

characterized by the same intellectual openness and rigor displayed in his scientific research.

See also

Avery, Oswald Theodore
Crick, Francis
DNA Structure
Franklin, Rosalind Elsie
Watson, James Dewey

Further Reading

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Williams Syndrome: A Neurogenetic Model of Human Behavior

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Williams syndrome (WMS) is a rare neurogenetic disorder, usually caused by a deletion at 7q11.23. Integrating the genetic with the distinctive clinical, cognitive, neurophysiological and neuroanatomical profiles of WMS provides an opportunity to understand the molecular basis of human cognition and behavior.

Introductory article

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Introduction

Even when times are bad we still try to shine a light upon other people, and to give that sense of glow to our friends... You have to accept things you cannot change. (Twin 1 with Williams syndrome)

First of all I am a human being, and I'm a man... And I want people to realize that I do have feelings, I'm not a freak... So respectability is a main factor in learning how to deal with people with Williams syndrome or any other syndrome. (Twin 2 with Williams syndrome)

These are quotes from patients who knew the impact that the diagnosis of Williams syndrome (WMS) had on their lives. However, researchers and doctors have only recently begun to realize the potential neurogenetic impact of WMS, as was first hinted at in 1952 by Fanconi *et al.*, who noticed patients with hypercalcemia and 'elfin' facial features. Later, in 1961, Williams, Barratt-Boyes and Lowe independently reported clinical findings of supraaortic stenosis and the same elfin facial features in patients. For a time, it was considered a genetic disorder of unknown

origin, until 1993, when it was discovered that WMS is caused by the deletion of one copy of a small set of genes on chromosome 7 (7q11.23).

WMS is a special syndrome for many reasons. It is a rare and complex genetic disorder, occurring in one in 20 000 live births. Due to a deletion in chromosome band 7q11.23, the patients have cardiovascular, connective tissue and neurodevelopmental deficits (**Table 1**). In addition, WMS patients have an unusual cognitive profile, with strengths and weaknesses in cognitive abilities, such as engaging language ability being masked by low IQ. Using WMS as a model, one of the greatest challenges faced in understanding the relationships between genetics, brain anatomy and cognition is the need to link investigations across disciplines within the neurosciences. Here we present studies on WMS that reveal distinctive profiles of clinical, genetic, cognitive, neurophysiological and neuroanatomical characteristics, which allow us to begin to infer anatomical and physiological interconnections and to understand the molecular basis of human behavior.

Table 1 Summary of major phenotypic features of Williams syndrome

Neurological	Cardiovascular	Genitourinary	Neurocognitive	Musculoskeletal	Endocrine	Facies
Average IQ 55 (range 40–80)	Supravalvular aortic stenosis	Nephrocalcinosis	Friendly, loquacious personality	Joint limitations	Transient infantile hypercalcemia	Medial eyebrow flare
Mild neurological dysfunction	Pulmonic valvular stenosis	Small, solitary and/or pelvic kidneys	Enhanced musical ability	Kyphoscoliosis		Short nasal palpebral fissures; epicanthal folds
• Tight heel cords	Peripheral pulmonary artery stenosis	Vesicoureteral reflux	General anxiety	Hallux valgus		Flat nasal bridge, small upturned nose
• Poor coordination	Ventricular or atrial septal defects		Delayed but relatively spared language development, enhanced vocabulary and social use of language versus significant visual–spatial processing	Hypoplastic nails		Stellate iris
Hyperacusis	Defects of arterial walls			Adult stature slightly smaller than average		Long philtrum
Harsh, brassy or hoarse voice						Prominent lips with open mouth
						Puffiness around the eyes
						Small, widely spaced teeth

Clinical Features

Diagnostic characteristics of WMS embody a set of specific physical and facial features that include a constellation of cardiovascular difficulties such as supraventricular aortic stenosis (SVAS), a narrowing of the aorta; failure to thrive in infancy; transient neonatal hypercalcemia; delayed language and motor milestones; and abnormal sensitivities to classes of sound (hyperacusis). The facial features of WMS patients are quite distinctive and have been described as 'pixie-like' and 'elfin'. Persons with WMS often look more like each other than like their own family members. **Table 1** lists other physical and cognitive features of WMS.

Molecular-genetic Profile

What are the genetic origins of the observed features in WMS? It is caused by a microdeletion on chromosome

7 that involves the gene encoding elastin (ELN) and approximately 20 other genes, some of which are described in **Table 2**. To investigate the size and extent of deletions in individuals with WMS, a physical map of the deleted region of chromosome 7 band 7q11.23 has been constructed, using multicolor fluorescence *in situ* hybridization (FISH) of bacterial artificial chromosomes (BACs) on metaphase and interphase chromosomes, large-fragment library screening, genomic Southern blot and pulse-field gel analyses, sequence tagged site (STS) and polymorphic-marker analyses.

A working model of the genome organization was developed to characterize chromosome band 7q11.2, and it suggests that this region includes highly homologous chromosomal duplications that are also characterized by a number of repeat-sequence families, genes and pseudogenes. The overall region is comprised of inner and outer duplicated regions organized as nested repeated structures that surround the largely unique region occupied by elastin and the

Table 2 Common deletions in genes in subjects with Williams syndrome

Symbol	Gene name	Possible functions
<i>FKBP6</i>	FK506 binding protein 6	Structural homolog to FKBP immunophilins, cellular receptors for the immunosuppressive drugs FK506 and rapamycin
<i>FZD9</i>	Frizzled homolog 9 (<i>Drosophila</i>)	Transmembrane receptor for WNT. Highly expressed in all areas of the brain, eye, testis, skeletal muscle and kidney
<i>BAZ1B</i>	bromodomain adjacent to zinc-finger domain, 1B	Structural motifs involved in chromatin-dependent regulation of transcription
<i>BCL7B</i>	B-cell CLL/lymphoma 7B	Gene encodes serine-rich protein product, unknown function
<i>TBL2</i>	Transducin (beta)-like 2	Member of beta transducin protein family, with four putative WD 40 repeats, high expression in heart, brain, placenta, skeletal muscle and pancreas
WBSCR14	Williams–Beuren syndrome chromosome region 14	Member of the family of transcription factors, with nuclear localization signal
<i>STX1A</i>	Syntaxin 1A (brain)	Involved in neurotransmitter release from synaptic vesicles
<i>CLDN4</i>	Claudin 4	Functional high-affinity receptor for CPE. Specific expression in lung, kidney and intestine. Absence in brain and spleen
<i>CLDN3</i>	Claudin 3	Putative apoptosis-associated gene. Specific expression in lung, kidney and intestine. Low levels in brain, heart, muscle and spleen
<i>ELN</i>	Elastin (supraventricular aortic stenosis, Williams–Beuren syndrome)	Major structural protein in the development of arterial walls and connective tissue. Mutation causes SVAS
<i>LIMK1</i>	LIM domain kinase 1	Plays a signaling role in actin reorganization and cell movement
<i>WBSCR1</i>	Williams–Beuren syndrome chromosome region 1	A positive regulator of protein synthesis during translation initiation
<i>WBSCR5</i>	Williams–Beuren syndrome chromosome region 5	Unknown function
<i>RFC2</i>	Replication factor C (activator 1) 2 (40 kDa)	A subunit of a five protein complex involved in DNA strand elongation during replication
<i>CYLN2</i>	Cytoplasmic linker 2	Mediates interaction between specific organelles to microtubules
<i>GTF2IRD1</i>	GTF2I repeat domain containing 1	Set of five GTF2I-like repeats that possess the ability to interact with other HLH proteins and function as a transcription factor
<i>GTF2I</i>	General transcription factor II, i	Plays a role in transcription and signal transduction, a potential phosphorylation target

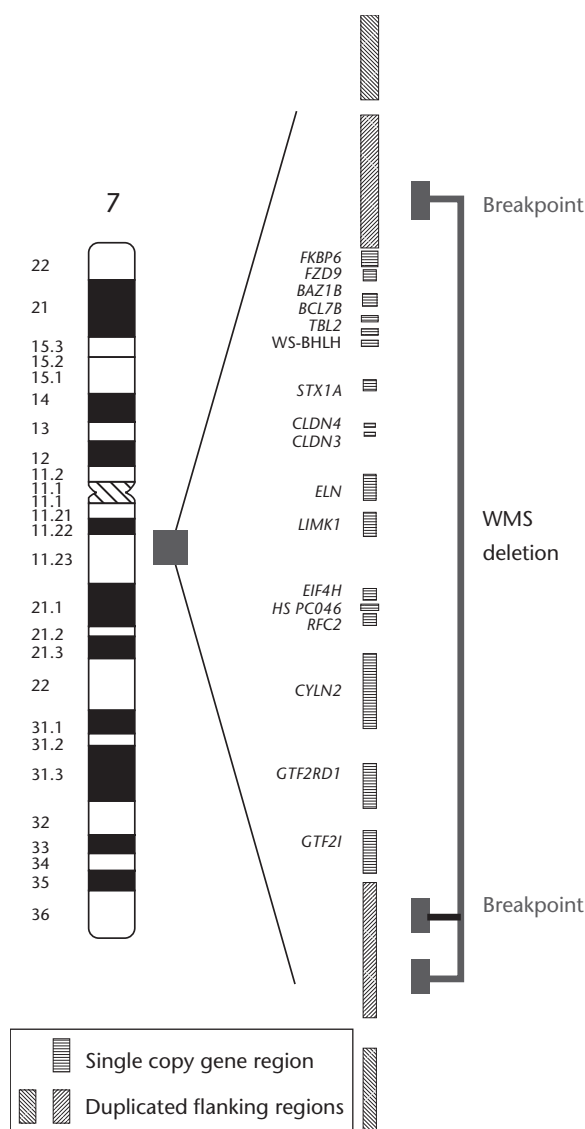


Figure 1 Region of chromosome 7, band 7q11.23, that is commonly deleted in Williams syndrome (WMS) is represented by the solid square. This region is expanded to the right to illustrate its genomic organization, a region of largely single copy genes flanked by a series of genomic duplications.

other deleted genes (**Figure 1**). This implies that the region of deoxyribonucleic acid (DNA) deleted in WMS individuals is located within an apparently single copy region of chromosome 7 that appears to be surrounded by a series of genomic duplications, some of which must be recent and others which have been duplicated earlier in primate evolution. The outer duplicated regions appear asymmetrically located with respect to the gene *ELN* (*elastin* (*supravalvular aortic stenosis*, *Williams–Beuren syndrome*)).

The common deletion breakpoints in WMS are located in the inner duplicated regions, clustered at one centromeric and two telomeric sites on chromosome 7.

Why do deletions occur? It is important to note that the causes of deletions involve a number of factors that may predispose to genomic instability. BAC and marker analyses have illustrated localization of the breakpoints, which suggest that particular sequences (i.e. frequency of Alu elements in the region, high degree of sequence conservation in the duplicated regions (99% identical), inversions) or chromatin structures may also contribute to regions of chromosome band borders that may themselves be unstable and may promote the tendency to delete. In any event, it is likely that the meiotic mispairing of subsets of the numerous repeated families, combined with crossing over, results in a series of different chromosomal aberrations of the deletion/duplication types. Because the deletion breakpoints in WMS occur largely in common regions, most individuals with WMS have the same genes deleted. In the following sections, unusual dissociations in higher cortical functioning and brain anatomy in WMS provide opportunities to explore some of the central issues of cognitive neuroscience that tie cognitive functions to brain organization and, ultimately, to the human genome.

Cognitive Profile

General cognitive functioning

From studies across different populations, a characteristic WMS cognitive profile is emerging. Although characterized with general anxiety, individuals with WMS have an excessively social personality and an increased appreciation of music. Moreover, WMS patients display characteristic ‘peaks’ and ‘valleys’ in specific cognitive abilities. Across an array of standardized conceptual and problem-solving tasks (some verbal, some nonverbal), WMS patients demonstrate a consistent, serious impairment in general cognitive functioning. In general cognitive tasks such as IQ probes, most individuals with WMS rank in the ‘mild-to-moderate mentally retarded’ range, with global standard scores on IQ test ranging from 40 to 80, with a mean of 55. A hallmark of WMS is the dissociation between language (which is a strength in adolescents and adults) and spatial cognition at global levels (which is profoundly impaired), as shown in **Figure 2**. Complex expressive language abilities and face-processing abilities are remarkably strong.

Expressive language abilities and linguistic affect

One striking aspect of WMS is the strong language ability in adolescents and adults, in contrast to the

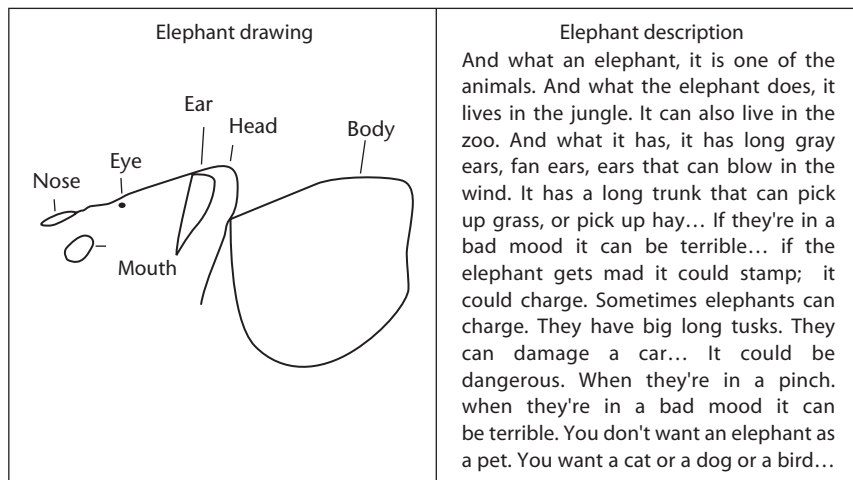


Figure 2 Contrasts of drawing and description of an elephant by a teenager with WMS. The dissociation between language and spatial cognition in WMS is evident (full-scale IQ of 49, verbal IQ of 52 and performance IQ of 54).



WMS, age 17, IQ 50:

Once upon a time when it was dark at night... the boy had a frog. The boy was looking at the frog... sitting on the chair, on the table, and the dog was looking through... looking up to the frog in a jar. That night he slept and slept for a long time, the dog did. But, the frog was not gonna go to sleep. The frog went out from the jar. And when the frog went out... the boy and the dog were still sleeping. Next morning it was beautiful in the morning. It was bright and the sun was nice and warm. Then suddenly when he opened his eyes... he looked at the jar and then suddenly the frog was not there. The jar was empty. There was no frog to be found.

DNS, age 18, IQ 55:

The frog is in the jar. The jar is on the floor. The jar on the floor. That's it. The stool is broke. The clothes is laying there.

Figure 3 WMS individuals use affective devices in storytelling, compared with subjects with Down syndrome (DNS). Examples from narratives of the *Frog, Where Are You?* story show the excessive use of narrative evaluative devices in adolescents with WMS.

overall impairment seen in cognitive abilities. In the earliest stages of language development, children with WMS show significant delay. However, once language is acquired, this acquisition tends to become a relative strength. Compared with age-matched and full-scale IQ-matched subjects with Down syndrome (DNS), subjects with WMS perform far better on a wide variety of grammar probes.

Another distinctive facet of the language abilities of WMS patients is their ability to use their heightened linguistic skills to engage others socially. Many individuals with WMS display a strong impulse toward social contact and affective expression. The intersection of language behavior and social engagement in individuals with WMS has been investigated and compared with DNS patients through a series of

narrative tasks in which subjects are asked to tell a story from a wordless book (**Figure 3**). The most obvious distinction between patients with WMS, DNS and age-matched normal controls is in the use of narrative enrichment devices (affective qualities) during the story-telling task by WMS patients. Individuals with WMS, therefore, exhibit a striking contrast to the social and language profiles of individuals with other disorders.

Visual-spatial cognition in WMS

In studies that examined global spatial cognition, in contrast to language, patients with WMS were significantly more impaired than subjects with DNS across all age ranges examined. For example, a WMS

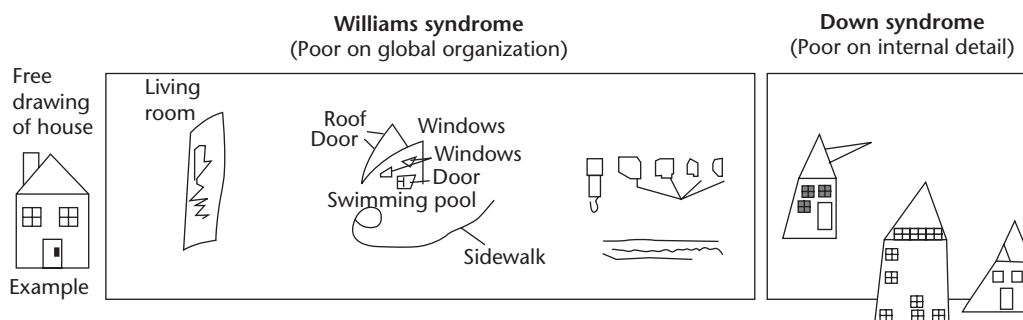


Figure 4 Free drawings of houses by age- and IQ-matched adolescents with WMS and DNS show different spatial deficits. The drawings by subjects with WMS contain many parts of houses but the parts are not organized coherently. In contrast, the DNS subjects' drawings are simplified but have the correct overall configuration of houses.

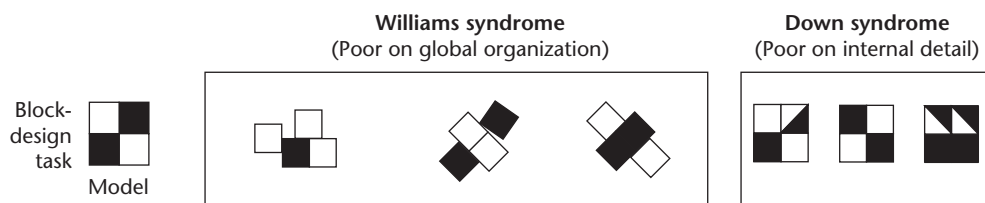


Figure 5 Block-design task showing spatial deficits in WMS and DNS. WMS subjects typically show disjointed and fragmented designs, while age- and IQ-matched DNS subjects tend to make errors in internal details while maintaining the overall configuration.

patient may draw different parts of a house as separate entities from the house itself, thus lacking global organization (**Figure 4**). On block-design tasks, both WMS and DNS subjects performed poorly, but in different ways: those with WMS were typically unable to organize the blocks into a global pattern, and patients with DNS instead made errors of internal detail (**Figure 5**). However, across difficult face-processing and recognition tasks, individuals with WMS showed strong performance in contrast to spatial cognition (**Figure 6**).

Neurophysiological Profile

Connections between cognition and neurophysiological characteristics of WMS are being revealed through studies of brain function (event-related potentials, ERPs). ERP techniques are used to assess the timing and organization of the neural systems that are active during sensory, cognitive and linguistic processing in patients with WMS and provide information about the timing and temporal sequence of neural activity.

Neurophysiological markers for auditory language and face processing

Are the spared abilities such as language and face processing normally organized in WMS brains or do

they show a different, perhaps unique pattern of functional organization? The ERP technique is ideally suited to examine this question. ERPs are recorded from electrodes placed on the scalp and measure the electrical activity of the brain time-locked to particular events. They are characterized by a series of positive and negative fluctuations in voltage (measured in microvolts) and reflect changes in brain activity over time on a millisecond by millisecond basis.

ERPs to auditory words are markedly different between WMS and controls. Individuals with WMS show larger amounts of neural activity within the first 200 ms after hearing a word than do same-age controls. This increased activity is reflected by larger ERP amplitudes for two positive ERP components peaking at 50 and 200 ms (P50 and P200; **Figure 7a**). These components, generated in primary auditory cortex, may index increased sensitivity to sound in WMS. Whether the hyperexcitability of the auditory system is related to the sparing of language abilities in WMS is unknown.

ERPs to faces presented one at a time in a face-recognition task show that the first negative component, peaking at 100 ms (N100), is abnormally small in WMS, whereas the second negative component (N200) is abnormally large (about 5 times the amount of activity in controls; **Figure 7b**). The abnormally small N100 amplitude reflects decreased neural activity in primary visual cortex and is likely to be linked to structural curtailment of the occipital lobes. In

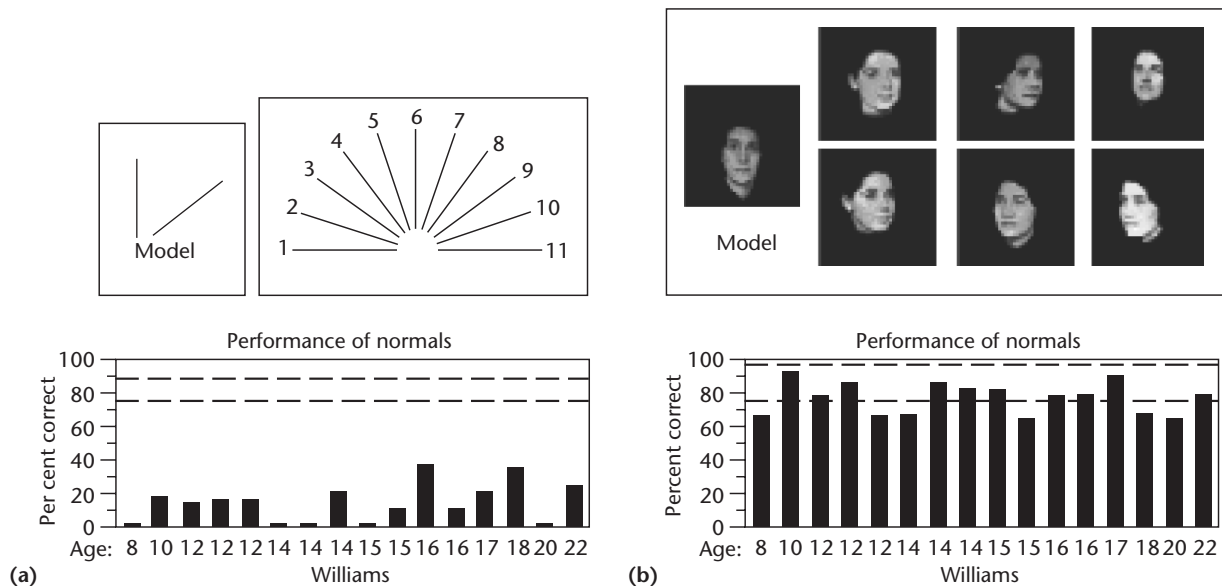


Figure 6 (a) Line- and (b) face-processing in WMS. The results are shown from two tasks that are both visuo-perceptual tasks, where the correct answer requires only pointing to a picture without any constructional component. The contrast in performance on (a) line orientation (Benton judgment of line orientation) and (b) face discrimination (Benton face recognition) is shown for 16 individuals with WMS. On the line-orientation task, several individuals with WMS could not even pass the warm-up items. In great contrast, another 16 subjects with WMS perform remarkably well on a very difficult face-discrimination task that involves recognizing the same individual under different conditions of lighting, shadow and orientation. In both tasks, performance of normal individuals is indicated by the broken lines.

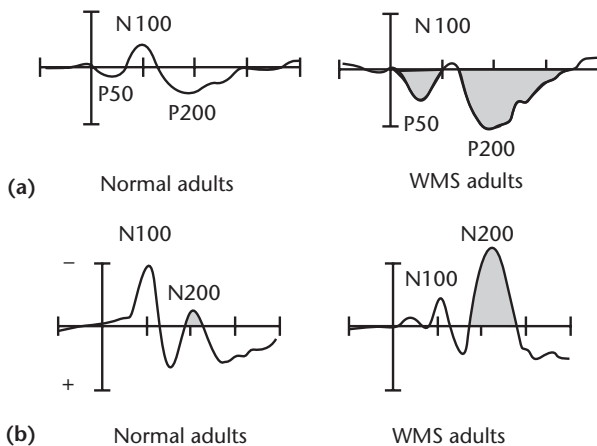


Figure 7 Neurophysiological markers for language and face processing: (a) ERPs to auditory words and (b) ERPs to upright faces.

contrast the abnormally large N200 is thought to be linked to increased attention to faces in WMS.

The ERP patterns observed for both auditory language and faces are characteristic of almost all WMS subjects, but not observed in normal adults, children or in other atypical populations that have been studied. Individuals with WMS show equal amounts of activity over the left and the right

hemispheres to both spoken words and faces. That is, they do not show the lateral asymmetries (i.e. left greater than right to words, and right greater than left to faces) observed in normal adults. Thus, the unique phenotypic markers for language and face processing may serve as neurophysiological indices that relate brain and behavior characteristic in WMS and, taken together, these findings suggest that, in individuals with WMS, the neural systems that subserve higher cognitive functions such as language and face processing are different from normal individuals.

Neuroanatomical Characteristics

With the presence of a predictable neurobehavioral phenotype, coupled with the availability of increasingly sophisticated technology for assessing brain structure and function, initial neuroimaging studies have been carried out to investigate the neural systems that mediate the cognitive profile of individuals with WMS. The results to date point to specific morphological differences between WMS and comparison groups and also provide clues as to the neuroanatomical basis of the uneven cognitive profile observed in individuals with WMS.

Two groups, WMS subjects and normal controls, were studied using magnetic resonance imaging

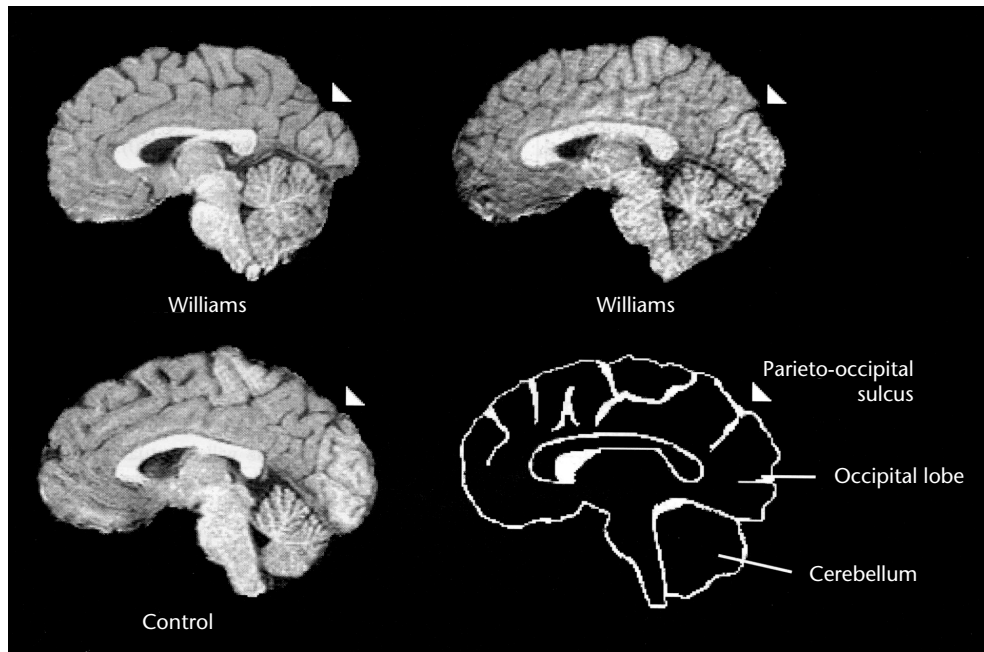


Figure 8 Occipital lobe reduction and preservation of cerebellum. Comparable sagittal MRI brain images from two subjects with WMS and a normal control. The images demonstrate that the occipital lobe, separated from the parietal lobe by the parieto-occipital sulcus (triangle), is greatly reduced in the subjects with WMS. Relative preservation of cerebellar size in WMS relative to controls is also shown.

(MRI). Initial findings from preliminary imaging studies suggested that the brains of individuals with WMS were reduced (15%) in volume overall compared with normal controls, with relative preservation of cerebellar volume. In addition, occipital lobe gray matter volume, particularly on the right, was noted to be decreased in the WMS group compared with controls (**Figure 8**). Other brain areas found to be preserved (or disproportionately enlarged) in subjects with WMS were the superior temporal region and midline cerebellum (vermis). The superior temporal region of the brain is thought to be important in the perception and processing of music, as well as in auditory and language processing, while the cerebellar vermis is involved in sensory information processing and social behavior.

Planned future studies will focus on limbic, mesial temporal and subcortical regions, as well as subregions of the cerebellum. Shape-based analyses of the cerebral lobes and their relation to the posterior fossa also are underway to more fully elucidate possible patterns of altered brain development in individuals with WMS. Eventual correlation of neurocognitive and structural imaging findings with results obtained from functional imaging studies will be particularly important in elucidating the topography of neuroanatomical function and dysfunction underlying cognition and behavior in individuals affected with this enigmatic genetic condition.

Development of a Phenotypic Map of WMS Cognition

To understand the pathways that bridge genes and behavior, the genes deleted in different individuals with WMS are correlated across levels. This encompasses neural information on gene expression, neuroanatomy, physiology and neurocognition. Since the common WMS deletion involves essentially the same genes deleted, accompanied by variable phenotypes observed in individuals with WMS, assigning specific genes to certain features has become an arduous task. Ideally, to link genes to features, some variability in deletions and variations in cognitive behavior are essential to determine the relationships. Based on that, a database of individuals who carry a partial deletion and show only some features of WMS has been started. It is by combining current molecular and cognitive data from these subjects with other individuals carrying atypical deletions that variability in specific neurocognitive features of WMS has been assigned to different regions with known genes. The current phenotypic map of WMS is shown in **Figure 9**.

The construction of the phenotypic map allows us to ask not only which genes are likely to affect cognition, but also which regions and their genes have been demonstrated in humans to be associated with changes in cognition when deleted. For example,

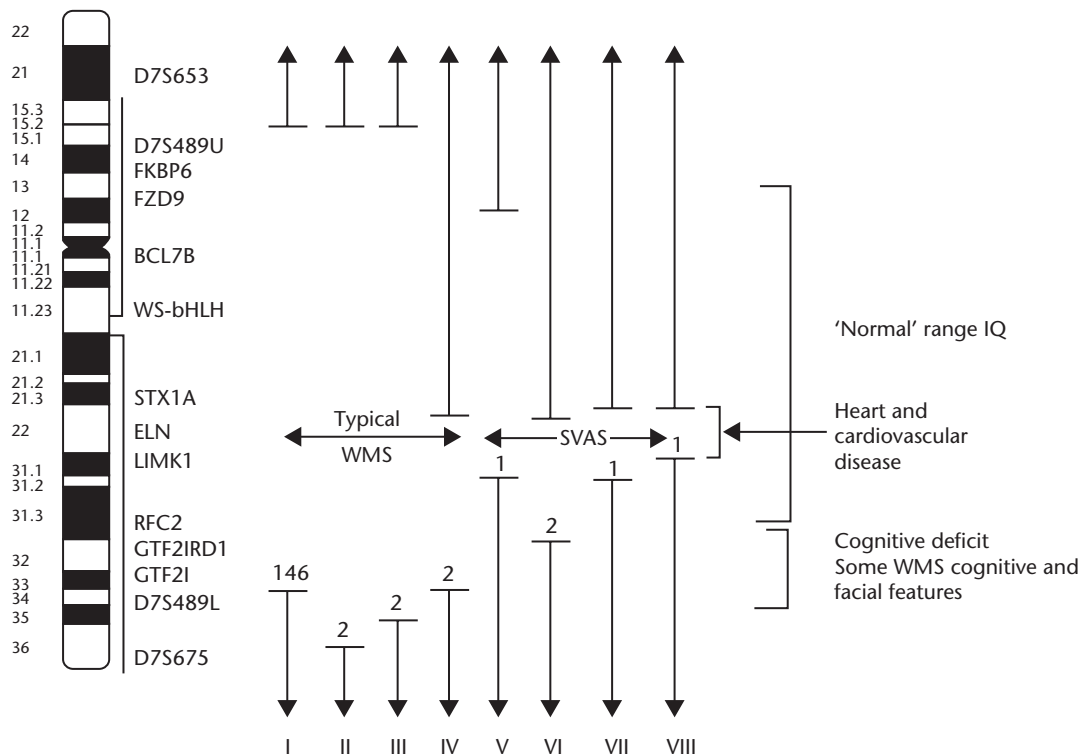


Figure 9 Phenotypic map of WMS. Spaces between vertical lines indicate the regions deleted, and the number of subjects carrying the deletion (i.e. typical deletion, $n=146$). Square brackets indicate regions that are likely to contain a gene or genes that when deleted contribute in some measure to the characteristic features of WMS. The significance of these data is that deletion of *FZD9* through *RFC2* does not appear to be associated with the characteristic facial features or cognitive deficits seen in WMS, although it could contribute.

from previous studies of isolated cases with small deletions and mutations of *ELN*, it appears that the absence of one copy of the gene is probably responsible for the cardiovascular defects in WMS. The lack of characteristic features (i.e. facies, hoarse voice) in individuals with *ELN* single-base mutations also suggests that none of the other physical features are largely due to deletion of *ELN*. In contrast, although the absence of one copy of *LIMK1* has been implicated in the spatial deficit characteristic of WMS, a study of three isolated subjects whose deletions included *LIMK1* reveals that the absence of this gene and others in the region is compatible with normal range function. Moreover, analyses of two individuals who carry a smaller deletion of the region from *FZD9* through *RFC2* indicate that the genes in this region are unlikely to be the major cause of variation characteristic of WMS cognitive and visual-spatial deficits or facial features. This is because both individuals have heart disease with essentially normal range or mildly impaired cognitive and physical features. Therefore, one can infer that the genes responsible for a significant part of mental retardation and other features are located in the region of *RFC2* through *GTF2I*, although genes located outside these regions

may also be involved. On the whole, these findings are important in setting out the approach for defining the consequences of specific deletions. Greater understanding of the range of such consequences thus requires further studies of further individuals and model systems.

Besides studying individuals with atypical deletions, what other molecular perspectives are considered necessary for understanding the factors underlying WMS cognition? To begin, it is important to note that the variable expression of genes that are not deleted may also contribute to phenotype. Sources of their variation may involve the effects of transcribed but not translated pseudogenes, including those for *GTF2I*. Further sources of phenotypic variability include interactions of genes in the deleted region, with others mapping both inside and outside of the WMS region, as well as possible regional disturbances of replication and transcription due to deletion and chromatin rearrangement. Such larger rearrangements that do not result in deletion may therefore be a cause of the WMS phenotype. Furthermore, some rearrangements may lead to the decreased expression of nondeleted genes located in the region close to the deletion. Other potential sources of genetic effects on cognition

include imprinting, or the phenomenon by which the expression of a gene is differentially modified by passing through the maternal versus the paternal germ line.

In summary, to increase the understanding of the genes and their role in the development of WMS features, future studies of rare WMS subjects with atypical deletions are necessary to identify gene candidates for human cognitive features and characteristic WMS phenotype. The resulting multidimensional data from well-studied individuals with atypical deletions will help elucidate the many levels requiring intersection in the neurosciences; the role of cellular processes and neuroanatomical structures in cognition and behavior; and the role of gene expression in determining structure, cognition and disease.

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See also

Microdeletion Syndromes
Microdeletions and Microduplications: Mechanism

Further Reading

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Web Links

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<http://www3.ncbi.nlm.nih.gov/htbin-post/Omim/dispim?130160>