Introduction

Williams syndrome is a genetic condition that occurs in 1 out of 20,000-50,000 births. Williams syndrome (WS) is also known as Williams-Beuren syndrome (WBS), idiopathic infantile hypercalcaemia, or Williams elfin face syndrome because of distinctive “elfin” facial features exhibited. It is commonly characterized by infantile hypercalcaemia, growth retardation, distinctive facies, cognitive impairment, an overfriendly personality, and cardiovascular disease including supravalvular aortic stenosis (SVAS). Other WS abnormalities include prematurely wrinkled skin, a hoarse voice, and hyperacusis – sensitive hearing.

History of Williams Syndrome

Williams syndrome was first reported as idiopathic infantile hypercalcaemia in 1952. The syndrome was then described independently by Williams et al. and Beuren et al. as a disorder involving an unusual facies, supravalvular aortic stenosis, and mental deficiency. WS is known for affecting the vascular connective tissue, endocrine and central nervous systems. When Dr. Williams first reported these patient’s clinical features, he had described low IQ’s varying from 42-72 therefore classifying these patients as mentally retarded. He noted: full facies, broad foreheads, widely set eyes, wide mouth, pointed chin, and prominent ears. Most of these children had low birth weights and all of them had blue eyes. Williams’ conclusion was that the presence of supravalvular aortic stenosis in mentally retarded patients with the unusual facial features here constituted a syndrome that had not been previously described.

Years after Dr. Williams made his first description of these children, he was offered a position at the Mayo Clinic in the USA. At the time, he was working in New Zealand and failed to show up for the position at Mayo. He then took a position in London and was once again offered a post at the Mayo Clinic. On his way to the Mayo Clinic, he disappeared, leaving only an unclaimed suitcase in a London luggage office. His whereabouts are still unknown today.

Clinical Presentation

Williams Syndrome can present clinically in various ways depending on many factors, some of which will be discussed later. However, the clinical features of this condition have been very well documented and there are many salient features that are distinctive to the disorder and aid greatly in the diagnosis. Perhaps the most famous is the elastin arteriopathy that present as supravalvular aortic stenosis, which, as mentioned earlier, was the main link between J.C.P. Williams’ patients. In addition to supravalvular aortic stenosis (SVAS), other peripheral pulmonary artery stenosis may be seen. In infancy, children with Williams Syndrome tend to have hypotonia and feeding difficulties, resulting in failure to thrive. Intrauterine growth retardation is seen in 35% of girls and 22% of boys with post-natal growth rates being about 75% of normal. Infants also have hyperextensible joints, which can contribute to delayed attainment of motor milestones. Hyperopia, strabismus, urinary frequency, enuresis, and chronic otitis media are seen in approximately 50% of patients. Williams Syndrome patients also have dental abnormalities including: microdontia, enamel hypoplasia, and malocclusion. Other complications include: renal anomalies including structural abnormalities of the urinary tract, esotropia, hypoplastic nails and hallux valgus.

Individuals with Williams syndrome are very distinct in their appearance, with facial characteristics often referred to as “elfin-like”. The facies show medial eyebrow flare, short palpebral fissures, depressed nasal bridge, epicanthal folds, periorbital fullness of subcutaneous tissues, antverted nares, a long philtrum and prominent lips with an open mouth. Many patients display a hoarse voice, which could be due to the reduced level of elastin resulting from a deletion of the elastin producing gene. Short stature is also very common, and in combination with the facial voice and behavioral characteristics of William Syndrome, it is easy to see why it has been suggested that the mythological elfin people were actually simply people with Williams Syndrome. Blue irides are seen in 77% of individuals, and a stellate iris pattern is seen in 51% of Williams Syndrome patients compared with 12% in a control group.
exemplified by the fact that they rarely forget names or social details of individuals that they meet. Children with Williams syndrome perform better on tests and tasks that require auditory input and verbal output than on tasks that require visual spatial construction or motor skill. Persons with WS are better at using social perception cues to solve problems (e.g., facial expressions), as opposed to social cognitive processes (e.g., complex understanding of the mind). Individuals with WS perform relatively well in reading, and adults may read at the high school level.

A common personality trait that has been observed is overfriendliness, especially toward complete strangers. This has been described as a "cocktail party personality," and brings with it a challenge for parents of children with Williams syndrome as they must be taught to suppress this personality trait in order to avoid exploitation. In one study of social and behavioral adjustment in children with WS, 79% of children were rated as behaving in a friendly and extroverted way. Generalized anxiety, excessive empathy, a loquacious personality, perseverative behaviors, sleep difficulties, and attention deficit disorder are all common in WS.

A reported affinity towards music among individuals with WS has resulted in the identification of an interesting aspect of their abilities; their musical abilities are higher than their overall cognitive abilities. While their attention span for many tasks is fleeting, they will spend hours listening to or making music. An excellent example is an individual with Williams syndrome who performs as a soprano singer and can sing nearly 2500 songs in more than 25 languages with a perfect accent and pitch. This ties in with a study completed at the University of California, Irvine that links Williams syndrome to a higher incidence of absolute or perfect pitch, a condition that normally occurs in one out of 10,000 people in Western populations.

When social interaction is addressed among people with Williams syndrome, they are found to be drastically less well adjusted than the control individuals. While some children with WS are described as being difficult, other descriptions include: hyperactive and antisocial. Adolescent subjects exhibited a strong desire for social interaction and relatively good literal language skills, but were able to distinguish between lies and ironic jokes in a psychological research study. This inability to distinguish different types of social, non-literal language was common among WS patients. The implication being that individuals with WS are not as socially mature as one would expect, especially in light of their good verbal communicative skills.

**Geneic Etiology**

The vast majority (90-99%) of individuals with clinically typical Williams Syndrome have a deletion of the gene at the locus 7q11.23, almost all of which are de novo deletions. This gene deletion may be found on either the paternally or maternally inherited chromosome with no phenotypic differences being seen between the two. The only gene to be undeniably linked to a particular aspect of Williams Syndrome is the ELN gene which codes for elastin, an elastic fiber found in the extracellular matrix of many tissues. Deletion of one copy of the ELN gene and the subsequent reduction in elastin levels is manifested primarily in the presence of SVAS and other cardiovascular difficulties. In addition to the cardiovascular phenotype, Jurado also suggests that ELN haploinsufficiency is responsible for other phenotypic traits such as: periorbital fullness, thick lips, skin and joint anomalies, inguinal hernias and diverticula of the bladder and intestine. It has previously been thought that a deletion of the LIMK1 gene was responsible for some of the visual-spatial deficits in Williams syndrome. However, recent studies by...
Karloff-Smith et al show that patients with smaller deletions involving the LIMK1 gene show no similarities with the Williams Syndrome cognitive profile. Jurado has suggested that the genes STX1A and CYL2 show promise as functional candidates for involvement in important brain functions, and they do show specific activity in the brain. Karloff-Smith et al have provided some support for this idea by providing evidence that phenotypic features apart of SVAS are caused by genes in the CYL2-NC1F2 region of the Williams Syndrome critical region. Much work remains to be done in the area of genotype-phenotype correlation in Williams Syndrome. Fortunately, great advancements are being made each year in this field as technology and awareness of this syndrome improve allowing greater ease of study and a more broad base of patients for evaluation, ultimately leading to a greater understanding of Williams Syndrome.

Gene map of commonly deleted region 7q11.2 in Williams syndrome with brief clinical phenotype corresponding to deletions of varying size. (Jurado, 2003)

**Diagnosis**

Aside from clinical diagnosis of the disorder, the most common method of confirming or making a diagnosis is by use of a fluorescent in situ hybridization (FISH) probe specific for the Williams Syndrome critical region. The probe spans approximately 160kb and includes the genes ELN, LIMK1, and D7S613. Since the great majority of individuals have a deletion of these genes, FISH testing is the standard diagnostic tool. However, mutation analysis of these genes is also available, and these may be useful in rare instances or for research investigations. Using real time quantitative PCR, the dosage of the genes ELN, LIMK1, and GTF2I can be determined and a deletion can be detected. Also, testing of short tandem repeats (STRs) in the Williams Syndrome critical region to determine if there is heterozygosity of the genes is feasible. While this should be as sensitive as the other two, it is primarily usually used for determination of the size of deletion rather than its presence.

**References**

8. Mervis, Carolyn. Williams Syndrome: 15 years of Psychological

**Organizations**

**WILLIAMS SYNDROME ASSOCIATION**

Website: [http://www.williams-syndrome.org/](http://www.williams-syndrome.org/)

The Williams Syndrome Association was formed in 1982 by, and for, families of individuals with Williams syndrome. It is the only group in the US devoted exclusively to improving the lives of individuals with Williams syndrome and their families. The WSA supports research into all facets of the syndrome, and the development of the most up to date educational materials regarding Williams syndrome.

For more information, visit website above or contact:

Telephone: 1-800-806-1871

Mail: Williams Syndrome Association
PO Box 297
Clawson, MI 48017-0297

**WILLIAMS SYNDROME FOUNDATION**

Website: [http://www.wsf.org/](http://www.wsf.org/)

The Williams Syndrome Foundation (WSF) seeks to create or enhance opportunities in education, housing, employment and recreation for people who have Williams Syndrome and other related or similar conditions. The WSF identifies, initiates, funds and provides strategic guidance for major, long-range development projects, either by itself, or by cooperating with other organizations.

For more information, visit above website or contact:

Mail: Williams Syndrome Foundation
University of California
Irvine, CA 92697-2300

Telephone: 949-824-7259

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12. Jones, Ken L. Smith's Recognizable Patterns of Human Malformation, 5th ed. pp 118-121

About the RCPU

The Raymond C. Phillips Research and Education Unit began in 1976 when the legislature established section 393.20 of what is now known as the "prevention" legislation. It is named after Raymond C. Phillips, who was the Superintendent of Gainesville's Tocachale (formerly Sunland) Center for 38 years, and was an acknowledged state and national leader in services for mentally retarded persons. The Unit is located on the Tocachale campus and is funded through a contract with the Department of Children and Families and the Department of Health, Children's Medical Services.

The purpose of the R.C.P.U. is to treat, prevent, and/or ameliorate mental retardation through medical evaluations, education and research. The unit provides direct evaluations and counseling to families and promotes service, education, and prevention projects. Some of the conditions currently under study at the RCPU involve Angelman, Velo-Cardio-Facial, Prader-Willi, Fragile X, Williams and Smith-Lemli-Opitz syndromes.

Acknowledgments:

The R.C. Phillips Unit is a resource for all Floridians interested in the diagnosis, treatment and prevention of mental retardation. Staff members are available for consultation and for educational programs for health professionals and for the community at large. The RCPU Newsletter is funded by the Raymond C. Phillips Research and Education contract with the Department of Health, Children's Medical Services.