



Williams syndrome

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Abstract | Williams syndrome (WS) is a relatively rare microdeletion disorder that occurs in as many as 1:7,500 individuals. WS arises due to the mispairing of low-copy DNA repetitive elements at meiosis. The deletion size is similar across most individuals with WS and leads to the loss of one copy of 25–27 genes on chromosome 7q11.23. The resulting unique disorder affects multiple systems, with cardinal features including but not limited to cardiovascular disease (characteristically stenosis of the great arteries and most notably supravalvar aortic stenosis), a distinctive craniofacial appearance, and a specific cognitive and behavioural profile that includes intellectual disability and hypersociability. Genotype–phenotype evidence is strongest for *ELN*, the gene encoding elastin, which is responsible for the vascular and connective tissue features of WS, and for the transcription factor genes *GTF2I* and *GTF2IRD1*, which are known to affect intellectual ability, social functioning and anxiety. Mounting evidence also ascribes phenotypic consequences to the deletion of *BAZ1B*, *LIMK1*, *STX1A* and *MLXIPL*, but more work is needed to understand the mechanism by which these deletions contribute to clinical outcomes. The age of diagnosis has fallen in regions of the world where technological advances, such as chromosomal microarray, enable clinicians to make the diagnosis of WS without formally suspecting it, allowing earlier intervention by medical and developmental specialists. Phenotypic variability is considerable for all cardinal features of WS but the specific sources of this variability remain unknown. Further investigation to identify the factors responsible for these differences may lead to mechanism-based rather than symptom-based therapies and should therefore be a high research priority.

Williams syndrome (WS; also known as Williams–Beuren syndrome; OMIM 194050) is a distinctive multi-system disorder (FIG. 1, Supplementary Box 1). The most common areas of involvement include the cardiovascular, central nervous, gastrointestinal and endocrine systems, although any organ system could be affected. The recognition of WS as a distinct clinical syndrome dates back to the mid-twentieth century^{1–3} and knowledge of the phenotype has steadily expanded over the ensuing ~60 years.

We now know that cardiovascular disease is present in most individuals with WS^{4–6}, with the most frequent abnormalities involving vascular stenoses of medium-sized and large-sized arteries (referred to as elastin arteriopathy)⁷. Depending on the location, severity and timing of onset, the management of the vasculopathy consists of non-invasive or surgical interventions complemented by lifelong monitoring. Additional cardiovascular features include hypertension and a small but increased risk of cardiovascular sudden death^{8–12}. The neurodevelopmental phenotype is unique and multifaceted. Mild-to-moderate intellectual disability is

common but not universal and is seen in conjunction with a distinct cognitive profile of relative strengths and weaknesses^{13,14}. In addition, there is a characteristic personality profile that includes overfriendliness, shortened attention span and/or distractibility, non-social specific phobias, and anxiety^{15,16}.

The genetic basis of WS was first identified in 1993, when fluorescence in situ hybridization (FISH) studies showed the deletion of an elastin allele (*ELN*) on chromosome 7q¹⁷. We now know that WS is caused by a <2-megabase pair (Mb) microdeletion on chromosome 7q11.23 and that the local genomic architecture predisposes to the de novo occurrence of this deletion¹⁸. Individuals with WS are therefore hemizygous for the 25–27 genes that map to this interval and the reduction in the gene product of several key genes contributes to specific aspects of the WS phenotype.

Since WS was initially described, advances have been made in our understanding of the complexity and changing nature of the phenotype, the genetic basis of WS, the mechanisms that lead to selected phenotypes, and the benefit of certain interventions.

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Yet, many more unanswered questions remain. Accordingly, our ability to optimize care and improve outcomes is modest. In this Primer, we provide a snapshot of selected WS features across the lifespan, outline current and emerging diagnostic technologies, discuss the genetic basis of some of the most impactful WS features, and elaborate on the pathophysiological mechanisms, where known. This information is key for the formulation of high-priority future research questions, the answers to which could accelerate WS-specific treatments.

Epidemiology

WS is a rare pan-ethnic genetic condition. Although this syndrome has been described in different populations around the world, most reports address clinical and molecular findings, with little focus on epidemiological data. The most widely cited epidemiological study is from Norway¹⁹, which reports a prevalence of 1 in 7,500 live births, a higher prevalence than that often cited in many non-epidemiological sources^{20,21}. WS is sufficiently rare that it is unfamiliar to most doctors, scientists and researchers.

The age of diagnosis of WS has trended towards younger ages over the past decades, most notably in high-income countries with greater availability of molecular diagnostic testing. In cohorts from the USA and Australia, the median age of diagnosis decreased by more than 2 years to around 1 year of age since the 1980s (B.A.K. and M.P., unpublished work). However, series from other countries indicate that diagnosis is often still established during childhood rather than in infancy, even with access to molecular confirmation^{22,23}. Several studies reported particular difficulty in diagnosing WS in African populations (or in those of African descent)^{24–26} owing to a variety of factors. Unfortunately, nearly all studies on WS, independent of topic, describe Caucasian individuals and few studies whose participants represent diverse populations have been published²⁷. Of note, the absence of clinically evident cardiovascular disease was associated with later diagnosis²⁸.

The prevalence of WS is comparable in males and females^{5,29}. However, males are more likely to have severe cardiac disease³⁰, especially supravalvar aortic stenosis (SVAS)^{29,31}. There is no evidence that WS prevalence changes with parental age. Moreover, consistent differences in phenotype have not been associated with the sex of the transmitting parent (that is, whether the deletion arose in the sperm or the egg)^{18,32}.

Vascular anomalies, such as SVAS and stenosis of other large arteries, including the pulmonary arteries, descending aorta, renal, mesenteric and coronary arteries, contribute to morbidity and mortality across the lifespan⁴. Other features, such as diverticular disease and aortic or mitral valve dysfunction, may also influence mortality in older age groups but are, to date, insufficiently quantified in the literature. Sudden death incidence has been reported as 1:1000 patient-years and is often associated with the administration of sedation or anaesthesia for cardiac surgery; this rate is 25 to 100 times higher than in the age-matched general population¹². Several adult cohorts have been described with participants as old as 86 years of age but few studies have included long-term adult follow-up^{33,34}, making it difficult to accurately estimate the life expectancy of individuals with WS.

Mechanisms/pathophysiology**General mechanisms underlying WS**

In the 1990s, compelling evidence emerged indicating that WS is a genetic disorder with an autosomal dominant mode of inheritance^{35–38}. Non-genetic risk factors are not known to contribute to the occurrence of WS.

Genomic structure and rearrangements. WS is caused by the pathological loss of the WS critical region (WSCR), a 1.55–1.83 Mb region that encompasses 25–27 unique protein-coding genes on chromosome 7q11.23. The WSCR frequently undergoes rearrangement due to the presence of large, complex segmental duplications termed low-copy repeats (LCRs), which are highly similar to one another and flank the WSCR³⁹. The LCRs extend for several hundreds of kilobases, are comprised of genes and pseudogenes organized into distinct blocks (designated A, B and C), and contain extensive stretches of >99% nucleotide identity. They are thought to have emerged during primate evolution, first by duplication of smaller segments and later by transposable element (for example, *Alu*-mediated) shuffling, to produce the complex arrangement that exists in humans today⁴⁰.

The LCRs mediate non-allelic homologous recombination (NAHR) events between the highly similar DNA sequences during meiosis, resulting in an increased rate of de novo copy number variation (CNV) events within the region^{39,41–43} (FIG. 2). The WS deletion commonly occurs through NAHR between B block sequences in direct orientation with respect to each other, with the specific breakpoints depending on the precise site of NAHR³⁹. The reciprocal event (that is, the duplication of the same genomic area) produces a condition referred to as 7q11.23 duplication syndrome, resulting in three copies of each WSCR gene. Recombination between B blocks (LCRs with the highest nucleotide identity) in an inverted rather than direct orientation results in an inversion of the intervening chromosome segment⁴² (FIG. 2). This inversion, which is present in 6–7% of the general population⁴⁴, does not cause symptoms⁴⁵ but seems to increase the incidence of subsequent meiotic rearrangements^{42,44}. Other LCR-specific rearrangements have also been observed at a higher frequency in the transmitting parents of children with WS⁴¹.

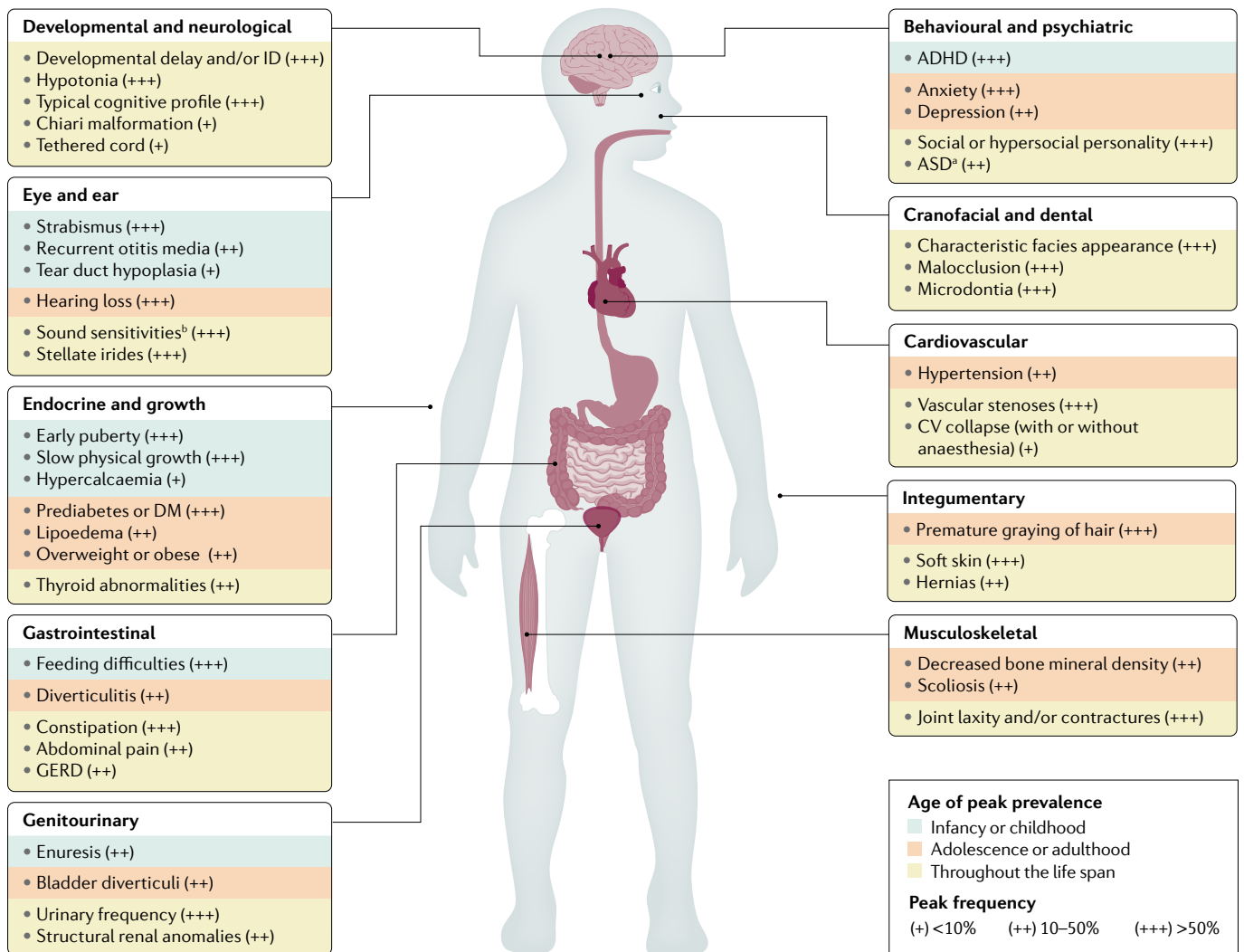


Fig. 1 | **Salient features of Williams syndrome.** The age of peak prevalence and the frequency of prominent signs or symptoms in organ systems affected in Williams syndrome (WS) are indicated. Further reading for selected features that were not the focus of the review is included in Supplementary Box 1. ^aEstimates of co-occurring autism spectrum disorder (ASD) vary (12–20%). Most individuals with WS who have ASD fit in Wing and Gould's²⁹³ active-but-odd subtype of ASD²³³ rather than the aloof subtype of ASD. As such, the diagnosis of and interventions for ASD in WS are complex and ideally benefit from the engagement of practitioners who are knowledgeable about both disorders. ^bSound sensitivities include one or more of the following: hyperacusis, odynacusis, auditory allodynia and auditory fascinations. ADHD, attention-deficit/hyperactivity disorder; CV, cardiovascular; DM, diabetes mellitus; GERD, gastro-oesophageal reflux disease; ID, intellectual disability.

Atypical deletions. While most deletions span the typical 1.55–1.83 Mb interval at 7q11.23, there are individuals with rare deletions that encompass smaller or larger segments of the WSCR, often with one common and one unique breakpoint. Larger deletions that extend beyond the WSCR generally cause additional features. When these deletions extend towards the telomere and span the *YWHAG* and/or *MAGI2* genes, seizures are common^{46,47}, although there are reports of epilepsy in individuals with the typical deletion⁴⁸. Inclusion of the *AUTS2* gene on the centromeric side may result in a smaller head size than is usually seen in WS⁴⁹ and larger deletions can also alter the characteristic WS behavioural profile^{49,50}. The deletion of *HIP1* (formerly *HSP27*) in particular has been associated with more severe intellectual disability^{50,51}.

Smaller deletions result in a subset of the phenotypic features seen in classic WS^{40,50,52–64} but clear-cut correlations between deletion size and specific phenotypic features are challenging, with the exception of *ELN*. This is likely due to the paucity and variety of small deletions, differing methods for phenotypic assessment and the high likelihood of the combinatorial effects of gene deletion. Several specific genotype–phenotype relationships are discussed in the next section.

Genomic analyses. CNV events of the 7q11.23 region have been shown to affect both gene transcription and DNA methylation across the entire genome. Initial studies in WS lymphoblast cell lines identified the dysregulation of genes involved in glycolysis and neuronal migration⁶⁵, while subsequent studies of blood RNA highlighted the

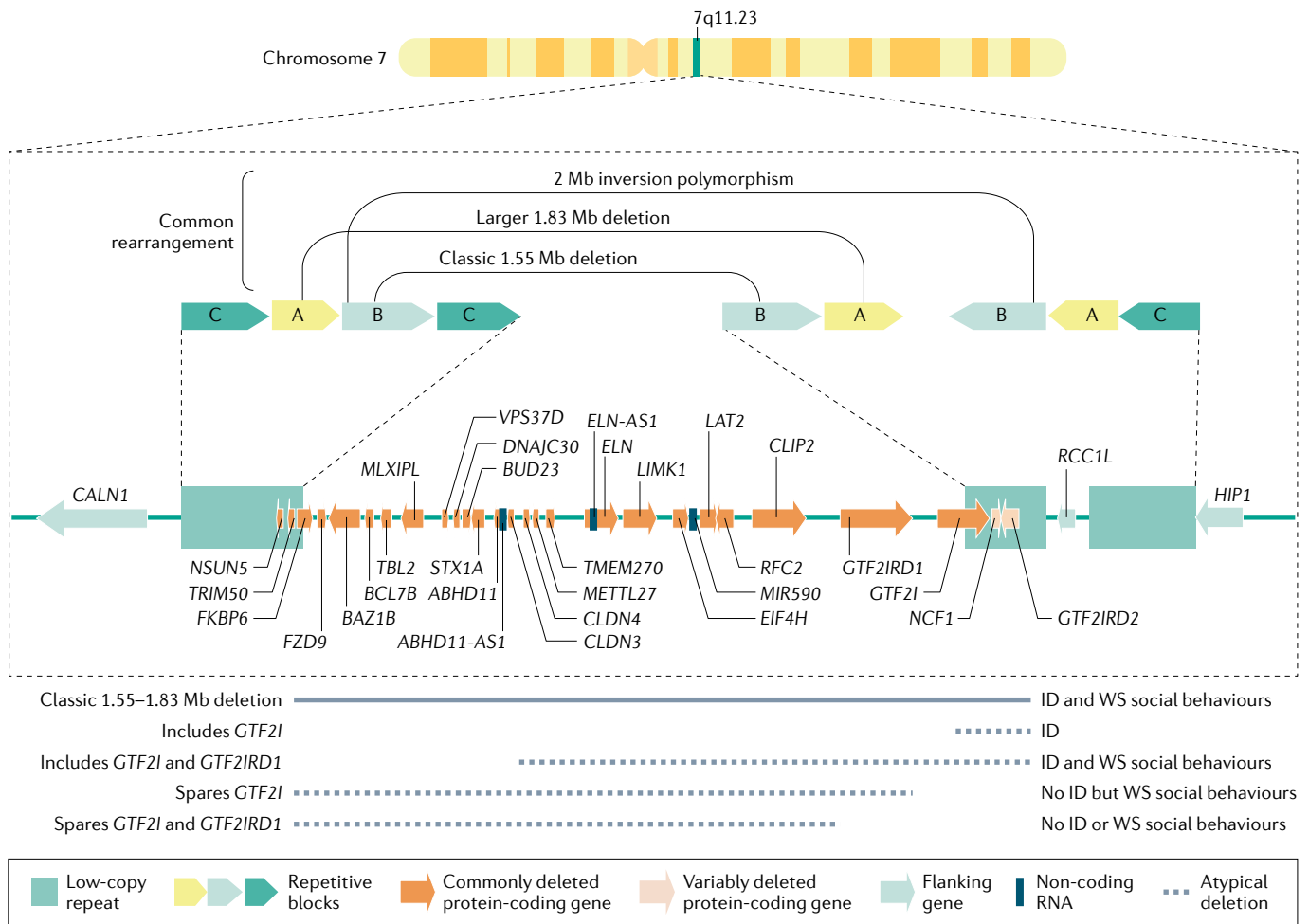


Fig. 2 | Genomic organization of the Williams syndrome critical region. The vast majority of Williams syndrome (WS) deletions (~90%) span a 1.55-megabase pair (Mb) region encompassing 25–27 protein-coding genes in the WS critical region on chromosome 7q11.23, with the remainder being slightly larger (1.83 Mb)³⁹. The larger, less common deletion occurs between low-copy repeats designated as ‘A blocks’, which are present in the great apes, whereas the smaller, more common deletion occurs between ‘B blocks’, which are only present in humans. B blocks originate from a more recent evolutionary duplication event and have a higher sequence identity than A blocks⁴⁰. The WS deletion commonly occurs through non-allelic homologous recombination between B block sequences in direct orientation with respect to each other³⁹; however, recombination between B blocks in an inverted orientation also occurs, resulting in inversion of the intervening chromosome segment⁴². Smaller, atypical deletions occur infrequently but can provide valuable insight into the genotype–phenotype relationship^{59,62,138–140}. Several names exist for many of the genes mapping to the WS critical region (see REF.²⁹⁴ and NCBI Gene). ID, intellectual disability. Adapted from REF.²⁹⁵, Springer Nature Limited.

upregulation of three gene expression modules linked to B cell activation, RNA processing and RNA transport⁶⁶.

Transcriptome analysis of more relevant cell types has been made possible by the ability to reprogramme somatic cells into induced pluripotent stem cells (iPSCs) and direct them down specific cell lineages⁶⁷. For example, iPSC-derived cortical neurons from individuals with WS show reduced expression of genes involved in neurotransmitter receptor activity, synaptic assembly and potassium channel complexes⁶⁸. A comparison of gene expression in WS iPSCs with those from individuals with 7q11.23 duplication syndrome revealed that many of the differentially expressed genes have a symmetrically opposite pattern of expression⁶⁹. A similar symmetrical gene–dose-dependent pattern was seen in DNA methylation analysis of blood DNA from individuals with WS (7q11.23 deletion) and those with the

7q11.23 duplication syndrome⁷⁰, suggesting that CNV in this area affects the epigenetic regulation of the genome.

Molecular mechanisms

The WSCR contains 25–27 genes and several non-coding RNAs. Knowledge about how each of these genes contributes to the WS phenotype is still growing (FIG. 3). Several mouse models inform these efforts, including single-gene knockouts as well as deletion of the entire WSCR (complete deletion (CD))^{71–73} and two half-deletions (proximal deletion (PD) and distal deletion (DD))⁷⁴. To refine genotype–phenotype correlations, we will focus only on selected single-gene knockout models.

Seven genes (*BAZ1B*, *VPS37D*, *STX1A*, *LIMK1*, *CLIP2*, *GTF2IRD1* and *GTF2I*) have a probability of loss-of-function intolerance (pLI) score of 0.9 or higher⁷⁵, suggesting that only a subset of the genes in the WSCR

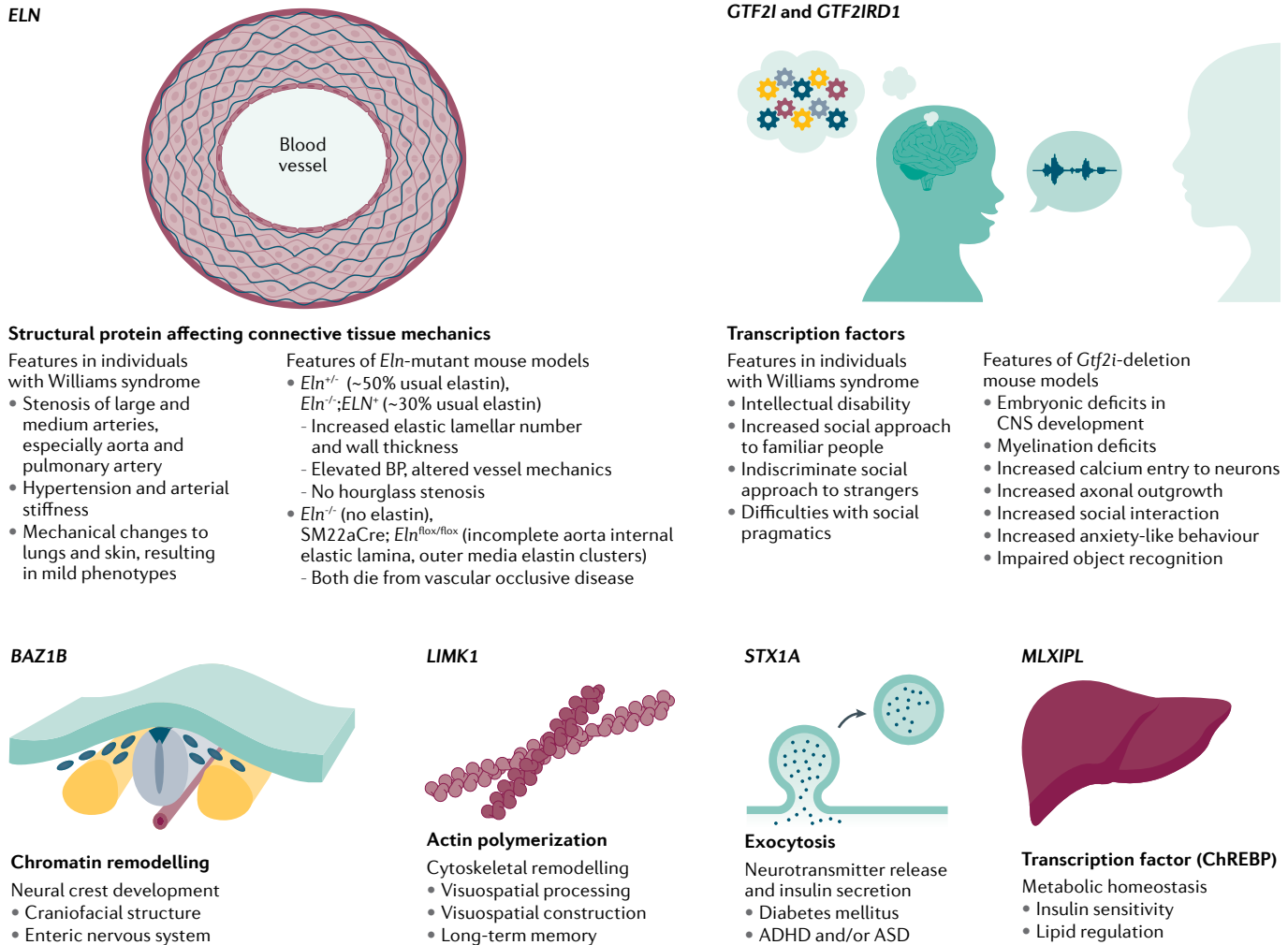


Fig. 3 | Phenotypic consequences of deleting key genes in the Williams syndrome critical region. Putative or elucidated genotype–phenotype relationships for six genes in the Williams syndrome critical region are depicted, including *ELN*, *GTF2I* and *GTF2IRD1*, *BAZ1B*, *LIMK1*, *STX1A* and *MLXIPL*, which encodes carbohydrate-responsive element-binding protein (ChREBP). Phenotypes in mouse models and in individuals with Williams syndrome are indicated for *ELN* and the *GTF2I* genes because, at present, their mechanisms of action are best delineated and they offer the best targets for therapy. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BP, blood pressure; CNS, central nervous system.

directly contributes to phenotype. A pLI score is calculated by examining the frequency of loss-of-function variants in a population; fewer variants than expected is associated with a higher score and implies a greater likelihood of pathogenicity. It is important to point out that the gene with the greatest support for a role in the phenotypic consequences of WS is *ELN*, which has a pLI of 0. Similarly, considerable evidence implicates the deletion of *MLXIPL* (pLI = 0.05) in metabolic aspects of WS. These two examples highlight the inadequacy of predictors such as pLI in identifying all pathogenetic genes. An overview of the best-characterized genotype–phenotype correlations for WSCR genes is provided below.

Elastin. The *ELN* gene is transcribed in tissues that stretch and recoil such as the lungs, skin and elastic arteries (including the aorta, where elastin accounts for up to 50% of the vessel's dry weight)^{76,77}. The protein consists of repeating hydrophobic and cross-linking domains. The cross-links allow monomers to be bound to one

another in a highly interwoven polymer that allows for the distribution of force, while the hydrophobic domains drive the recoil process through entropy when they are exposed to an aqueous environment with tissue expansion (stretch)^{78,79}. The polymer is long-lived, with a short window for deposition and a calculated half-life of 74 years⁸⁰. Interestingly, although robust elastogenesis occurs only during early growth and development, *ELN* is thought to be continually transcribed throughout the lifespan⁸¹. Outside of this tight developmental window, *ELN* transcripts are quickly turned over^{82,83}. As such, this connection between transcription, translation and assembly is ripe for investigation.

Individuals with loss-of-function point mutations^{84–86} or intragenic deletions⁸⁷ within *ELN* have *ELN*-associated familial SVAS and develop cardiovascular manifestations that are indistinguishable from those found in WS. Common features include focal or long-segment stenosis (narrowing) of the large elastic arteries in the setting of a globally narrow and thick-walled vasculature^{4,6,7,30,88}.

Stenosis of the supravalvar aortic and supravalvar pulmonary arteries are the most common and show considerable variability in severity^{29,89}. While pulmonary artery stenoses often improve with age, narrowing on the aortic side may stay the same, improve or worsen with time^{5,88,90}. Other vessels, such as the descending aorta, renal arteries, mesenteric arteries and coronaries may also exhibit stenosis, with symptomatology pointing to hypoperfusion of the associated end-organ (hypertension, abdominal pain, and cardiac hypoperfusion with ST elevation or sudden death). Even in the absence of stenosis, individuals with either WS or familial SVAS have high rates of hypertension and vascular stiffness, which are detectable as early as infancy and childhood^{8,91}. An increased sudden death relative risk with and without anaesthesia has been reported^{10,92–94}; the precise mechanism by which this occurs is not currently known but it is expected to be multifactorial, reflecting the complex vascular pathophysiology⁹⁵.

Heterozygous *Eln* knockout (*Eln*^{+/-}) mice recapitulate relevant cardiovascular features of WS, including aortic wall thickening, hypertension and cardiac hypertrophy⁷; however, it has been difficult to replicate the hourglass-type supravalvar stenoses commonly seen in individuals with WS or familial SVAS. Neither *Eln*^{+/-} nor transgenic *Eln*^{-/-} mice expressing the human *ELN* gene (*Eln*^{-/-}; *ELN*⁺ mice, which have 30% of normal elastin levels) develop frank stenosis, although *Eln*^{-/-}; *ELN*⁺ mice exhibit more severe arterial wall thickening, luminal narrowing, hypertension and cardiac hypertrophy than *Eln*^{+/-} mice⁹⁶. Discrete stenosis or coarctation (congenital narrowing) of the aortic arch as well as the development of neointima (thickening of the intima characteristic of segmental aortic stenoses in WS) have been described in mice with a homozygous *Eln* deletion restricted to vascular smooth muscle cells⁹⁷. Unfortunately, most of these mice do not survive past postnatal day 18.

Several hypotheses have been postulated for the mechanism by which elastin insufficiency causes large vessel arteriopathy. Segmental stenoses are thought to develop through the increased proliferation and migration of vascular smooth muscle cells due to a reduction or lack of elastin^{98–100}. Lineage tracing in *Eln*^{-/-} mice indicates that the excess cells responsible for inward remodelling of the arterial wall are not clonal but are derived from multiple existing smooth muscle cells in the media layer¹⁰¹. Inward remodelling is caused, in part, by excess integrin $\beta 3$ signalling as genetic or pharmacological inhibition of this pathway reduces vascular pathology and extends lifespan in *Eln*^{-/-} mice¹⁰¹. Other work suggests that, rather than an increase in proliferation, elastin insufficiency produces medial fibrosis, altered mobility of smooth muscle cells and abnormal circumferential growth, leading to a smaller lumen size and thicker arterial walls¹⁰². Additional studies suggest that hypertension arises in *Eln*^{+/-} mice as part of a developmental adaptation to normalize vessel wall stress, capitalizing on the increased pressures to prop open the narrow, stiff elastin-insufficient vessels¹⁰³, although more recent studies indicate that reactive oxygen species (ROS) production may also play a role⁷⁴. Several additional molecular and cellular mechanisms impact the pathogenesis of elastin arteriopathy, including

mechanistic target of rapamycin (mTOR) perturbation of smooth muscle mechanosensing^{104–106}, and the adaptive immune system²⁹.

In addition to vascular disease, patients (and mice) with elastin insufficiency have impaired pulmonary^{107–109} and skin^{110,111} elastic fibres, leading to impaired tissue mechanics. Other common connective tissue features of WS may also be linked to elastin insufficiency such as periumbilical or inguinal hernias¹¹², hoarse voice¹¹³, earlier-onset skin wrinkling¹¹¹, atypical scar formation¹¹¹ and genitourinary phenotypes¹¹².

NCF1 modification of elastin-mediated hypertension. *NCF1* resides at the telomeric end of the WSCR. Two *NCF1* pseudogenes, *NCF1B* and *NCF1C*, are present in the LCR regions that flank the typical deletion. *NCF1* is the regulatory subunit for several NADPH oxidase (NOX) complexes and generates ROS in multiple cell types, including endothelial cells, smooth muscle cells and leucocytes, following various stresses^{114,115}. A deletion that removes *NCF1* is found in ~50% of individuals with WS^{91,116}. Loss of *NCF1* has been associated with relative protection from hypertension and vascular stiffness in individuals with WS^{91,116} and in animal models^{74,117,118}.

GTF2I and GTF2IRD1. *GTF2I* and *GTF2IRD1* are paralogous genes located on adjacent loci at the telomeric end of the WSCR. They encode transcription factors and contribute to typical WS behaviour and development. At the molecular level, *GTF2IRD1* and *GTF2I* encode BEN and GTFII-I, respectively, which are members of a versatile protein family with broad functional activities^{119–121}. GTFII-I is a highly conserved and ubiquitously expressed multifunctional transcription factor^{122–125} that regulates gene expression^{120,126,127} through interactions with tissue-specific transcription factors and complexes related to chromatin remodelling¹²⁵. GTFII-I is activated in response to various extracellular signals and then translocates to the nucleus^{121,125,126,128}. GTFII-I has been shown to be involved in multiple processes, which include regulating embryonic development^{122,129,130}, the cell cycle^{125,127,131,132}, actin cytoskeleton dynamics, axon guidance¹³² and epigenetic regulation^{133,134}. Indeed, an iPSC-based study showed that *GTF2I* alterations are responsible for 10–20% of the transcription dysregulation in disease-relevant pathways in WS and in the 7q11.23 duplication syndrome, beginning in the pluripotent state and further amplified during development⁶⁹.

From a phenotypic standpoint, individuals with classic deletions of the WSCR¹⁴ and those with shorter deletions that result in the loss of *GTF2IRD1* and *GTF2I*⁶² (FIG. 2) typically show intellectual disability, high social approach to familiar persons and indiscriminate social approach to strangers (also referred to as social disinhibition or hypersociability), and difficulties in social communication (pragmatics). By contrast, individuals with deletions that spare these two genes typically exhibit neither intellectual disability^{40,54,56,59,135–137} nor these social characteristics^{59,138}. Interestingly, individuals with shorter WS deletions that spare *GTF2I* but remove *GTF2IRD1* also typically do not exhibit intellectual disability or hypersociability^{136,139} but they do

show an increased social approach to familiar people and a difficulty with social pragmatics¹³⁶. Further evidence for the role of *GTF2I* gene dose in intellectual ability comes from a family with a very short duplication affecting *GTF2I* but not *GTF2IRD1*; all family members with the *GTF2I* duplication had intellectual disability, whereas the intellectual ability of those with the usual two copies of *GTF2I* was average¹⁴⁰.

As in humans, partial hemizygous deletion of the mouse WSCR including *Gtf2i* results in increased sociability but also impairs motor coordination in mutant mice⁷¹. The homozygous deletion of *Gtf2i* in mice results in embryonic lethality owing to severe developmental abnormalities^{122,124,141}, such as exencephaly and neural tube disclosure, whereas heterozygous mice show impaired social habituation to an unfamiliar mouse^{141,142}. The selective deletion of *Gtf2i* in excitatory neurons leads to myelination alterations, motor deficits and hyper-sociality, which normalize with the pharmacological rescue of myelination^{143,144}. Intracisternal *Gtf2i*-gene therapy in the CD mouse model resulted in beneficial effects on behavioural deficits related to motor, social and anxiety-like behaviours¹⁴⁵.

Taken together, these findings suggest that the loss of a *GTF2I* allele is a major contributor to the intellectual disability and social disinhibition that are characteristic of individuals with WS. Deletion of *GTF2IRD1*, even without deletion of *GTF2I*, likely contributes to the social communication difficulties and generally increased social approach. Findings of dose-dependent *Gtf2i*-specific social and anxiety phenotypes in mouse models^{146,147} converge with those observed in the human hemideletion and duplication syndromes^{14,146,148,149}. In a study of the effects of *Gtf2i* copy number on cortical neuron maturation and function, mice with a single copy of *Gtf2i* showed increased axonal outgrowth, whereas this outgrowth was decreased in mice with three *Gtf2i* copies¹⁵⁰. The axonal growth effects of GTFII-I might occur through the regulation of the expression of the homeobox proteins DLX5 and DLX6 (REF.¹⁵¹), thereby affecting the excitatory/inhibitory balance in the brain¹⁵². This balance has been suggested as a possible mechanism that causes autism spectrum disorder (ASD)¹⁵³. In this regard, it is noteworthy that both deletion^{154,155} and duplication¹⁵⁶ of the WSCR are associated with elevated rates of ASD.

Other candidate genes. For several other genes within the WSCR, there is emerging evidence of an association with components of the WS phenotype (FIG. 3). *BAZ1B*, a member of the B-WICH chromatin remodelling complex, is essential for correct neural crest cell migration in vitro¹⁵⁷ and in vivo¹⁵⁸ and has been proposed as a master regulator of human craniofacial development¹⁵⁷. As the enteric nervous system is also derived from the neural crest¹⁵⁹, it is possible that abnormal innervation of the intestine contributes to WS gastrointestinal phenotypes such as dysmotility and chronic constipation.

LIMK1 regulates actin cytoskeleton assembly and disassembly and has been linked with visuospatial cognitive ability in individuals with WS⁶⁴ and in the general population¹⁶⁰. *Limk1*^{-/-} mice show visuospatial

deficits, an altered dendritic spine morphology and reduced synaptic plasticity, leading to reduced long-term memory. *Limk1* expression can be upregulated by both brain-derived neurotrophic factor¹⁶¹ and cAMP response element-binding protein¹⁶², suggesting potential therapeutic avenues.

Syntaxin 1A (STX1A) is a key member of the protein complex that mediates exocytic vesicle fusion, thereby allowing the release of neurotransmitters into the synapse. Neuropsychiatric disorders found in individuals with WS have been associated with *STX1A* variants^{163,164}. Insulin secretion from the pancreas is also dependent on exocytosis¹⁶⁵ and STX1A levels are indeed reduced in members of the general population with type 2 diabetes mellitus¹⁶⁶. Diabetes is common in adults with WS¹⁶⁷, suggesting a possible physiological link with *STX1A* hemizygosity. As the *MLXIPL* gene, which encodes the ChREBP transcription factor that regulates both glucose^{168,169} and lipid metabolism¹⁷⁰, is also located within the WSCR, both ChREBP and STX1A could contribute to the metabolic phenotypes in WS.

Biallelic missense variation in *DNAJC30* was recently associated with Leber's hereditary optic neuropathy in humans¹⁷¹, a mitochondrial condition. Similar features have not, to date, been reported in WS. Biallelic deletion of *DNAJC30* in mice also produces mitochondrial dysfunction and behavioural changes¹⁷². More work is needed to investigate the impact of isolated hemideletion in humans but the potential impact of this gene on neurodevelopment should be considered.

Diagnosis, screening and prevention

Clinical diagnosis

WS is a multisystem disorder with a broad but characteristic pattern of organ involvement (FIG. 1), including a distinctive facial appearance^{173–175} (FIG. 4). As there is no newborn screening for WS, clinical consideration of the diagnosis is prompted by the presence of suggestive signs and/or symptoms. Below, we outline the most common presenting features prompting the consideration of a WS diagnosis. Of note, the extent and exact distribution of system involvement can vary considerably from patient to patient.

Craniofacial differences. Individuals with WS often present with facial features that are not typical for their family. Prominent features in infants and young children include a broad forehead, peri-orbital fullness, flat bridge of the nose, full cheeks, long philtrum and a small delicate chin. Adolescents and adults often continue to have micrognathia but the face elongates over time, the nasal bridge is no longer flat and there is fullness of the lips with a wide mouth (especially appreciated when smiling). Children and adults of different ethnic backgrounds from Brazil with molecularly confirmed WS are depicted in FIG. 4.

Cardiovascular anomalies. Cardiovascular disease in WS typically presents with a heart murmur. Evaluation in children most commonly reveals SVAS and/or stenosis of the main or branch pulmonary arteries. Pulmonary vascular disease is often less prominent in older individuals



Fig. 4 | **Facial features of children and adults with Williams syndrome of different ethnic backgrounds.** Facial photos of individuals of different racial and/or ethnic backgrounds aged 2 months to 52 years with molecularly confirmed Williams syndrome. Distinctive features in infants and children include broad forehead, peri-orbital fullness, flat bridge of the nose, full cheeks, long philtrum and a small delicate chin. Many adolescents and adults continue to have micrognathia and the face often elongates over time while the nasal bridge is no longer flat and there is fullness of the lips with a wide mouth (especially appreciated when smiling). Parents or caregivers for all individuals signed consent for the publication of their family member's image. The presence of more male than female photos in adolescents and adults solely reflects the availability of patients.

with WS. Other WS cardiovascular features, such as stenosis in other vessels, septal defects, hypertension, vascular stiffness or ECG abnormalities, are generally not the reason for referral but may be present at the time of diagnosis.

Hypercalcaemia. Actionable hypercalcaemia (serum calcium >12.0 mg/dl) is seen in 5–10% of children with WS and, when present, usually occurs between 6 and 30 months of age¹⁷⁶. While some children with hypercalcaemia are irritable and show poor oral intake, other cases are detected incidentally by laboratory testing.

Growth concerns. On average, children and adults with WS are shorter than expected for age¹⁷⁷. Once a diagnosis is made, WS-specific growth charts are available for plotting children's expected growth^{178,179}. In addition, many infants with WS exhibit prolonged colic, may have difficulty feeding due to oral motor delays or sensitivities, and have difficulty gaining weight.

Developmental delay, intellectual disability and behavioural profile. Developmental delay is almost universal and 75% of older children and adults with WS have intellectual disability (IQ <70)¹⁷⁸, with most other individuals

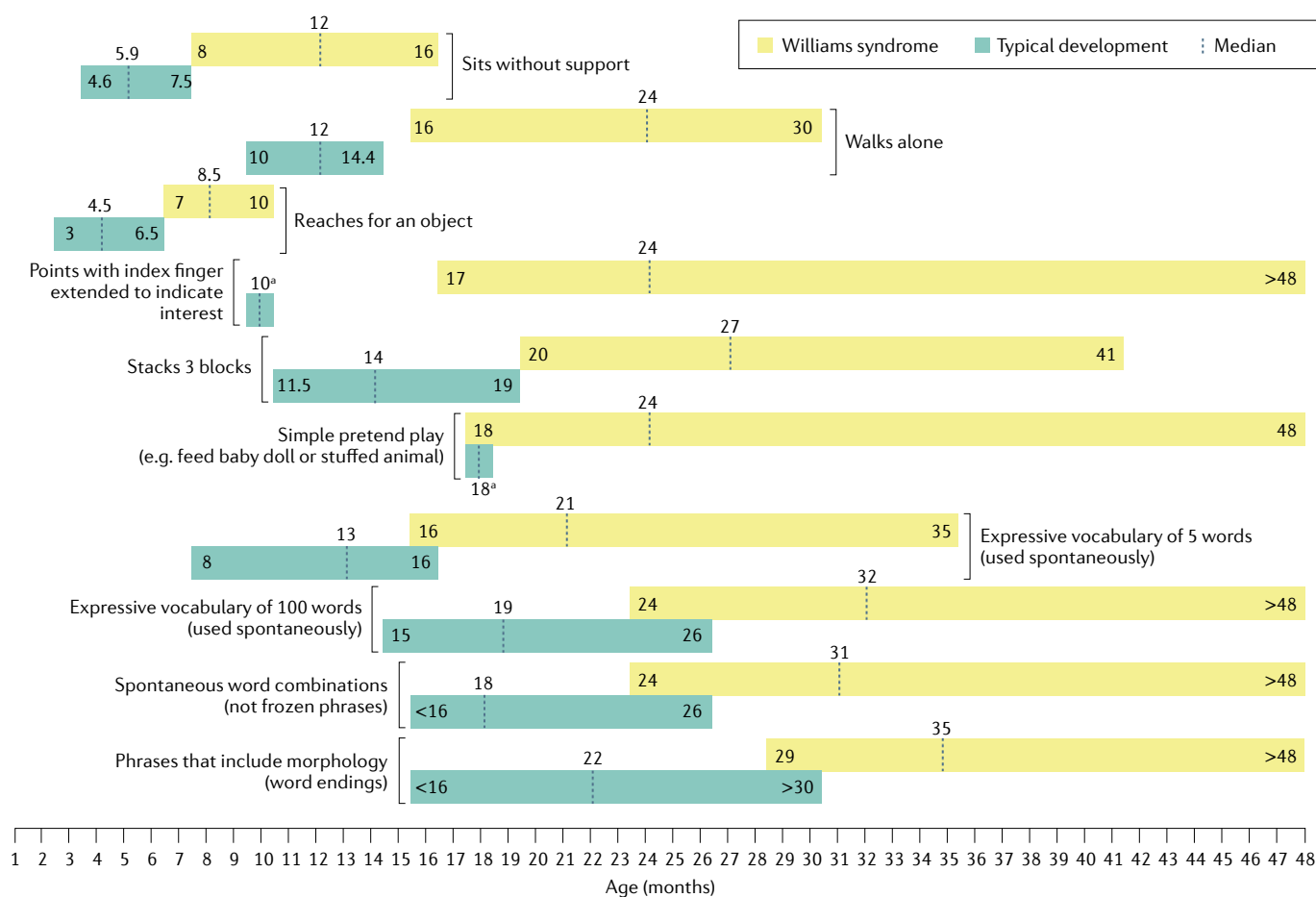


Fig. 5 | **Developmental milestones for very young children with Williams syndrome.** Median ages (in months) and 90th and 10th percentiles for attainment of various gross motor, fine motor, cognitive and language milestones by very young children with Williams syndrome relative to typically developing children^{154,296–304}. Numbers above the dashed line indicate median age; numbers within the bars indicate the 10th (left) and 90th (right) percentiles. ^aNot possible from the available literature to determine the 10th and 90th percentiles for typically developing children.

displaying borderline IQ (70–79) and/or more specific neuropsychological impairments^{13,14}.

Many experienced parents almost immediately notice differences from typically developing infants but other parents may not become concerned until they realize their child with WS is not meeting motor or language milestones (FIG. 5). Features of ASD may also lead to referral.

Differential diagnosis

It is important to distinguish WS from other syndromes with overlapping features. Certain highly suggestive features (such as SVAS, hypercalcemia and characteristic facial features) exist that, when seen in combination by an experienced examiner, readily yield a correct clinical diagnosis of WS. Although a few other disorders (such as fetal alcohol syndrome, rasopathies and FG syndrome) are evocative of WS, in that they have a similar pattern of organ involvement, detailed examination of their specific features reveals distinct differences from WS. However, some individuals come to medical attention owing to a single prominent feature. Depending on the specific presenting symptom, the differential diagnosis

varies; Supplementary Table 1 is presented to aid practitioners in that setting. A clinical suspicion of WS should always be confirmed with genetic testing (see below).

Testing approaches

The most widely used laboratory methods available to detect the 7q11.23 microdeletion include FISH, polymorphic microsatellite markers, multiplex ligation-dependent probe amplification and chromosomal microarray analysis (CMA) (TABLE 1). CMA is the only current method that does not require the clinician to suspect a specific diagnosis of WS prior to testing. In addition to providing mapping for deletion boundaries and offering the ability to detect atypical deletions, CMA can also identify additional CNV events elsewhere in the genome. Multiplex ligation-dependent probe amplification and polymorphic microsatellite markers are often used in low-income and middle-income countries owing to their lower cost than FISH and CMA^{22,23,180,181}.

Newer technologies, such as facial recognition software^{182–184}, may help focus the differential diagnosis and have been evaluated in individuals from various racial and ethnic backgrounds; the diagnostic precision of

Table 1 | Overview of methods for diagnosing WS

Method	Current advantages	Current disadvantages
Available methods		
Microsatellite markers	Low cost	May be uninformative Need of trio sample
Multiplex ligation-dependent probe amplification	Low cost Highly effective Possibility of detecting other microdeletions or duplications (as determined by probe coverage)	Requires ordering provider to suspect WS to order correct probe
Fluorescence in situ hybridization	High sensitivity May detect translocations (depending on availability of probe coverage)	Higher cost False negative for smaller deletions Not possible to determine deletion size Requires ordering provider to suspect WS to order correct probe
Chromosomal microarray	High positivity Able to determine deletion size Able to determine CNVs elsewhere in the genome Ordering provider does not need to suspect WS to order this test	Highest cost of currently available tests Cannot detect balanced translocation or inversion
Emerging methods		
Non-invasive prenatal testing	Prenatal diagnosis of aneuploidies and large deletions or duplications	Low resolution (detects deletions >3 Mb)
Facial recognition software	Cost varies, with some free software available online	Diagnosis is limited by the number of photographs available in the database May have different efficacy based on race or ethnicity of patient
Whole-exome sequencing	Deletion detection performed in research settings	Currently used clinically for single-nucleotide variants High cost Low accuracy for deletion detection
Whole-genome sequencing	Combined single-nucleotide variant and CNV or structural variant detection performed in research settings	High cost Slow turnaround in most settings

WS, Williams syndrome; CNV, copy number variant; Mb, megabase pairs.

the software will likely continue to improve over time. Additional testing (gene sequencing or trinucleotide repeat expansion testing) may be indicated based on the differential diagnosis (Supplementary Table 1). In the future, whole-genome sequencing may provide CNV and single-nucleotide polymorphism detection in a single test that will simultaneously assess for WS and other possible differential diagnoses.

Recurrence risk

If a parent has WS, the risk of WS in offspring is 50% for each pregnancy. However, owing to the complex medical and neurodevelopmental challenges associated with WS, few adults with WS have children. The recurrence risk for couples where neither parent has clinical findings of WS is extremely low¹⁸⁵, since the 7q11.23 microdeletion arises de novo in the vast majority of cases. For these couples, parental testing for a 7q11.23 microdeletion is not indicated and neither is invasive prenatal testing of subsequent pregnancies (although many parents opt for the latter, especially in countries where molecular diagnostic testing is widely available). However, there

are rare reports of recurrence in phenotypically normal parents. This recurrence is likely attributed to parental mosaicism¹⁸⁶ or to one parent carrying an inversion of the WSCR¹⁸⁵. The inversion has been associated with an approximately fivefold increase in the risk of having a child with WS in each pregnancy; nevertheless, testing for the presence of inversion in phenotypically normal parents is not recommended because their recurrence risk — despite being five times higher — remains well below 0.1%^{42,44,185}.

Pregnancy and prenatal testing

Limited clinical information exists on pregnancies in women with WS^{187,188}. A review of this literature suggests that mothers and fetuses (affected by WS or not) may require close monitoring, especially with regard to the maternal cardiovascular system. In addition, there is no routine prenatal test that adequately screens for WS, although prenatal ultrasonography can sometimes detect relevant fetal anomalies. The most common prenatal finding is non-specific, namely intrauterine growth retardation¹⁸⁹. Various cardiovascular anomalies can

also be seen and range from non-specific (for example, ventricular septal defect) to nearly pathognomonic for elastin arteriopathy (for example, SVAS, although this finding is quite difficult to make by prenatal ultrasonography)¹⁶⁵. The prenatal detection of growth retardation combined with any cardiovascular defect may warrant performing high-resolution prenatal ultrasonography and genetic testing.

Non-invasive prenatal testing (NIPT) involves the sequencing of fetal DNA circulating in the maternal circulation and can detect common fetal chromosomal aneuploidies in the first trimester. Currently, as even enhanced NIPT platforms can only detect deletions of >3 Mb, they cannot be used to diagnose WS¹⁸⁹. However, further technical advances in the NIPT technology are likely to enhance prenatal diagnosis and therefore affect the epidemiology of WS in the future. In addition, whole-genome sequencing may eventually be utilized to perform combined single-nucleotide polymorphism, copy number variant and structural variant detection in fetal samples. Prenatal diagnosis offers the opportunity to provide genetic counselling to families sooner, allowing them to avoid a diagnostic odyssey that can potentially last months and years after the child's birth.

Management

The management of various aspects of WS has been extensively outlined in numerous research studies, reviews and guidelines^{173,174,176–178,190–195}. Here, we focus on the management of three key areas where better therapeutics would have the greatest potential to improve health outcomes: elastin-associated vasculopathy, hypertension, and intellectual disability, social functioning and anxiety.

Elastin-associated vasculopathy

As mentioned previously, individuals with elastin insufficiency can develop focal stenosis and other vascular features. Vascular disease severity varies among individuals with WS, with ~20% requiring intervention for SVAS, for example, while 30–40% have little to no stenosis in this location. At present, large vessel stenosis is predominantly managed surgically. To alleviate SVAS, patch aortoplasty is the most common approach¹⁹⁶ and has undergone several technical improvements over time, evolving from the single-patch method^{197,198} to the pantaloan-shaped patch that enlarges the aorta and two aortic sinuses¹⁹⁹. The most advanced method, which involves applying a patch to each of the three aortic sinuses²⁰⁰, exhibits notably lower residual pressure gradients and reoperation rates²⁰¹ than the single-patch approach. Stenoses of pulmonary arteries can be treated with angioplasty but catheter-based interventions on other arteries are often unsuccessful^{11,90,202}. The surveillance of stenosis occurs through regular examinations by a cardiologist and associated imaging, and should continue throughout an individual's lifetime.

Individuals with WS experience increased rates of cardiovascular collapse with and without anaesthesia^{10,12}, although the mechanism of this phenomenon is not completely understood. Young individuals and those with the most severe cardiovascular features (that is,

biventricular outflow tract obstruction¹⁰) seem to have the highest risk, although some individuals with only minimal stenosis suffered sudden cardiac death in the setting of anaesthesia. This severe outcome may be influenced by various risk factors, including anatomical anomaly of the coronaries and a reduction in perfusion pressure at induction and/or maintenance of anaesthesia. Therefore, careful preoperative screening should be performed to assess the anaesthesia-associated cardiovascular risk and the administration of intraoperative anaesthesia should ideally be provided by an anaesthesia team with knowledge of WS anaesthesia risks^{93–95,203,204}. Care should be taken not to acutely lower blood pressure at induction of anaesthesia in order to maintain adequate perfusion of the coronaries during this sensitive time.

Studies suggest that novel pharmacological therapies may improve elastin-associated vasculopathy. Minoxidil, an ATP-dependent potassium channel opener, has received considerable attention based on evidence that it increased elastin production in cellular studies²⁰⁵ and in animal models^{206,207} of genetic elastin deficiency and that it ameliorated the age-related degeneration of elastic fibres in mice^{208,209}. However, a randomized, double-blind, placebo-controlled trial (NCT00876200) investigating the effect of a year-long minoxidil treatment in 8 treated subjects with WS failed to show improvement in the primary outcome measure (carotid intima-media thickness)²¹⁰. This trial did show an increase in lumen size (a secondary finding, in line with previous mouse studies²⁰⁷) over the same time interval, along with an expected common adverse effect of hypertrichosis²¹⁰.

Alternative therapeutic approaches may target various regulatory pathways that influence elastin expression. For example, both the coding region and the 3' untranslated region of the *ELN* mRNA are enriched in binding sites for miR-29 and miR-15, two microRNAs that are upregulated in the late postnatal aorta, at the same time that the level of mature *ELN* mRNA decreases⁸². The antagonism of miR-29 increases elastin expression in haploinsufficient cells and bioengineered vessels²¹¹.

Hypertension

Elastin insufficiency is also associated with hypertension but the risk of clinically significant blood pressure increases is modified by deletion size and *NCF1* gene dosage^{91,116}. Blood pressure should be measured in both arms and at least one leg due to possible right arm flow acceleration (the so-called Coanda effect) and/or coarctation of the aorta²¹². If consistent blood pressure elevations or pressure differentials (in the arms or as an arm–leg discrepancy, respectively) are detected, additional imaging of the heart and ascending aorta (by echocardiography) and the renal/abdominal vasculature (by Doppler ultrasonography, CT angiography or MRI/MR angiography) should be considered (when available), to assess the presence of focal or long-segment stenosis that affects renal perfusion and may benefit from surgical intervention^{5,9}. Auscultation of the abdomen can also reveal a bruit (abnormal sound) in the region of the stenosis.

Blood pressure elevation often starts in childhood and increases in frequency with age^{8,9,116,213}. Unlike stenosis,

Table 2 | Pattern of relative strengths and weaknesses in individuals with Williams syndrome^a

Category	Ability	Details	Level relative to overall intellectual ability
General pattern	Verbal	Vocabulary breadth and verbal analogies	Stronger than expected
	Non-verbal reasoning	Matrix reasoning and pattern completion	Stronger than expected
	Visuospatial construction	Drawing, writing and block construction	Considerably weaker than expected
Language profile	Phonological processing	Knowledge of the sound structure of language and ability to manipulate that structure	Stronger than expected
	Vocabulary breadth	Concrete vocabulary, picture identification and naming	Stronger than expected
	Verbal short-term memory	Ability to repeat back what was said verbatim	Stronger than expected
	Grammatical ability	Ability to speak grammatically and understand sentences someone else produced	At the expected level
	Verbal working memory	Ability to repeat back what was said in a different order (for example, in the reverse order) from the original	At the expected level
	Vocabulary depth	Ability to define words accurately and specifically	At the expected level
	Relational vocabulary	Understanding and use of spatial, temporal, and quantitative concepts and of complex conjunctions (for example, however) or disjunctions (for example, neither nor)	Considerably weaker than expected
	Non-literal language	Understanding and use of metaphor and irony	Considerably weaker than expected
	Discourse skills	Event sequencing, asking and answering questions appropriately, maintaining the conversational topic	Considerably weaker than expected
	Comprehension monitoring	Evaluating whether one understood what was said or read and then taking appropriate action if one had not understood	Considerably weaker than expected

^aStrengths and weaknesses relative to overall intellectual ability for broad categories of intellectual ability and within the language domain.

most cases of hypertension are treated pharmacologically^{5,8}. Currently, there is no expert consensus on the best antihypertensive medication for individuals with WS²¹⁴. Similarly, work in *Eln*^{+/-} mice revealed no superior drug class for the treatment of elastin-mediated hypertension²¹⁵. However, because blood pressure influences lumen size, which in turn affects end-organ blood flow, care must be taken not to decrease pressure to the extent that lumen size, and therefore end-organ blood flow, is pathologically diminished.

For this reason, among others, diuretics may not be the ideal or initial choice for blood pressure management in individuals with WS. In addition, when reno-vascular causes of hypertension are suspected, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors should be used with caution. As the risk of hypertension has been linked to ROS production through the NOX signalling pathway, potential therapeutic strategies could include treatments that limit ROS production or affect signalling through ROS^{74,118,216}.

Intellectual and social functioning

The deletion of multiple genes within the WSCR likely contribute to intellectual disability, altered social functioning and anxiety, although the roles of *GTF2I* and *GTF2IRD1* (as outlined above) are the best described to date. WS is associated with developmental delay (the expected

developmental milestones are shown in FIG. 5). The delays typically lead to mild-to-moderate intellectual disability, although a few individuals have severe intellectual disability or, at the other extreme, average intellectual ability^{14,217}. This overall level of ability masks a phenotypic pattern of strengths and weaknesses relative to expectations for the overall level of intellectual ability. In general, language and non-verbal reasoning abilities are stronger than expected for overall intellectual ability, whereas visuospatial construction (for example, handwriting and block construction) is considerably weaker than expected^{13,14,218}. Visuospatial construction is facilitated by visual processing regions. Interestingly, research using resting-state functional MRI showed that, for children in the general population, the intraparietal sulcus is functionally connected to more superior-anterior visual processing regions, whereas it is instead connected to social regions in children with WS¹⁶⁰. The lack of this specific functional connection in individuals with WS contributes to their considerable weakness in visuospatial construction²¹⁹. A more detailed description of the pattern of relative strengths and weaknesses within the language domain is provided in TABLE 2.

Current information indicates that cognitive ability remains stable at least to mid-adulthood^{220–223}. There is a possibility of IQ decline in older adults³⁴, but the data sets are limited. WS is also associated with a characteristic

behavioural profile that is consistent across both Western and Eastern cultures²²⁴. At its most basic level, this profile includes gregariousness and hypersociability (or 'overfriendliness'), accompanied by attention problems (often meeting diagnostic criteria for attention-deficit/hyperactivity disorder), social problems, anxiety and emotional overreactivity^{15,16,225–229}. Mastery motivation (that is, willingness to persist on a task one finds moderately difficult) is typically very limited^{14,227}. The most common psychiatric problems associated with WS and estimates of their prevalence based on meeting formal diagnostic criteria outlined in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition²³⁰, are delineated in FIG. 6.

In most cases, the previously described learning and developmental differences are addressed by the school system through specialized education and therapy services, which are outlined below. In general, physical, occupational, and speech and language therapy are recommended for infants through school-aged children in the USA^{178,231} and in Australia¹⁹². By contrast, according to a parent survey in the UK, only 20–40% of school children with WS receive these services²³². The behavioural and psychiatric components of WS are managed with the help of structural and environmental supports at home and in school and vocational settings, including counselling and behavioural therapies^{14,156,178,233}. For individuals whose symptoms greatly affect their daily functioning and quality of life (QOL), referral to a psychiatrist for the consideration of pharmacological intervention

may be indicated¹⁷⁸. The anxiety associated with WS has been particularly difficult to treat. Trials are needed to identify appropriate therapeutics for anxiety, although, as has been shown for typically developing individuals, cognitive behaviour therapy seems promising as an effective treatment for anxiety in WS^{234,235}. The same medication classes available for anxiolysis in the general population have been studied in small series of individuals with WS^{236,237} and are already widely used in clinical practice but result in varying symptom relief. Furthermore, the risk–benefit ratio may be more unfavourable for some of these medications in individuals with WS (reviewed elsewhere²³⁸). Specifically, anxiety, mood, cardiac function and blood pressure all need to be monitored given the overlap between the common adverse effects of attention-deficit/hyperactivity disorder medication in the general population and the psychological and physical difficulties associated with WS.

Educational and vocational provision

In high-income countries, a large proportion of primary school-aged children with WS are educated in mainstream schools and spend at least part of the day in classes with typically developing age-mates; these proportions decrease considerably for secondary school^{232,239}. Although there are no data specifically for children with WS, in low-income and middle-income countries, school attendance is much less common for children with disabilities than for typically developing children²⁴⁰ due not only to financial difficulties but

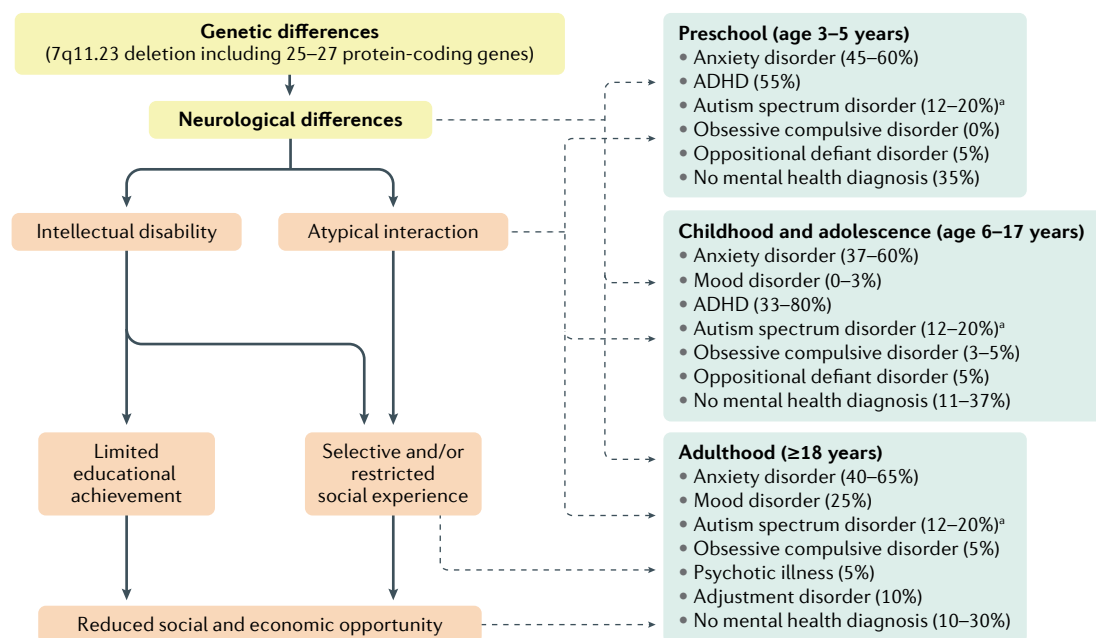


Fig. 6 | **Prevalence of psychiatric diagnoses in individuals with Williams syndrome throughout the lifespan.**

The genetic deletion in Williams syndrome (WS) has cascading effects on social, educational and vocational opportunities and on psychopathology. The estimated prevalence of psychiatric disorders in preschool-aged children, school-aged children and adolescents, and adults with WS^{154,213,267,305,306} is depicted. Studies with participants over a wide age range that did not report results separately for children and adults were excluded^{237,307–309}. The term 'anxiety disorders' includes generalized anxiety disorder, specific phobia, separation anxiety or social anxiety, and panic disorder with agoraphobia. ^aMost individuals with WS who have autism spectrum disorder fit in Wing and Gould's²⁹³ active-but-odd subtype of autism spectrum disorder²³³ rather than the aloof subtype. ADHD, attention-deficit/hyperactivity disorder. Adapted from REF.³¹⁰, Springer Nature Limited.

also to the discriminatory and negative views of persons with intellectual disability²⁴¹.

Postsecondary education for individuals with WS is very limited worldwide, although opportunities are increasing in some high-income countries. In a US survey whose respondents were, on average, upper-middle class, 29% of individuals with WS had attended a postsecondary education programme²⁴². These programmes typically focus on combinations of academics, vocational training (including job placement and coaching) and independent living skills. After completing school, most adults with WS continue to live with their parent or another relative; <10% live independently^{242,243}. Only 38–54% of adults are working at least part-time, generally in a special employment arrangement, either for pay or as a volunteer^{242,243}.

Within the academic sphere, reading skills are considerably stronger than mathematics skills^{13,244} and range from an inability to read at all to reading comprehension at age or grade level^{244–247}. About 30% of adolescents and adults with WS have functional reading capability²⁴⁵. Children who were taught to read using systematic phonics instruction, which emphasizes letter–sound relations, read and comprehend significantly better than those taught using other instructional approaches^{247,248}. There has been no research on written composition and very little is known about the mathematical abilities of individuals with WS²⁴⁹.

Within the adaptive behaviour domain, socialization and communication skills are stronger than daily living and motor skills for children and adolescents with WS²⁵⁰. In longitudinal studies, adaptive behaviour standard scores declined significantly during childhood²⁵¹ and in adulthood²²², owing to the stagnation or failure to increase adaptive skills at the rate needed to maintain a consistent standard score over time. For adolescents and adults with WS, adaptive behaviour is more limited than expected for their IQ^{252,253}.

High but realistic parental expectations combined with better behavioural regulation²³⁵ and higher levels of mastery motivation are expected to positively affect both adaptive behaviour and academic achievement¹³. Even so, in a survey of teachers, most indicated that they were not given adequate resources to teach children with WS²³⁹ and most parents surveyed thought their child's teachers had little knowledge about WS²³⁹. Much more research is needed on effective instructional strategies for individuals with WS at all educational levels²⁵⁴.

Quality of life

The combination of intellectual disability, medical problems, and behavioural, psychological and adaptive impairments leads to considerable limitations on QOL in individuals with WS. Parents and teachers of children with WS report difficulties with peers, including problems establishing and maintaining friendships and increased social exclusion or isolation²⁵⁵. Although social vulnerability is high, self-awareness is limited²⁵⁶. Seventy-three percent of parents reported victimization of their child²⁵⁷, with the social interaction style of individuals with WS contributing significantly to their social vulnerability²⁵⁸. Even adolescents and adults with

WS are typically not cognizant of stranger danger^{259,260}. Intervention studies addressing these issues^{259,261} are both rare and crucial²²⁹.

Almost all children with WS require multiple encounters with the healthcare system for the management of medical or surgical problems²⁶². These encounters place a financial and emotional burden on the individuals with WS and their families²⁶³ and often contribute to anticipatory anxiety about medical encounters and procedures²⁶⁴. Several studies of adults with WS ≥30 years of age demonstrated an increased frequency, variety and severity of medical morbidities^{33,34,213} and this trajectory accelerates among those >65 years of age (authors' personal observation).

Prominent adult issues include cardiovascular disease, obesity (with/without lipoedema), diabetes mellitus, incontinence, hearing loss, consequences of poor oral health, gastrointestinal problems (including diverticulitis), decreased bone mineral density and sleep apnoea^{174,213}. Psychiatric concerns are often paramount. Health issues such as these may result in narrowed residential and vocational placements as well as in restricted mobility and physical activity and, collectively, they promote further social isolation. Medical complications require focused management based on established guidelines, whereas general health could be improved by participation in programmes that promote healthy eating and increasing physical exercise activity to the recommended adult levels^{265,266}.

The presence of a child with WS may affect the QOL of other family members. Both generalized anxiety disorder²⁶⁷ and borderline or clinically significant levels of stress^{268,269} occur in a significantly higher proportion of mothers of children with WS than expected for same-aged women in the general population. Sensory modulation problems are very common among children with WS and are associated with a more difficult temperament, more limited adaptive behaviour, emotion regulation difficulties and behavioural problems²⁷⁰. In turn, child behavioural problems (especially externalizing problems) contribute to increased maternal stress^{268,271} or challenges with raising the child (owing to, for example, the child's difficulties with social skills or obsessions)²⁷². The discrepancy between the general perception that children with WS are happy and have 'easy' temperaments and the reality that most children with WS have relatively difficult temperaments is in itself likely to increase maternal stress²²⁷. Worries regarding the child's future are very common among family members and mothers in particular^{232,272,273}. At the same time, most mothers also reported positive aspects of having a child with WS, including that the child brought joy and changed the mother's outlook on life²⁷² (BOX 1).

Outlook

Much has been learned about WS since its initial description but important questions remain (BOX 2). These questions centre on three major themes: molecular mechanisms of disease, interindividual variability and effective treatment strategies. A more complete understanding of the genes and pathways contributing to the phenotypes of individuals with WS would allow

clinicians to move beyond symptom management and to instead use precisely targeted therapies to improve organ function and ultimately health outcomes.

Molecular mechanisms of disease

To date, only *ELN*, *GTF2I* and *GTF2IRD1* have been definitively linked to key phenotypes that are identifiable in individuals with WS but, even for these genes,

a significant knowledge gap between disease phenotype and gene function remains. For example, the published literature has not yet clarified whether the global vascular narrowing seen in WS is driven by changes in cell proliferation⁹⁹, radial growth of the vessel¹⁰² or alterations in cell–matrix interactions. In addition, the characteristic hourglass-type stenosis feature in WS seems to be driven by entirely different mechanisms than the more general narrow and stiff vessel pathology seen throughout the rest of the vasculature^{7,97}. While for *GTF2I* and *GTF2IRD1* clear effects on brain development and function are evident, the direct effect of reduced gene products on neural circuits, white matter properties²⁷⁴, developmental timing and brain activity is unknown.

To answer these questions, further studies on the roles of individual genes in human pathophysiology, at the cellular and molecular level, and in model systems are needed. In humans, a traditional approach has been to clinically characterize individuals with smaller WSCR deletions in an effort to create more specificity for the traits associated with each gene (FIG. 2). Currently, clinical exome and whole-genome sequencing are being used to identify rare single-gene variations in individuals with phenotypes that overlap with WS (a phenotype-to-gene approach). In the future, the move towards big-data and genotype-first methods (a gene-to-phenotype approach) may offer new hope in the identification and further refinement of genotype–phenotype relationships that are part of the complex multisystem disorder of WS.

Further clarification of gene function can be obtained from studies in model systems. Cell systems offer ease of manipulation and provide precise ways to study protein–protein interactions and gene expression. However, they lack much of the complexity (for example, multiple cell types, tissue movement and endocrine signalling) needed to truly model human disease. Similarly, animal models (usually mice) may imperfectly match human disease outcomes; for example, the *Eln*^{+/-} mouse does not have SVAS and, in the case of cognitive conditions, mouse behaviours may incompletely or inaccurately correspond to human behaviours. The advent of iPSCs, tissue engineering and ‘organs in a dish’ may offer the potential to bridge some of the gaps that are present in traditional cell culture systems^{68,69,275–277}. As in all disease modelling, the biggest challenge lies in the ability of the in vitro system to truly mimic the complex in vivo environment. Brain organoids have shown promise for modelling developmental disorders such as autism and epilepsy^{278,279}. Vascular organoids²⁸⁰ and numerous tissue-engineering approaches²⁸¹ are being applied to the study of blood vessels. Progress is being made but it has been difficult to design complex vascular tissues that deposit mechanically competent and mature elastin^{282,283}. Rapid improvement in these systems is expected in the coming years as more precise genetic approaches to adapting both cellular and animal systems facilitate the study of specific outcomes.

Interindividual variability

Phenotypic variation is readily apparent in WS despite the vast majority of individuals carrying the typical 1.55–1.83 Mb WS deletion. Currently, the mechanisms

Box 1 | Perspective of a patient with Williams syndrome and their family

Molly (not her real name) is a 30-year-old woman with Williams syndrome who lives with her parents in a rural town in Australia. She has mild-to-moderate intellectual disability and the typical Williams syndrome personality. She completed school in a mainstream setting for the first six years, then moved to a special school. She currently works 3 days a week in sheltered employment after failed attempts to work in mainstream employment due to bullying. Molly enjoys music, softball and line dancing. Molly has struggled with many of the medical and psychological difficulties associated with Williams syndrome but, due to her determined nature and strong family support, she has made many wonderful life achievements. Please see Supplementary Box 2 for the full interview.

Interviewer: Do you feel that others treat you any differently because you have Williams syndrome?

- Molly: The way people talk to you is different and they talk to mum instead of me ... about my medical things ... and I am like: “Hello, I am over here. Mum doesn’t have Williams syndrome. I do”.

Interviewer: What are the good things about having Williams syndrome?

- Molly: I make people laugh and feel good. At home I am demanding. I love older people and their stories. I love to hear what they were up to back in the day.

Interviewer: What are the not so good/hard things about having Williams syndrome?

- Molly: Lots of people don’t know about Williams syndrome. Most doctors don’t know about Williams syndrome. When I go to hospital, I always take an information sheet [about Williams syndrome].
- I get bullied a lot. I think because of the way ... oh this makes me feel sad ... [now teary] ... I think because of the way I act some people don’t realize it is hard to always be happy.
- I know this might sound stupid, but I can’t tie my shoelaces. I wear shoes with elasticated shoelaces.

Interviewer: What is the biggest thing that having a child with Williams syndrome has taught you?

- Parent: The biggest thing we have learnt is that a person with Williams syndrome is no different to you and me. We all have different personalities, have different needs and process information differently. We have a greater level of acceptance and empathy by having a person with Williams syndrome in our lives.

Interviewer: What have been the major challenges associated with having a daughter with Williams syndrome?

- Parent: At first it is hectic. Appointments are ongoing and seem to be never-ending. You are always planning for the next stage. Learning how to feed and care for your child with Williams syndrome is the first step. Then, moving on to therapy and the first stage of learning with early intervention and transition to school.
- Also, stranger danger is a big concern as Molly accepts everyone as her best friend.

Interviewer: What is your take-home message to new parents of a child with Williams syndrome?

- Parent: Don’t be afraid to ask for support especially in the early years as there are times that you will be overwhelmed but, as time goes on, the positives can outweigh the negatives.

Interviewer: What are the three main points you want to make about Williams syndrome?

- Parent: Williams syndrome is challenging but can be rewarding. The person with Williams syndrome is just like you and I but processes information slower. We just need to be more accepting, tolerant, non-judgmental. Treat a person with Williams syndrome with respect.

Box 2 | Key questions for future work in Williams syndrome

Long-term health in individuals with Williams syndrome (WS)

- How do health needs change for individuals with WS across the lifespan? What recommendations can be made to optimize the health of older individuals with WS?
- Do different pathologies arise in WS at different developmental stages and are any reversible? If treatments are designed targeting early processes, will this 'normalize' future outcomes or will it be necessary to target multiple stages and processes?

Phenotypic variability

- What are the biological and environmental contributors to variability in outcomes in WS?
- How do the ~20 WS critical region genes without a specific phenotype designation affect health and development in people with WS? How should the combinatorial effects of multiple genes on disease variability be assessed?
- How does variability in WS critical region genes contribute to phenotypic variability in the general population?

Disease mechanism

- What are the developmental neuropathological mechanisms underlying the social and anxiety-related behaviour impairments in WS?
- What factors impact the transcription, translation and deposition of elastin? Can those genes or pathways be harnessed to appropriately re-initiate elastin deposition outside of its normal developmental window?
- What underlies metabolic differences in WS, such as glucose dysregulation, aberrant growth and aberrant body composition? How do changes in the genes contributing to these phenotypes affect the health of people with and without WS?

Interventions and treatment

- What interventions (medical, psychological or behavioural) would best improve the quality of life for people with WS, especially pertaining to anxiety, mastery motivation and social vulnerability?
- Should hypertension be aggressively treated in WS? What are the effects on short-term end-organ perfusion and longer-term organ function?
- What risk factors for adverse anaesthesia events need further refinement, such that management guidelines can be generated and widely shared?

Research priorities for WS

- How can resources be developed to facilitate collaborative data collection and treatment trial coordination to optimize the delivery of new treatments for people with WS?

underlying this variability are mostly unknown. It is likely that both environmental factors and genetic modifiers contribute to the overall penetrance of specific signs and symptoms in an individual with WS.

The study of polygenic risk is still in its relative infancy but offers essential insight into features of WS that overlap with common health conditions in the general population^{284,285}. Variation in genes that globally influence hypertension or IQ, for example, likely act together with genes in the WSCR in additive and synergistic ways to produce much of the observed variation²⁸⁶. In this way, the study of genetic modifiers in individuals with microdeletion disorders may offer a shortcut to identify relevant disease pathways by acting as a sensitivity screen of sorts, with the notable downside being the difficulty in acquiring truly robust sample sizes.

Sets of polygenic risk genes for more unique WS features (such as SVAS or odynacosis²⁸⁷) are currently unavailable but, if identified, they may provide insight into targetable pathways that could impact these important outcomes. For example, ~20% of all individuals with WS require surgical correction for SVAS but, if it has

been established that those who do need surgery have a variation in a particular pathway, treatment could be targeted to the modifier pathway rather than to elastin insufficiency itself. Some work has already been initiated in this area²⁹ but larger studies covering a broader racial and ethnic distribution are needed.

Other, understudied areas of potential variation include epigenetic effects and somatic variation. In addition, little is known about how differences in the flanking LCR regions, which are difficult to study by current short-read sequencing methods, may affect disease outcomes. Another area requiring further study is the influence of environmental factors, prenatally and throughout life, on disease outcomes. The gut microbiome, which is potentially affected by feeding difficulties, early hospitalizations and increased medication use, also deserves consideration. Environment and gene–environment interactions, in particular, are likely to play a crucial role in educational achievement^{14,245,247,248} and adaptive functional outcomes^{13,223,250}.

Effective treatment strategies

Treatment strategies can be designed using a variety of approaches: targeting the genes and/or gene products themselves, targeting functional pathways and aiming to treat disease symptoms and signs. For the gene-based strategies, CRISPR-based and viral vector-based gene therapy technologies^{288,289} are currently being studied in other rare conditions^{290,291}. However, unlike single-gene diseases, microdeletion disorders such as WS offer particular challenges that relate to the large size of the material to be delivered and the sheer number of locations where the genes would need to be targeted to alter the relevant phenotypes. It is possible that a subset of genes could be delivered using the methods previously described, which may improve the efficiency of delivery and function. However, it is known that the 7q11.23 duplication syndrome^{149,292} results from increased dosage of at least some of the genes in the WSCR and, therefore, any therapeutic approach must involve carefully regulated gene expression or protein replacement. Although the ability to identify and modify target genes, either in utero or in the early postnatal stages, offers the potential to greatly improve precise treatment in WS, much work is required before this strategy becomes a reality.

In the coming years, therapies are expected based on individual genes or pathways that are known to be important for influencing phenotype in WS. Studies in mouse models, for example, suggest that anti-microRNAs (such as anti-miR29a) may be useful for increasing elastin deposition²¹¹ and that influencing smooth muscle cell behaviour using inhibitors of mTOR¹⁰⁶ or integrin $\beta 3$ (REF.¹⁰¹) could improve the vascular features of WS. Moreover, new pharmacological strategies targeting myelination have been proposed for improving neural outcomes¹⁴³. However, each of these potential strategies comes with challenges in delivery, specificity or longevity. For example, miR29a regulates multiple transcripts; thus, although anti-miR29a administration may lead to increased elastin message stability (and therefore to increased translation)²¹¹, other transcripts bound by

miR29a may also be affected, potentially leading to other complications. The development of additional (non-rodent) WS models may be useful preclinical modalities prior to the initiation of human trials. As people with WS retain one copy of each gene from the WSCR, future studies could be aimed at developing methods to target and upregulate the expression of the remaining allele.

In addition, patient-derived iPSCs may soon offer platforms through which to test novel therapeutics for impact on the unique WS transcriptional pathways and phenotypes. Initial investigations incorporating this technology have been used to screen for medications that impact the increased proliferation of smooth muscle cells seen in WS¹⁰⁵. Rather than a goal of preventing stenosis, future studies that focus on resolving or reducing existing stenoses may be more relevant to treatment and lead to improved clinical outcomes, especially in young children who often come to medical attention with stenosis already present. When iPSCs or gene-edited versions thereof are being considered as deliverable therapeutics themselves, the timing and delivery mechanisms will be critically important.

In the interim, clinicians manage specific symptoms in individuals with WS (such as hypertension, anxiety and hypercalcaemia) using medications and interventions that have been developed for these indications in the general population, without knowing if the mechanism of disease in WS is the same. For example, several classes of antihypertensive drugs are available and monotherapy or polytherapy can reduce blood pressure in most individuals with WS. However, the targeting of these drugs is not mechanism based and

formal studies on which medications in these classes are best for symptom control in the WS population are lacking²¹⁴. The mechanistic and modifier studies previously defined could help narrow the options needed to pursue hypothesis-driven clinical trials. In the near term, longitudinal studies and open label and double-blind randomized clinical trials on common and high-impact medical and behavioural problems are needed, the findings of which could provide valuable clinical algorithms to guide treatment.

Moving forward

To improve the health outcomes for people with WS, a multifaceted translational approach is needed that brings together more investigators with expertise in the range of conditions and genes represented in WS. Newer topics, such as metabolic and immune differences^{29,66,190} in WS, are also in need of innovators. Funding is required to allow for the creation of a large international consortium that will collect prospective standardized data focused on the most relevant questions in WS and will incentivize the broad sharing of data acquired in diverse populations. Such a consortium will allow the more rapid collection and dissemination of natural history data that are needed to understand long-term outcomes and to choose appropriate endpoints for subsequent clinical trials. In addition, biospecimen collection can be optimized by the same mechanism. Ultimately, clinical trials focusing on therapies are critically needed to increase the QOL of individuals with WS and their families.

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Author contributions

B.A.K. and B.R.P. developed the outline for the manuscript, engaged the contributors and synthesized the final manuscript. All authors participated in the research, writing, and editing of the document and all approved the final version of the manuscript. C.A.K. provided clinical photos and M.P. conducted the family experience interview.

Competing interests

The authors declare no conflicts of interest.

Informed consent

The authors affirm that human research participants provided informed consent for: publication of the photographs in Fig. 4 and Supplementary Table 1 and taking part in the family experience interview.

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