

Preface

Late one evening in 1984 the phone rang in Dr. Ursula Bellugi's lab at the Salk Institute. The woman on the phone began by saying "Noam Chomsky told me to call you. . . ." The woman described her daughter, age 14, who seemed to have a rare syndrome, in which her engaging language abilities remarkably masked her low IQ of 49. After some coaxing, as this was not her area of expertise, Bellugi reluctantly agreed to meet with the child who had been diagnosed with Williams syndrome (WMS). In an exciting first meeting, the girl exemplified what would turn out to be one of the hallmarks of the syndrome: A dissociation between visuospatial and language abilities (see Figure 1). Her drawing of an elephant was unrecognizable without the verbal labels we added as she talked her way through the drawing. In contrast, her description of an elephant was grammatically fluent with complex sentences, including what an elephant is, what it does, what it has ("It has a long trunk that can pick up grass or pick up hay . . . you don't want an elephant as a pet, you want a cat or a dog or a bird"). Bellugi agreed to meet with the child weekly, and every imaginable cognitive test was given to her over the following year in an attempt to begin to understand what appeared to be an unusual profile of the syndrome in one individual. At the time these studies began, Bellugi had expertise in the effects of right- and left-hemisphere lesions and the relative sparing and impairment of language and spatial abilities, resulting from her studies of the neurobiology of language in deaf signers. Although not known at the time, this would turn out to be an interesting background with which to approach the WMS puzzle.

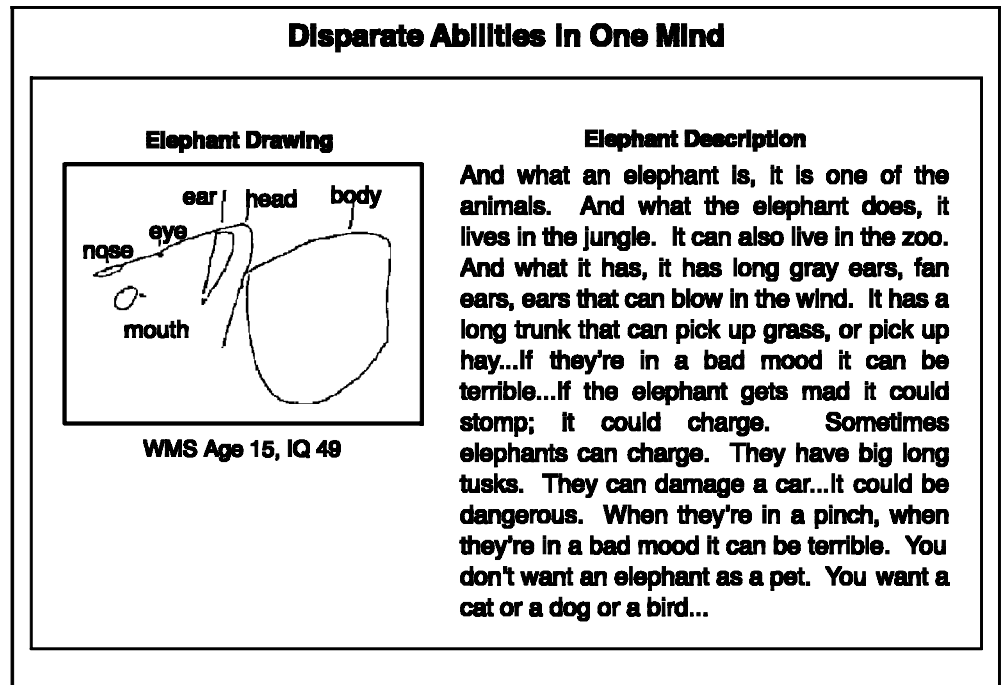
Near the end of this initial year of testing, the first meeting of a Williams Syndrome Association was held in San Diego, CA in 1984, with several families attending. At this time, there were only 60 identified cases of WMS in the country. Nothing was known of the genetics of the syndrome. In fact, little had been published at all on WMS other than a few studies of IQ, which were inconclusive. A medical intern had begun to study the possible contribution of high levels of calcium in the blood to the syndrome. This idea sparked a first attempt at finding the gene associated with WMS based on the hypothesis that it might be related to calcitonin gene-related peptide. This first attempt, however, was not as fruitful as the following would be.

The first big breakthrough came during the next decade, as Bellugi built up a laboratory dedicated, in

part, to the study of the cognitive and brain bases of WMS contrasted with Down syndrome (DNS), with the help of grants from NICHD, NINDS, and NIDCD. She began to uncover the fascinating phenotypic profile of WMS, leading to a series of papers, and a growing interest in WMS. A second breakthrough occurred around 1993, when it was discovered that the gene for elastin was part of the microdeletion in WMS (Bellugi & Morris, 1995; Ewart et al., 1993). The road was paved for a molecular genetics branch of the study of WMS. Who would do it? During the whole of her career at the Salk Institute, Bellugi had yearned to be able to integrate results from cognition, brain, and molecular genetics. This was perhaps her chance. After studying WMS individuals for years, developing a cognitive phenotype, uncovering aspects of the brain bases of WMS, setting up a WMS clinic, organizing local, regional and national family meetings, and contributing regularly to the family newsletter, in 1994–1995 Bellugi et al. began a program project through NICHD—which was one of the first of its kind—to investigate this genetically-based syndrome with its well-defined phenotype across cognitive, neuroanatomical, neurophysiological, and molecular genetic levels, as opposed to merely the investigation of mental retardation. Bellugi gathered a team of scientists whose research is included in this special issue to participate. The true strength of the program project is that all of the five levels, from cognition to brain structure and function, as well as molecular genetics, are investigated with the *same* individuals with WMS (with the exception, obviously, of the cytoarchitectonic studies; see Figure 2 for a diagram of the five levels of the program project.)

As this special issue unfolds, you will learn that WMS is a special syndrome for many reasons. As Jonas Salk said of WMS, "I never knew talent was a birth defect." The discrepancy between language ability and IQ is startling, and many who hear about the syndrome are skeptical until they meet someone with WMS. Their remarkable language provides a window into what it is like to have WMS in that it allows them to be able to explain eloquently what it feels like to be mentally retarded. It is difficult to grasp their sophistication with language, their connection to their own emotions, and their ability to express those emotions without actually talking to someone with WMS. Below is an excerpt from an interview by Bellugi of twins, both men age 32, with WMS. The first quote is from one twin, the second from the

Figure 1. The dissociation between language and spatial cognition in WMS is evident in this contrast between the drawing and verbal description of an elephant by a teenager with WMS (Full Scale IQ of 49, Verbal IQ of 52, and Performance IQ of 54).



other twin, when asked what they would want other people to know about WMS.

It is what you're born with, it is what you have to accept, and it is something that you go on day to day, year to year, month to month with. And no matter how people treat people with Williams syndrome, you always have to stand tall and ignore the things that are said because they are, they don't understand the things that we go through every day that we wake up. We should be treated the same way somebody else should be treated. 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).

We are respectable, loving, understanding people. With pride, and dignity, and grace. And people should understand that Williams people don't really care about the bad things in life and what goes on in the world because we as people have enough problems of our own living day to day ... First of all I am a human being, and I'm a man, and I'm an older adult. 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).

I gotta tell you, Dr. Bellugi, we love everyone that we meet. And if people would be, show us love and kind that we try so much to do to other people, I think

doors would open and people would understand that, um, we don't need to carry on wars, that we don't need to carry on gang violence. Peace and love. And that's all that everyone with Williams syndrome has been asking for years. For someone to give us a break. As much as the break we have been giving to them. (Twin #1).

In addition to expressing themselves linguistically with clarity and eloquence, they frequently take up another form of self-expression, with similarly remarkable performance, in the form of music. People with WMS seem to have a special love of music—both playing instruments and singing, as well as listening to others make music. There are many anecdotes about WMS and music. The fact is that there is something very special about both their attraction, as well as their ability to perform. Some can't tie their shoes but can repeat and create complex rhythms on a musical instrument. The incidence of perfect pitch may be greater in WMS than in the general population. Several people with WMS can play a song on the piano after listening to it once. One woman with WMS can sing over a thousand songs in 22 different languages. In one of our first experiences with WMS and music, we discovered a love song written by a woman with WMS to a man with DNS. It was a touching song to her "sweet petunia."

History of Williams Syndrome

Williams Syndrome was discovered independently by Fanconi (1952) and a British cardiologist, Williams,

Williams Syndrome Bridging Cognition, Brain & Gene

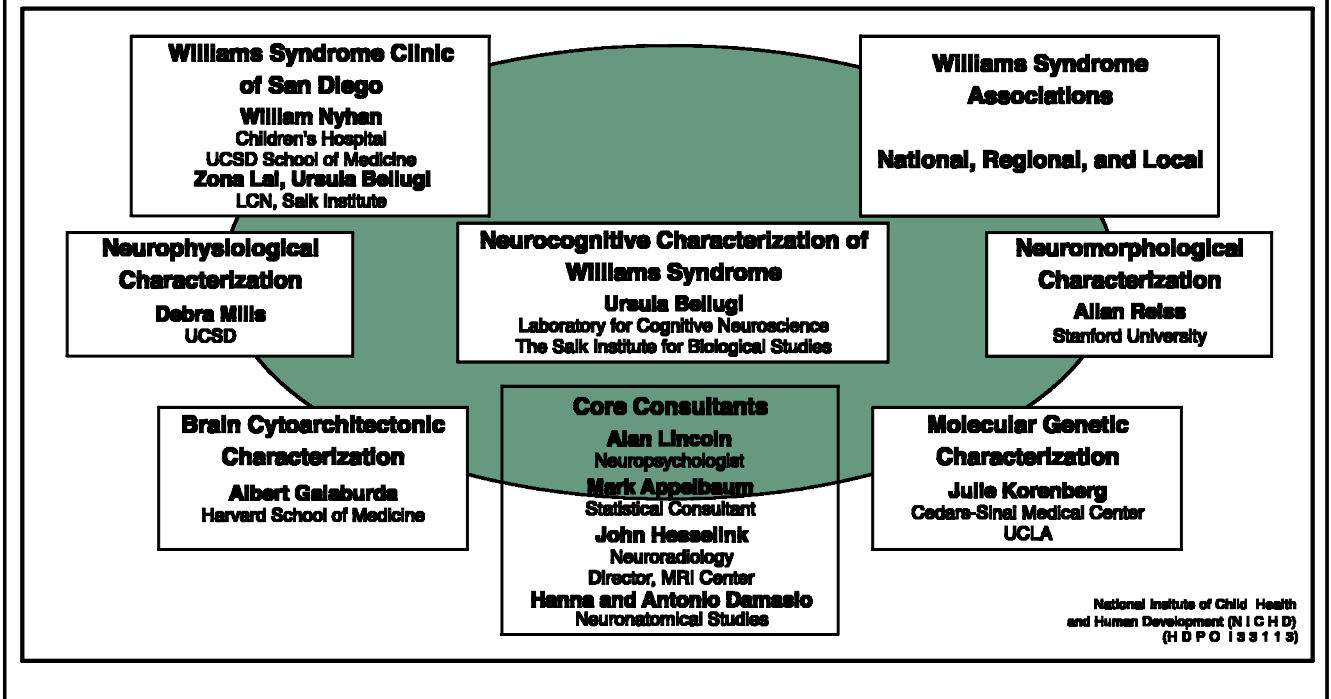


Figure 2. The organization of the Program Project (PPG), from the National Institutes of Child Health and Human Development (NICHD PO1 HD 33113). Most of the research in this special issue stems from studies under this grant involving adolescents and adults with WMS or DNS. The chart represents the major projects of the program project, each of which is represented in one of the chapters in this issue: Neurocognitive characterization at The Salk Institute Laboratory for Cognitive Neuroscience (Bellugi et al., Chap. 1 and Jones et al., Chap. 2); Neurophysiological characterization at UCSD Center for Research on Language (Mills et al., Chap. 3); Neuromorphological characterization at Stanford University (Reiss et al., Chap. 4); Brain cytoarchitectonics at Beth Israel Hospital and Harvard Medical School (Galaburda & Bellugi, Chap. 5); and Molecular genetic characterization at Cedars-Sinai Hospital and University of California, Los Angeles (Korenberg et al., Chap. 6). The chart also shows the Williams Syndrome Clinic we have set up at Children’s Hospital in San Diego, (Nyhan, Lai and Bellugi), and our interconnections with the National and Local Williams Syndrome parent organizations. The special power of these studies is that the same individuals are carefully screened and diagnosed, and then undergo the same probes across multiple levels and disciplines. Studies of infants and children with WMS and DNS are supported as part of two center grants from the National Institute of Deafness and Other Communication Disorders (DC 02189) and from the National Institute of Neurological Diseases and Stroke (NS 22342).

Barratt-Boyes, & Lowe (1961). The name Williams is the one that stuck. Early on, the disorder was also called Williams–Beuran syndrome, as well as Infantile Hypercalcemia. Since 1993, we have learned that WMS is caused by the deletion of one copy of a small set of genes on chromosome 7 (7q11.23), which includes the genes that code for elastin, LIM1kinase, Frizzled, WSCR1, and Syntaxin1A, among others (Korenberg et al., 1997; Ewart et al., 1993). The syndrome occurs in approximately 1 in 25,000 births. Some of the frequent physical manifestations of WMS include a specific heart defect (a narrowing of the aorta), a defect in the production of elastin, and hypercalcemia. Their facial features are quite distinctive, and have been described as “pixie-like” and “elfin.” People with WMS often look more like each other than they do to people in their own families (see Figure 3 for a collage of photographs). In fact, later in the interview with the WMS twins quoted earlier, they were asked what it felt like to finally meet other people with WMS at a WMS convention. They had never seen

anyone else with WMS, other than each other, and at age 30 or so, they met a room full of other WMS people. The first twin said that upon seeing a room full of WMS, he thought, “This is like a giant *cloning convention!*”

Today, special schools and music camps for WMS are springing up in many places. Publicity abounds, with stories about WMS in the *New York Times*, Discover, Newsweek, Nightline, 60 Minutes, National Public Radio, several PBS and BBC programs, including one with Oliver Sacks, as well as articles in the international press. The scientific community has responded with just as much enthusiasm as the popular media. Studying WMS turned out to be a “geneticist’s dream,” in the words of Julie Korenberg, and progress in this area is advancing at an amazing rate.

The first paper of this special issue, “The neurocognitive profile of Williams syndrome: A complex pattern of strengths and weaknesses” (Bellugi et al., this volume) introduces the cognitive profile of WMS. General cognitive functioning typical of WMS is thoroughly de-

Photos of Children with Williams Syndrome



Figure 3. Photos of individuals with WMS. Note the similarity in facial features. (Used with permission).

tailed and referenced to normal controls and an age and IQ-matched group with DNS, as well as to several other contrast groups. In addition, the developmental time-course for cognitive domains is illuminated. While there are fascinating peaks in abilities associated with WMS, as we have been discussing, there are also dramatic valleys. Although language processing and face recognition are remarkably “spared,” their visuospatial skills are exceedingly poor. The juxtaposition of poor visuospatial skills and near-normal face recognition—two visual domains—is explored in this paper, as well as the intriguing apparent separation between language and general cognitive functioning.

The focus of the next paper in this special issue “Hypersociability in Williams Syndrome” (Jones et al., this volume) is the dramatic hypersociability in WMS. When coupled with their linguistic abilities, the hypersociability of WMS often keeps people from guessing that they are mentally retarded. They are socially forward and carry on conversations with such ease that it is not until it becomes obvious during the course of conversation that they do not know some facts that most people know—e.g., that the sun rises in the east—that you might not realize they are mentally retarded. Sociability in WMS was investigated with a number of experiments, testing such things as linguistic affect in story-telling and rating the approachability of unfamiliar faces, as well as data from questionnaires and interviews. Both the experimental and the descriptive data are contrasted with data from normal controls, as well as those with DNS and Autism. The differences are striking.

In the following paper, “Electrophysiological studies of face processing in Williams Syndrome” (Mills et al.,

this volume), the organization of brain activity linked to relatively spared cognitive functions in WMS is examined. Using event-related brain potentials (ERPs), they tested the hypothesis that brain systems mediating these seemingly spared cognitive functions, namely language and face processing, may be abnormally organized in individuals with WMS. Specifically, is the organization similar to that of a normal brain at an earlier point in development (which would indicate normal but delayed brain development), or are WMS brains processing information in a different way? In light of previous research on normal developmental changes in the functional organization of the brain, they have identified two domain-specific electrophysiological markers of abnormal brain function in WMS. The abnormal morphology in the ERPs for both face processing and for auditory-language processing has been observed in virtually all of over 50 adults and children tested with WMS. In contrast, these patterns have not been observed in normal adults, children, or infants at any age, nor in any other populations studied. In both language and face processing, the closer the behavioral performance of WMS came to normal, the more unusual their ERP components looked.

In “Neuroanatomy of Williams Syndrome: A high-resolution MRI study” (Reiss et al., this volume), detailed neuroimages of individuals with WMS were analyzed and compared with those of 14 normal controls. Overall, those with WMS had decreased brain and cerebral volumes, relative preservation in cerebellar- and superior-temporal regions, and a substantial decrease in the volume of the brainstem. Additionally, the cerebral gray matter in WMS subjects was relatively preserved compared to controls. However, they had disproportionately low white-matter volume. The different cerebral-lobe volumes are also reported for both groups, and results are discussed in relation to the molecular genetics, the neurocognitive profile, and the neurophysiology of WMS. Hypotheses regarding, e.g., what the larger-than-normal gray matter volume of the superior-temporal region in WMS might reflect in terms of WMS cognition, are suggested.

In the next paper, “Multi-level analysis of cortical neuroanatomy in Williams Syndrome,” (Galaburda et al., this volume) begin to link the anatomical findings to the genetic, and the behavioral aspects of the disorder. Galaburda employs an even finer level of analysis of the neuroanatomical data through the use of autopsy specimens. He examined blocks of tissue selected from most classes of cortex from several WMS brains for architectonic differentiation. The WMS brains were studied at four levels: (1) gross anatomy (brain shape, cortical folding, asymmetry), (2) cytoarchitectonic appearance of the cortex, (3) histometric measurements (neuron size and packing density), and (4) immunocytochemistry results. A consistent gross neuroanatomical finding is the abnormal length of the central sulcus,

producing an unusual configuration of the dorsal-central region, including the dorsal portions of the superior-parietal lobe and the dorsal-frontal gyrus. The WMS brains also show a lack of asymmetry in the planum temporale, abnormalities in cortical folding, and some curtailment in posterior regions. Most regions show normal cortical cytoarchitecture; however, area 17 shows increased cell size and decreased cell packing density, which suggests the possibility of abnormal connectivity in this region. In an attempt to link genetics to neuroanatomy, molecular observations of Elastin and LIM kinase staining are reported, as both of these proteins are products of the genes that are included in the WMS deletion.

The final paper in this special issue, "Genome structure and cognitive map of William Syndrome" (Korenberg et al., this volume), elucidates why the unusual neurocognitive profile of WMS makes it a compelling model of the pathways between genes and human cognition. A unique genomic organization may make WMS an important model of human chromosomal evolution and disease as well. WMS is known to be caused by a small deletion on chromosome 7 that includes the gene-encoding elastin (ELN), and perhaps 20 other genes. The WMS region was analyzed in a large panel of subjects for whom the neurocognitive profile, brain structure and function were also determined. Korenberg et al. describe a model of genome organization, deletion structure, and evolution of the 7q11.2 region. WMS is located within a largely single-copy region of chromosome 7 that is flanked by an array of genomic duplications, part of which were duplicated in primate evolution. WMS, with typical deletions, shows no significant evidence of genetic imprinting on neurocognition; however, WMS subjects with smaller deletions suggest candidate regions for parts of the cognitive-phenotypic profile. These exciting data may ultimately provide tools for investigating the mechanisms of primate evolution and human cognition.

Portions of the papers in this volume were originally presented at a symposium called "Bridging cognition, brain, and gene: Evidence from Williams Syndrome," for the Fifth Annual Meeting of the Cognitive Neuroscience Society, in San Francisco, CA in early April 1998. Subsequently, Marie St. George (1998) published a review of the meeting and the symposium called "What studying genetically based disorders can tell us about ourselves" in *Trends in Cognitive Sciences*, in which she wrote "One thing that was clear from all of the presenters was that they were excited about the project and the nature of the collaboration." A natural outcome was the proposal to develop these presentations as a Special Issue of the *Journal of Cognitive Neuroscience*, with contributions from cognitive neuroscience to molecular genetics.

The studies in this volume represent a synthesis of crossdisciplinary research, and provide opportunities to

explore some of the central issues of cognitive neuroscience that tie cognitive functions to brain organization and ultimately to the gene.

Ursula Bellugi and Marie St. George are editors of this Special Issue. Ursula Bellugi is Director of the Laboratory for Cognitive Neuroscience at The Salk Institute for Biological Studies. Marie St. George is a scientist with the Center for Research on Language at the University of California, San Diego.

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Acknowledgments

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