

# Williams Syndrome / Williams-Beuren Syndrome

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## First descriptions:

The syndrome was first described by Williams et al. (1961) in four patients with supravalvular aortic stenosis (SVAS) in association with intellectual disability and an unusual facial appearance, and by Beuren et al. (1964). Black and Carter (1963) associated this characteristic facial appearance with that found in idiopathic infantile hypercalcaemia, a name initially used for the syndrome.

## Genetic aspects:

Williams syndrome is a genetically determined neurodevelopmental disorder caused by a heterozygous deletion of about 1.6 Mb (approx. 26-28 genes) on chromosome 7 (7q11.23). A deletion of the elastin gene (ELN) which occurs in >99% of individuals with WS) is associated with congenital heart disease and connective tissue abnormalities including hernias and premature ageing of the skin. Several genes are also implicated in the intellectual disabilities and cognitive deficits observed in WS, including GTF2I, LIMK1 and CYLN2 (see Morris, 2017 for review). Transmission is autosomal dominant and although most cases are de novo occurrences, some instances of parent to child transmission have been reported (Donnai & Karmiloff-Smith, 2000).

## Incidence:

The condition is estimated to occur in 1 per 20,000 individuals although higher rates (1 in 7500) have been reported (Morris, 2017).

## Physical phenotype and natural history:

The condition typically presents in infancy with difficulties in feeding, irritability, constipation and failure to thrive. The physical phenotype is remarkably consistent across the world (Kruszka et al., 2018) and the principal characteristics are well summarised by Morris (2017). The main features include: endocrine and growth abnormalities (pre-natal growth deficiency, failure to thrive in infancy, infantile hypercalcaemia, hypercalciuria, hypothyroidism, early puberty); cardiovascular disease (mainly supravalvular aortic stenosis) and renal abnormalities; connective tissue abnormalities (hoarse voice, inguinal/umbilical hernia, bowel/bladder diverticulae, rectal prolapse, joint and skin laxity), and distinctive facies (broad brow, short nose, long philtrum, bitemporal narrowness, periorbital fullness, full lips, wide mouth, malocclusion, small jaw and prominent earlobes).

With age, subcutaneous tissue is lost, giving rise to a prematurely aged appearance. Premature greying of the hair occurs in many adults. A characteristic posture may develop with sloping shoulders, exaggerated lumbar lordosis and flexion at the hips and knees. Progressive multi-system medical problems have been reported in some adults, which can

lead to premature death. These include cardiovascular complications, gastrointestinal problems and urinary tract abnormalities. Progressive joint limitations are also common.

### **Behavioural and psychological characteristics:**

Most individuals have moderate to mild intellectual impairments, although some may be of low-average to average IQ (Royston et al., 2019). Overall cognitive ability generally remains fairly stable across the life span (Fisher et al., 2016) but verbal IQ is typically higher than non-verbal IQ and there are complex, and often subtle, pattern of peaks and valleys within each of these domains. Research into the nonverbal abilities of individuals with WS has highlighted particular deficits in domains such as number skills, planning, problem solving and spatial cognition. In contrast, face processing and some aspects of social cognition tend to be relative strengths. Within the verbal domain, auditory rote memory and receptive vocabulary are viewed as strengths, while spatial language (e.g. using spatial terminology), expressive vocabulary, syntax, semantics and grammatical comprehension are generally delayed (see Martens et al., 2008; Skwerer & Tager-Flusberg, 2011; Royston et al., 2019 for reviews); pragmatic language difficulties may also become more apparent with age (Van Den Heuvel et al., 2016). Adaptive behaviour skills are often relatively poor (Howlin et al., 2010) but research findings on the association between IQ and adaptive behaviour are inconsistent. Profiles of adaptive functioning also vary with age although Social/Communication skills tend to be more advanced than Daily Living Skills, especially in children and adolescents (Brawn and Porter, 2018).

Individuals with WS tend to show particular patterns of emotional and behavioural difficulties (Einfeld et al., 2001; Morris, 2017). An intense drive for social interaction is one of the most characteristic traits and is evident from early childhood (Riby et al., 2017). However, older children and adults with WS have difficulties making and sustaining friendships and because of their desire to make social contact they have a high risk of being bullied, exploited or abused (Fisher et al., 2017; Fisher & Morin, 2017). Other difficulties include hyperacusis, attentional problems, impulsivity, and externalizing (oppositonality and aggression) and internalizing problems (anxiety and withdrawal) (Klein Tasman et al., 2017; Royston et al., 2019). A significant minority of children shows autistic-type symptoms (social communication deficits, stereotyped and repetitive behaviours; Klein Tasman et al., 2018); however, reported rates of self-injurious behaviours are lower than in other genetic developmental disorders (Huisman et al., 2018)

Rates of mental health problems in adulthood are high and include phobias, preoccupations and obsessions, depression, bipolar disorder and hypomania. The most commonly reported mental health problem is anxiety, which occurs more often in WS than in individuals with other developmental genetic disorders and is significantly more frequent than in the general population (Royston et al 2017; Stinton et al., 2010; 2012)

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#### **Further information**

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

**Patricia Howlin 2019**

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