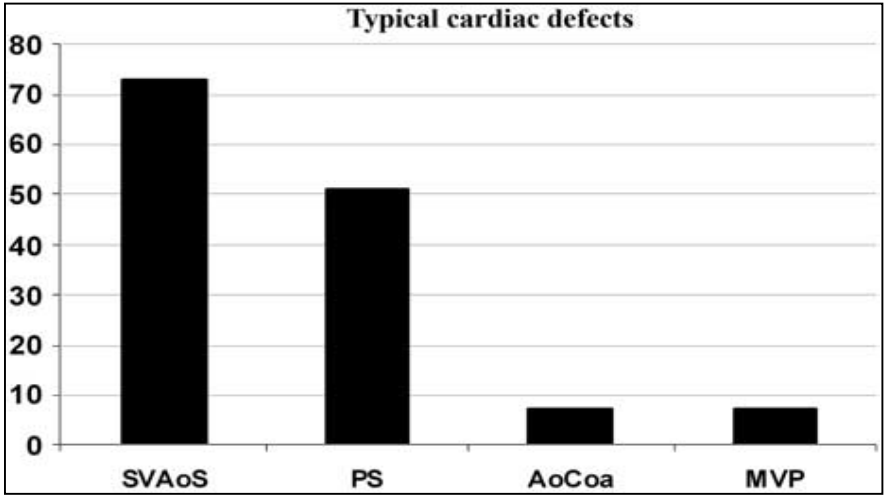
Health Care Supervision for Children With Williams Syndrome

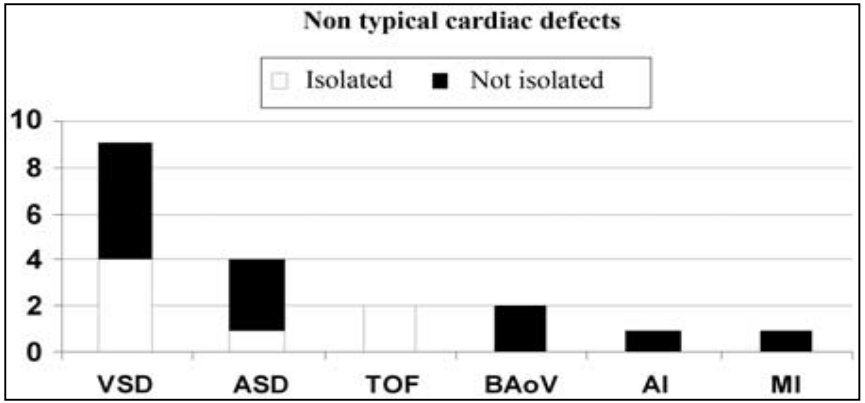
THE DIAGNOSIS

CONGENITAL HEART DEFECT

- SUPRAVALVULAR AORTIC STENOSIS
- PERIPHERAL PULMONARY STENOSIS

TYPICAL AND ATYPICAL

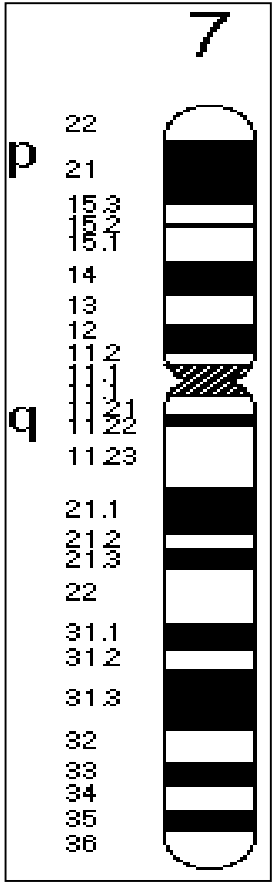




New Findings concerning Cardiovascular Manifestations emerging from Long-term Follow-up of 150 patients with the Williams-Beuren-Beuren syndrome

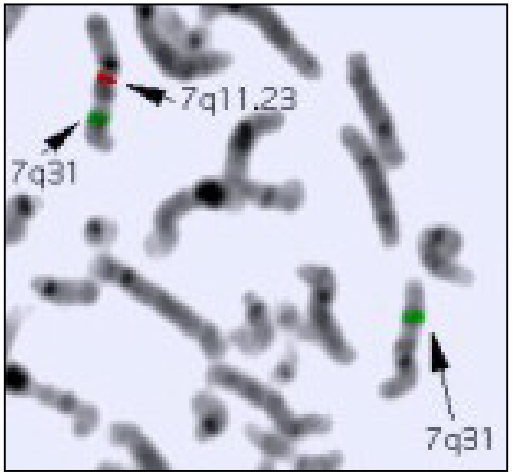
Alessia Del Pasqua, Gabriele Rinelli, Alessandra Toscano, Roberta Iacobelli, Cristina Digilio, Bruno Marino, Claudia Saffirio, Sergio Mondillo, Luciano Pasquini, Stephen Pruett Sanders, Andrea de Zorzi

Cardiology in the Young (2009), 19, 563–567



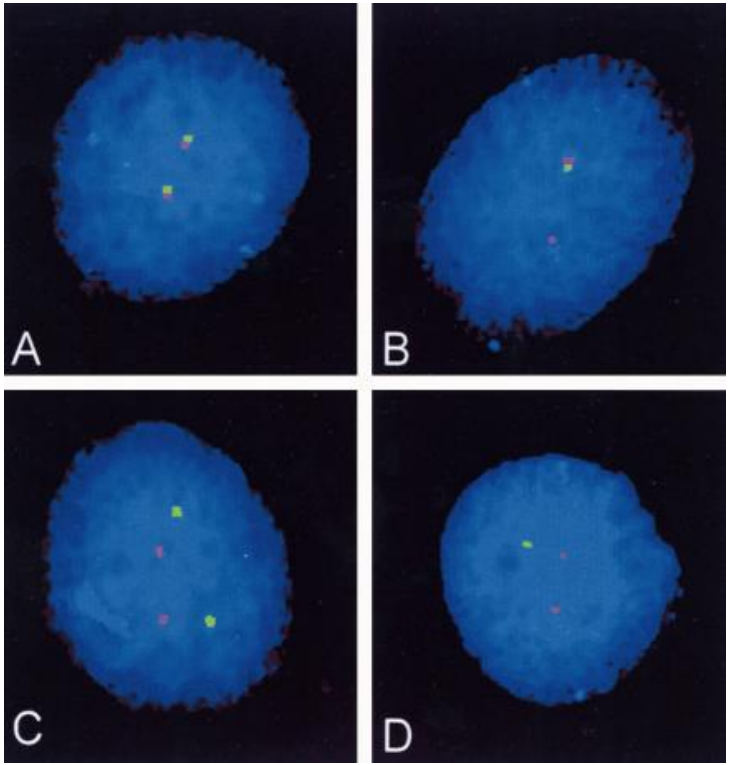
THE DIAGNOSIS

Microdeletion 7q11.23



FISH

Fluorescent in situ hybridization



THE DIAGNOSIS

Diagnosis of DiGeorge and Williams syndromes using FISH analysis of peripheral blood smears

A. Novelli, M. Sabani, A. Caiola, M. C. Digilio, A. Giannotti, R. Mingarelli, G. Novelli* and B. Dallapiccola

Molecular and Cellular Probes (1999) **13**, *303–307*

THE DIAGNOSIS

Atypical deletions

- **ELN gene: cardiovascular malformations and facial anomalies**
- **Geni ELN + LIMK-1: cardiovascular anomalies and typical cognitive profile**
- **Large deletions (HIP1 and YWHAG genes): susceptibility to autistic traits and epilepsy**
- **Deletions excluding BAZ1B and FZD9 genes; mild facial features and moderate cognitive deficit**

Smaller and larger deletions of the Williams Beuren syndrome region implicate genes involved in mild facial phenotype, epilepsy and autistic traits

Fusco C, Micale L, Augello B, Pellico MT, Menghini D, Alfieri P, Digilio MC, Mandriani B, Carella M, Palumbo O, Vicari S, Merla G.

Eur J Hum Genet (2014) 22, 64–70

THE DIAGNOSIS

Atypical deletions

Atypical deletion
DISTAL
NOT including ELN gene

Including
CLIP2, GTF2IRD1 e GTF2I , HIP1 genes

Neurobehavioral phenotype
Facial anomalies
Autism (HIP1)

Atypical 7q11.23 deletions excluding ELN gene result in Williams–Beuren syndrome craniofacial features and neurocognitive profile

Viola Alesi | Sara Loddo | Valeria Orlando | Silvia Genovese | Silvia Di Tommaso | Maria Teresa Liambo | Daniele Pompili | Daniele Ferretti | Chiara Calacci | Giorgia Catino | Roberto Falasca | Maria Lisa Dentici |Antonio Novelli | Maria Cristina Digilio | Bruno Dallapiccola

Am J Med Genet. 2021;185A:242–249

• CLINICAL MANAGEMENT

Clinical Guidelines

- **Dyscherne**
- **American Academy of Pediatrics**
- **Italian guidelines**

Management of Williams Syndrome Clinical Guidelines

Recommendations for the management of Williams Syndrome

~ in neonates & infancy (1) ~

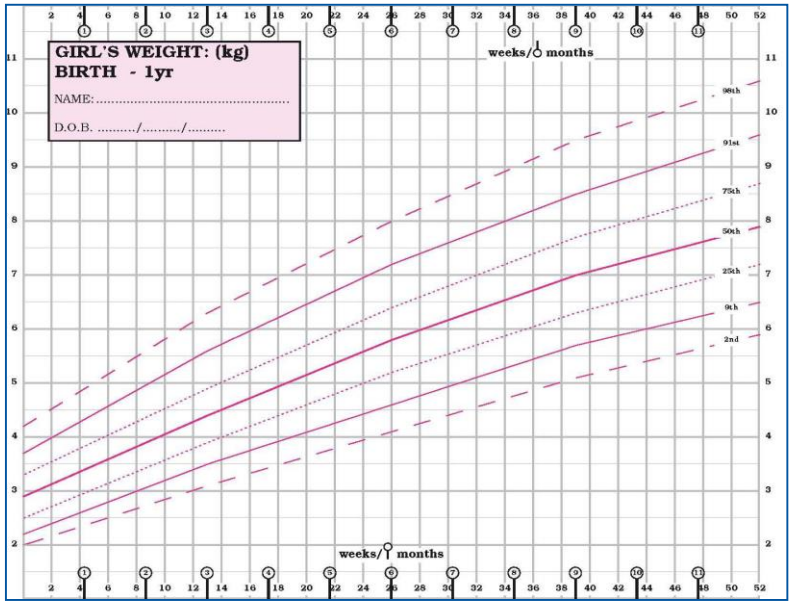
~ in childhood (1) ~

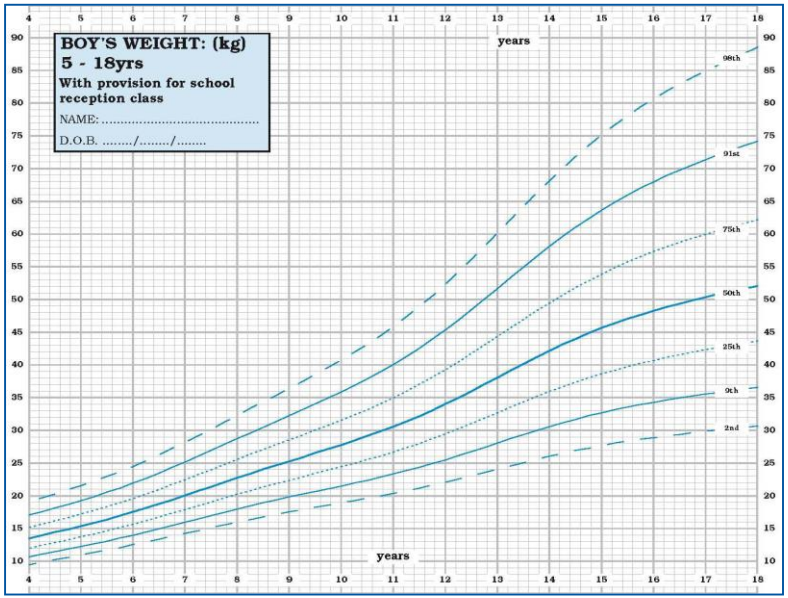
~ in adolescence (1) ~

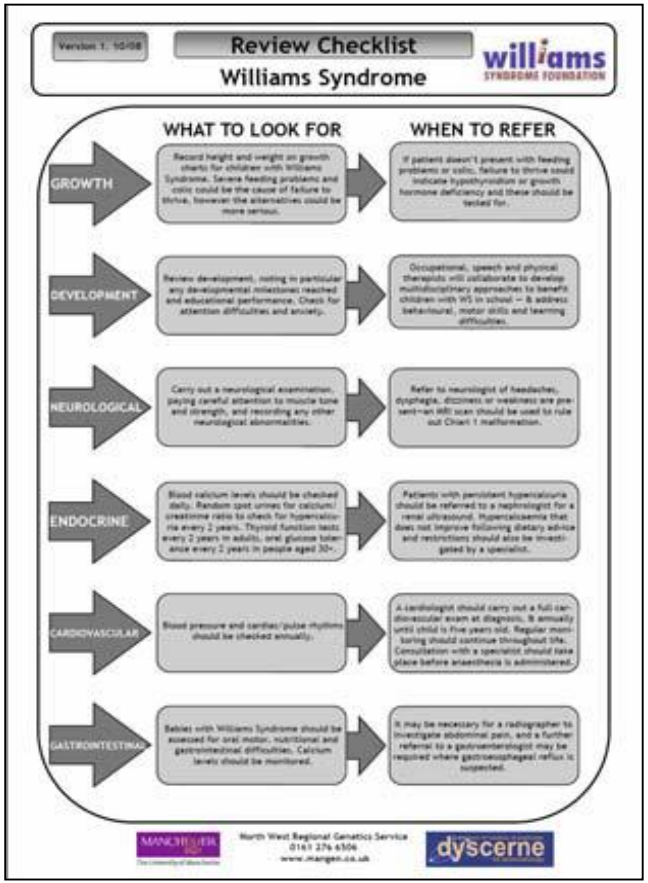
~ in adulthood (1) ~

• CLINICAL MANAGEMENT

Management of Williams Syndrome Clinical Guidelines







Version 1. 10/08

Review Checklist

Williams Syndrome

williams SYNDROME FOUNDATION

	WHAT TO LOOK FOR	WHEN TO REFER
GROWTH	Record height and weight on growth charts for children with Williams Syndrome. Severe feeding problems and colic could be the cause of failure to thrive, however the alternatives could be more serious.	If patient doesn't present with feeding problems or colic, failure to thrive could indicate hypothyroidism or growth hormone deficiency and these should be tested for.
DEVELOPMENT	Review development, noting in particular any developmental milestones reached and educational performance. Check for attention difficulties and anxiety.	Occupational, speech and physical therapists will collaborate to develop multidisciplinary approaches to benefit children with WS in school – to address behavioural, motor skills and learning difficulties.
NEUROLOGICAL	Carry out a neurological examination, paying careful attention to muscle tone and strength, and recording any other neurological abnormalities.	Refer to neurologist of headaches, dysphagia, dizziness or weakness are present–an MRI scan should be used to rule out Chiari 1 malformation.
ENDOCRINE	Blood calcium levels should be checked daily. Random spot urines for calcium/creatinine ratio to check for hypercalciuria every 2 years. Thyroid function tests every 2 years in adults, oral glucose tolerance every 2 years in people aged 30+.	Patients with persistent hypercalciuria should be referred to a nephrologist for a renal ultrasound. Hypercalcaemia that does not improve following dietary advice and restrictions should also be investigated by a specialist.
CARDIOVASCULAR	Blood pressure and cardiac/pulse rhythms should be checked annually.	A cardiologist should carry out a full cardiovascular exam at diagnosis, & annually until child is five years old. Regular monitoring should continue throughout life. Consultation with a specialist should take place before anaesthesia is administered.
GASTROINTESTINAL	Babies with Williams Syndrome should be assessed for oral motor, nutritional and gastrointestinal difficulties. Calcium levels should be monitored.	It may be necessary for a radiographer to investigate abdominal pain, and a further referral to a gastroenterologist may be required where gastroesophageal reflux is suspected.

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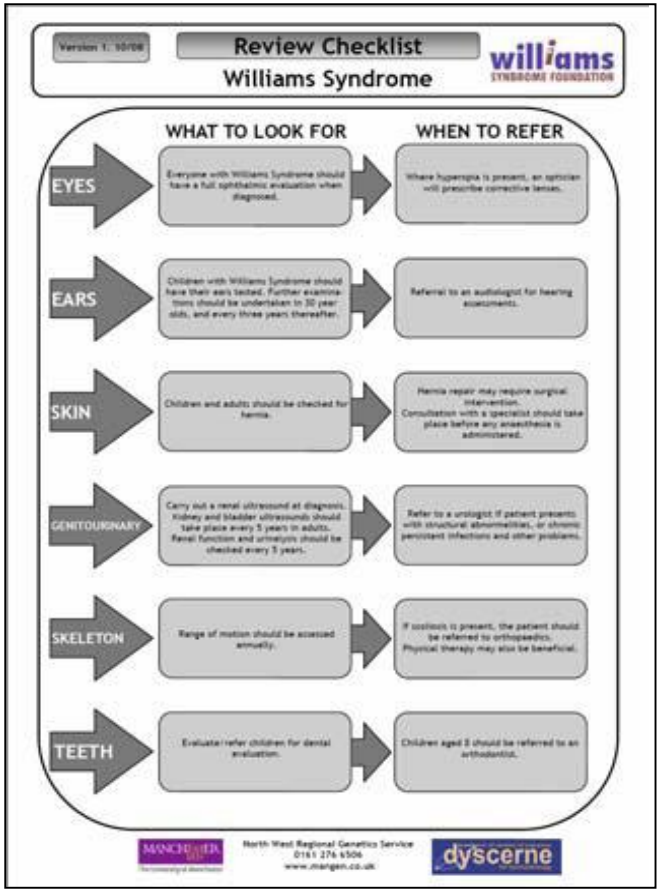
dyscerne



Version 1. 10/08

Review Checklist

Williams Syndrome

williams SYNDROME FOUNDATION

	WHAT TO LOOK FOR	WHEN TO REFER
EYES	Everyone with Williams Syndrome should have a full ophthalmic evaluation when diagnosed.	Where hyperopia is present, an optician will prescribe corrective lenses.
EARS	Children with Williams Syndrome should have their ears tested. Further examinations should be undertaken in 30 year olds, and every three years thereafter.	Referral to an audiologist for hearing assessments.
SKIN	Children and adults should be checked for hernia.	Hernia repair may require surgical intervention. Consultation with a specialist should take place before any anaesthesia is administered.
GENITOURINARY	Carry out a renal ultrasound at diagnosis. Kidney and bladder ultrasounds should take place every 5 years in adults. Renal function and urinalysis should be checked every 5 years.	Refer to a urologist if patient presents with structural abnormalities, or chronic/persistent infections and other problems.
SKELETON	Range of motion should be assessed annually.	If scoliosis is present, the patient should be referred to orthopaedics. Physical therapy may also be beneficial.
TEETH	Evaluate/refer children for dental evaluation.	Children aged 3 should be referred to an orthodontist.

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dyscerne

- CLINICAL MANAGEMENT

FREQUENCY OF CLINICAL FEATURES

- DEVELOPMENTAL DELAY: 97%
- CONGENITAL HEART DEFECT: 80%
- STRABISMUS: 50%
- HERNIAE: 40%
- HYPERTENSION: 20%

• CLINICAL MANAGEMENT

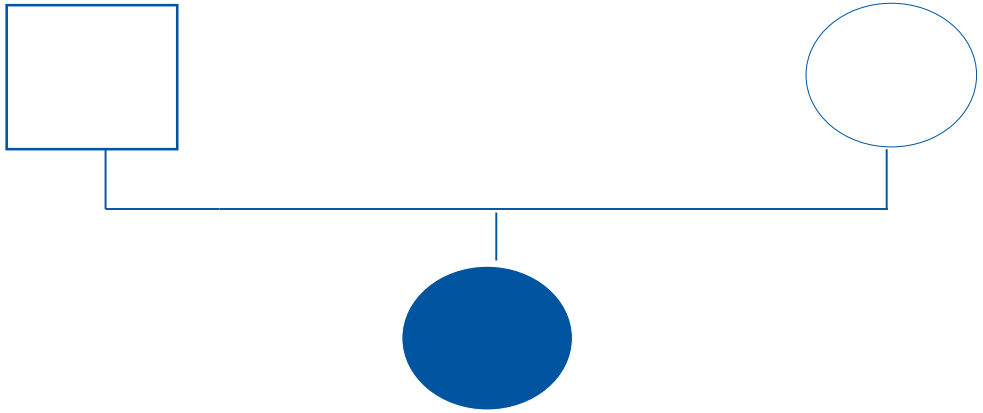
- **Attention to vasculopathies (peripheral, coronaric, cerebral)**
- **Possibility to perform coronaric angiography before cardiac surgery**
- **Consider the possibility to experience intubation difficulties or abnormal reaction to drugs**
- **Attention to miocardial functional anomalies of the left ventricle (also in the absence of SVAS or hypertension)**
- **Attention to coronaric stenosis (also in the absence of SVAS)**

Genetic syndromes and congenital heart defects: how is surgical management affected?

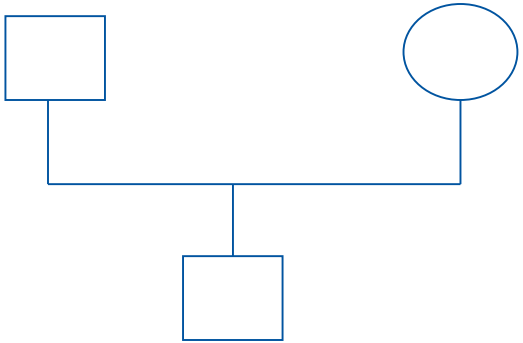
Formigari R, Michielon G, Digilio MC, Piacentini G, Carotti A, Giardini A, Di Donato RM, Marino B.

European Journal of Cardio-thoracic Surgery 35 (2009) 606—614

GENETIC COUNSELING

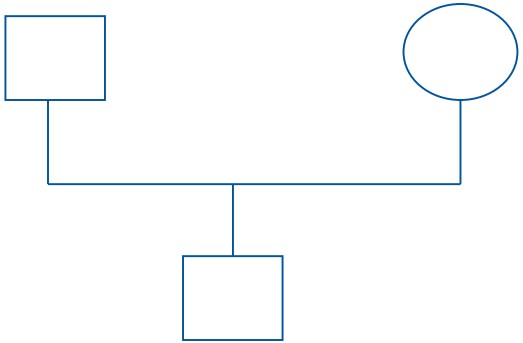


GENETIC COUNSELING



- GENERALLY “DE NOVO” DELETION IN THE FAMILY

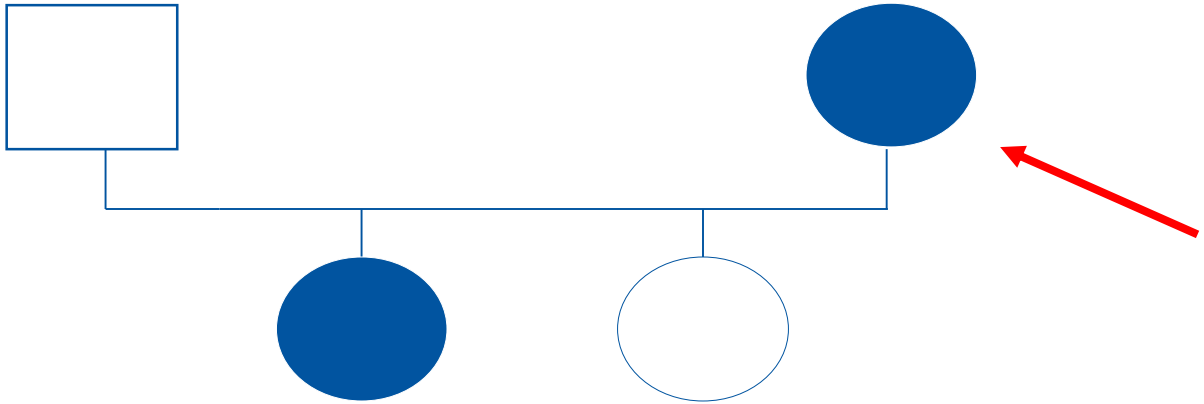
GENETIC COUNSELING



- “DE NOVO” DELETION IN THE FAMILY
- HEALTHY PARENTS: REPRODUCTIVE RISK FOR WS IS THE SAME OF THAT IN GENERAL POPULATION

GENETIC COUNSELING

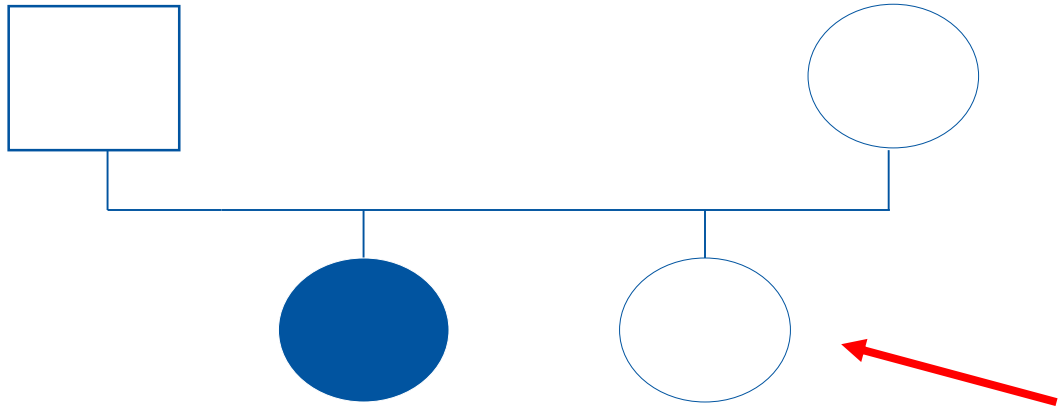
PATIENT WITH WILLIAMS SYNDROME:



RECURRENCE RISK FOR WS : 50%

GENETIC COUNSELING

BROTHERS / SISTERS OF A PATIENT WITH WS



REPRODUCTIVE RISK FOR WILLIAMS SD IS

THE SAME OF THAT OF GENERAL POPULATION

Thank you