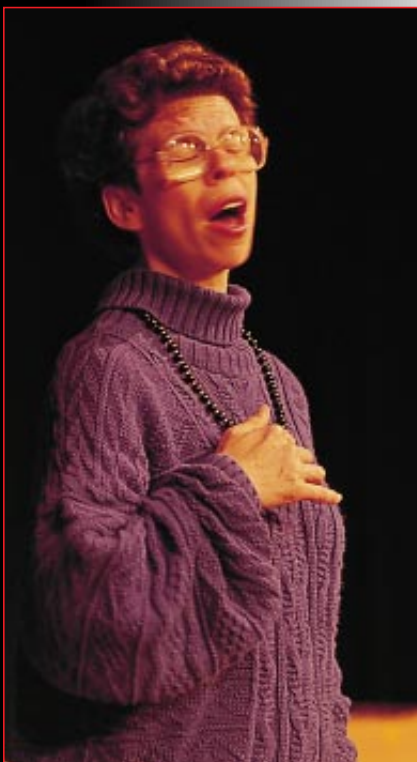


Williams Syndrome and the Brain

To gain fresh insights into how the brain is organized, investigators are turning to a little known disorder

by Howard M. Lenhoff, Paul P. Wang, Frank Greenberg and Ursula Bellugi



When a teenager with an IQ of just 49 was asked to draw an elephant and tell what she knew about the animal, her sketch was almost indecipherable. But her description was impressively rich, even lyrical. As part of that description, she noted, “It has long, gray ears, fan ears, ears that can blow in the wind....”

In her verbal ability, that young woman is fairly typical of people who have Williams syndrome, a rare condition that has recently started to draw the attention of a range of scientists. Affected individuals, sometimes called Williams people, are not all alike but often are similar to one another. They are frequently diagnosed as mildly to moderately “retarded” and generally score below average on standard IQ tests. They usually read and write poorly and struggle with simple arithmetic. Yet they display striking strengths in some realms. They generally demonstrate a facility not only for spoken language but also for recognizing faces. And, as a group, they tend to be empathetic, loquacious and sociable.

What is more, anecdotal evidence implies that some Williams people possess extraordinary musical talent. Even though their attention span for most tasks is short, many will listen to music,

sing and play instruments with astonishing persistence. Most cannot read musical notes, yet some have perfect or nearly perfect pitch and an uncanny sense of rhythm. One boy quickly learned to play an extremely complex drumbeat in 7/4 time with one hand while drumming in 4/4 time with the other hand. A number of individuals retain complex music for years, remembering melodies and verses of long ballads; one even sings songs in 25 languages. Experienced Williams musicians also sing harmonies, improvise and compose lyrics readily.

Such anecdotes have recently led to the first systematic study of musical ability in Williams children. The results indicate that the youngsters discriminate melodies well; they also show significantly more interest in and emotional responsiveness to music than do subjects from the general population. As one Williams child said, “Music is my favorite way of thinking.”

Investigators are attracted to Williams syndrome in part because they suspect the dramatic peaks and valleys in the abilities of affected individuals will provide a new window to the organization and adaptability of the normal brain. Some groups are attempting to pinpoint characteristic properties of the Williams brain and to determine how those prop-

PEOPLE WITH WILLIAMS SYNDROME display a striking mix of abilities and disabilities. For instance, when asked to draw and describe an elephant, an adolescent having an IQ of 49 produced a scribble that was incomprehensible without labels, yet she offered a rich verbal description (*opposite page*). Some individuals also display strong musical talent; this past summer those at the left—from top, Julia Tuttle, Brian Johnson and Gloria Lenhoff (daughter of author Howard M. Lenhoff)—attended a music and arts camp for Williams people, held at Belvoir Terrace in Lenox, Mass.

JESSICA BOYATT

erties influence performance in intellectual and other realms. At the same time, researchers are trying to uncover the genetic abnormalities responsible for Williams syndrome.

In 1993 they learned that the disorder is caused by loss of a tiny piece from one of the two copies of chromosome 7 present in every cell of the body. The deleted piece can contain 15 or more genes. As the lost genes are identified, scientists can begin to determine how their absence leads to the neuroanatomical and behavioral features already observed. This integrated approach to the study of Williams syndrome—connecting genes to neurobiology and, ultimately, to behavior—may become a model for exploring how genes affect brain development and function.

Medical scientists are interested in Williams syndrome in its own right as well. Analysis of the genes in the deleted region has already explained why Williams people commonly suffer from certain physical ailments. It has also provided a means of prenatal testing and is helping to diagnose the disorder earlier, so that children who are affected can be helped from infancy to live up to their fullest potential; lack of familiarity with Williams syndrome in medical circles and the absence of reliable tests have hindered prompt diagnosis in the past.

Understanding Grew Slowly

Although Williams syndrome, which occurs in an estimated one in 20,000 births worldwide, has gained increased attention lately, it is not by any

means new. An investigation by one of us (Lenhoff) suggests that Williams people were the inspiration for some age-old folktales about elves, pixies and other “wee people” [see box on page 73].

The medical community became aware of the syndrome fairly recently, however—only about 40 years ago. In 1961 J.C.P. Williams, a heart specialist in New Zealand, noted that a subset of his pediatric patients shared many characteristics. Beyond having related cardiovascular problems, they also had elfin facial features (such as a turned-up nose and a small chin) and seemed to be mentally retarded. The cardiac problems Williams observed often included heart murmurs and narrowing of major blood vessels. In particular, Williams people frequently suffer from supravalvular aortic stenosis (SVAS), a mild to severe constriction of the aorta.

Since that time, physicians have noted other traits, some of which can be seen quite early in life. In infancy, babies may have difficulty feeding and may suffer from stomach pains, constipation and hernias. They may also sleep poorly and can be irritable and colicky, behavior sometimes caused by another frequent sign: elevated amounts of calcium in the blood. As the children get older, they reveal hoarse voices and show delayed physical and mental development. They begin walking at an average of 21 months, often on the balls of their feet and usually with an awkwardness that persists throughout life. Fine motor control is disturbed as well. In addition, Williams people are extremely sensitive to noise, are often short compared with

their peers and seem to age prematurely (for instance, their hair grays and their skin wrinkles relatively early).

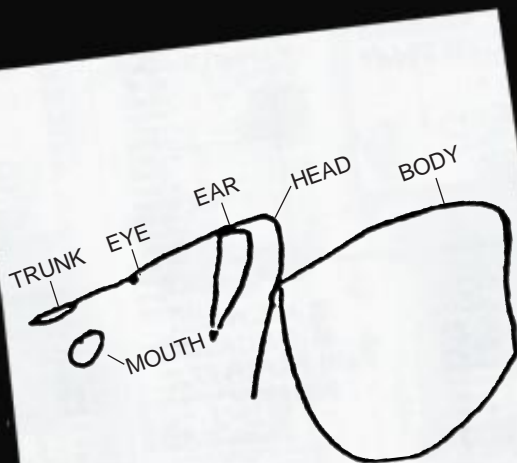
Description began to give way to genetic understanding about four years ago, thanks in part to a study of SVAS in people who did not have Williams syndrome. In 1993 Amanda K. Ewart and Mark T. Keating of the University of Utah, Colleen A. Morris of the University of Nevada and other collaborators discovered that for a segment of this population, SVAS stemmed from an inherited mutation in one copy of the gene that gives rise to elastin—a protein that provides elasticity to many organs and tissues, such as the arteries, lungs, intestines and skin.

Missing Genes Are Identified

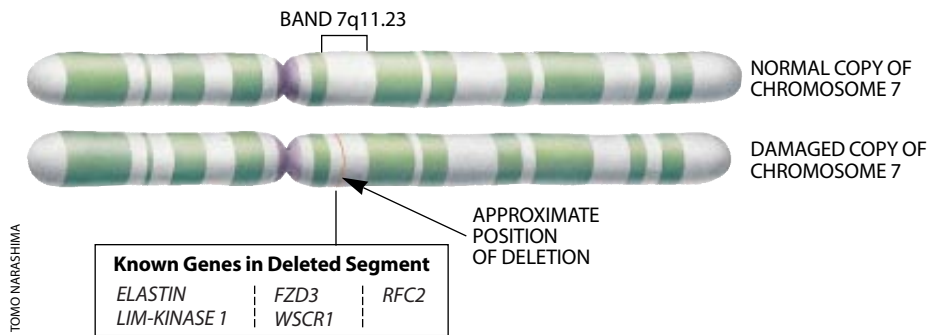
Aware that SVAS is common in Williams people and that individuals with familial SVAS alone and individuals with Williams syndrome both suffer disturbances in organs that require elasticity, the workers wondered whether Williams syndrome, too, involved some kind of change in the gene for elastin. Sure enough, they found the gene was deleted from one of the two copies of chromosome 7 in cells. Today it is evident that the deletion of the gene occurs in approximately 95 percent of patients with Williams syndrome. The loss is harmful presumably because both gene copies are needed to make adequate amounts of the elastin protein.

The investigators knew that a reduction in the elastin supply could contribute to various physical features of Wil-

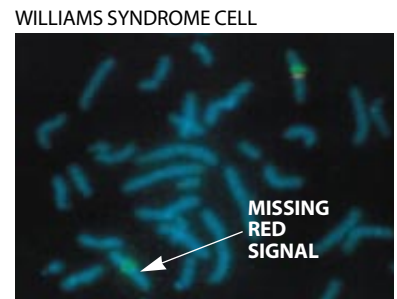
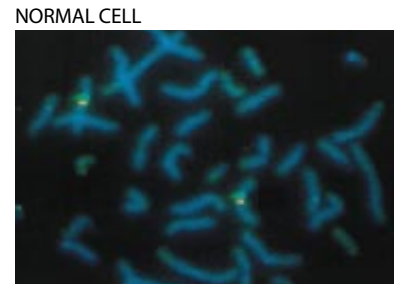
Drawing and Description of an Elephant by a Teen with Williams Syndrome



“What an elephant is, it is one of the animals. And what an elephant does, it lives in the jungle. It can also live in the zoo. And what it has, it has long, gray ears, fan ears, ears that can blow in the wind. It has a long trunk that can pick up grass or pick up hay. If they’re in a bad mood, it can be terrible. If the elephant gets mad, it could stomp; it could charge. Sometimes elephants can charge. They have big long tusks. They can damage a car. It could be dangerous. When they’re in a pinch, when they’re in a bad mood, it can be terrible. You don’t want an elephant as a pet. You want a cat or a dog or a bird.”



TINY DELETION from one of the two copies of chromosome 7 in cells is the cause of Williams syndrome (*drawing*). The excised region can contain 15 or more genes, only some of which have been identified. A diagnostic test is based on the discovery that the gene for elastin is usually among those lost. The test flags copies of chromosome 7 with a fluorescent green tag and flags the gene for elastin with a fluorescent red tag. Chromosomes (*blue*) from a cell in a normal subject (*top micrograph*) will show two green and two red signals, indicating that both copies of chromosome 7 are present and that each carries the gene for elastin. But Williams people lack one copy of the gene, and so one copy of chromosome 7 will lack a red signal (*bottom micrograph*).



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Williams syndrome (such as SVAS, hernias and premature wrinkling), but it could not by itself account for the cognitive and behavioral signatures. After all, their first subjects, who had SVAS alone without cognitive impairment, would also have had low IQs if a diminution of elastin could unilaterally produce all the symptoms of Williams syndrome. This awareness led them to suspect that more genes were affected. In support of that idea, direct examinations of chromosomes from Williams patients indicated that the region deleted from chromosome 7 extended beyond the boundaries of the gene for elastin and probably encompassed many genes.

Several of those other genes are now being uncovered. Among them are three (*LIM-kinase 1*, *FZD3* and *WSCR1*) that are active in the brain—a sign that they could influence brain development and function. The exact activities carried out by the encoded proteins are not known, although Ewart and her colleagues have proposed that *LIM-kinase 1* (which is invariably deleted with the gene for elastin) may be involved in the ability to grasp spatial relationships. This role could help explain why Williams people have difficulty drawing simple common objects accurately from memory. Another gene from the deleted area, *RFC2*, specifies a protein involved in replication of DNA, but its contribution to Williams syndrome has not been established.

The genetic understanding of Williams syndrome is far from complete. Still, discovery of the deletion in chromosome 7 has yielded some practical

rewards. That the deletion occurs in all cells of the body in Williams people tells mothers nothing they did or failed to do during pregnancy caused their child's condition. The disorder stems from a sperm or egg that, by chance, suffers a loss of genes from chromosome 7 before donating its chromosomes to the creation of an embryo. That knowledge also tells healthy siblings of Williams people that their copies of chromosome 7 are free of the deletion; therefore, any children they bear are no more likely than other children to acquire Williams syndrome. Finally, the microscopic technique that originally revealed the deletion of the gene for elastin—fluorescent in situ hybridization, or FISH—has now been adapted for use as a diagnostic tool.

A Cognitive Profile Emerges

Work on the genetics of Williams syndrome is complementing efforts to specify the neurobiological hallmarks of the disorder. That research, which today involves several laboratories, began about 15 years ago, when one of us (Bellugi) answered a late-night telephone call in her laboratory at the Salk Institute for Biological Studies in La Jolla, Calif. The caller knew that Bellugi investigated the neurobiological underpinnings of language and believed her daughter, who had Williams syndrome, would interest the Salk group. The girl, then 13, had an IQ near 50 and was considered mentally retarded. Consistent with that profile, she read and wrote at the level of a first grader. Yet she spoke beautifully.

Then, as now, scientists had difficulty distinguishing the brain processes controlling language from those controlling reasoning, because in the general population, adeptness at language and cognition usually go hand in hand. The dichotomy in the caller's daughter suggested that study of Williams people might help tease apart those processes.

Fascinated, Bellugi agreed to meet the girl and then continued to see her regularly. She also sought literature detailing the cognitive strengths and weaknesses of Williams people but found little beyond general assertions. Before Bellugi could hope to uncover the areas of the brain and the neurological processes that accounted for the unique cognitive characteristics of Williams people, she would need a finer-grained profile of the traits distinguishing that population from others. She and her colleagues therefore began to devise tests of specific abilities and to compare the scores of Williams people with those of the general population and of another cognitively impaired group: people with Down syndrome.

The investigations, which continue, examine populations of adolescents matched for sex, age and IQ level. (Williams people range in IQ from 40 to 100, but their mean score is about 60.) Early on, the team saw that Williams subjects, in contrast to their generally weak performance on overall tests of cognitive ability, commonly used well-formed grammar in their spontaneous speech. On the whole, they also performed significantly better than the group with Down syndrome did on all

tasks of grammatical comprehension and production.

Many also did well at the rather complex task of constructing tag questions, such as adding “doesn’t she?” to the statement “Leslie likes fish.” The person being tested must first take the original statement (“Leslie likes fish”) and substitute a matching pronoun for the subject (“*She* likes fish”). Then the individual must add a conjugated auxiliary verb, negate it and contract it (“*She doesn’t* like fish”), omit the original verb and object (leaving only “*She doesn’t*”) and invert the word order to form a question (“... , doesn’t she?”).

The Salk researchers further found, as others did later, that the Williams subjects frequently had vocabularies larger than would be expected for their mental age. When asked to list some animals, they often did not stick to easy words but chose such exotic examples as yak, Chihuahua, ibex, condor and unicorn.

Beyond possessing richer vocabularies, subjects with Williams syndrome tended to be more expressive than even normal children were. This animation was demonstrated amusingly when Williams children were asked to provide a story for a series of wordless pictures. As they told their tale, they often altered their pitch, volume, length of words or rhythm to enhance the emotional tone of the story. Similarly, they added more drama to engage their audience (“And suddenly, splash!”; “And BOOM!”; “Gadzooks!”) than subjects with Down syndrome did. (Sadly, the gift of gab and sociability of Williams children can mislead teachers into thinking the children have better reasoning skills than they actually possess; in those cases, the children may not get the academic support they need.)

One possible explanation for the strong verbal performance of Williams individuals is that their chromosomal defect, in contrast to that of Down subjects, may not significantly disrupt certain faculties that support language processing. Other researchers, for instance, have reported that short-term memory for speech sounds, or “phonological working memory”—a form that seems to assist in language learning and comprehension—is relatively preserved in the Williams population.

Interestingly, recent studies of French and Italian Williams subjects suggest that one aspect of language known as morphology—the facet of grammar that deals with verb conjugation, gender as-

signment and pluralization—may not be completely preserved in Williams people. (These languages are much richer in morphology than English is.) This discovery implies that the brain regions preserved in Williams syndrome and the presence of an intact short-term memory for speech sounds support many verbal aptitudes but may not suffice for full mastery of language.

In contrast to their generally good showing on verbal tests, Williams subjects typically do poorly on tasks involving visual processing, such as copying drawings. But they often fail on such tasks in different ways than Down

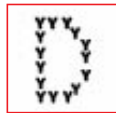
subjects do, suggesting that the deficits in the two groups may stem from differences in brain anatomy. For example, Williams people, in common with patients who have suffered a stroke in the right hemisphere of the brain, may attend to components of images but fail to appreciate the overall pattern (the gestalt). Down people, however, are more likely to perceive the global organization but to overlook many details [see top illustration in box on this page], just as individuals do who have suffered left-hemisphere strokes.

In some ways, the general profile revealed by the various cognitive tests im-

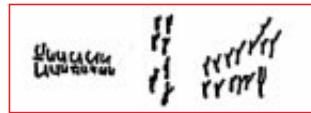
The Making of a Cognitive Profile

As part of an effort to pinpoint cognitive features that are characteristic of Williams people, investigators have compared subjects with Williams and with Down syndrome on tests of specific abilities. One test (*top*)—which asked adolescents to copy from memory a letter D that was built from a collection of small Y’s—revealed impairment in integrating details into a larger configuration. The Williams group tended to draw only Y’s, whereas the Down group tended to maintain the overall configuration but omit local details. Another test (*bottom*)—in which subjects had to invent a story for a series of wordless pictures—revealed that Williams people can often generate well-structured narratives.

Task:
REPRODUCE
IMAGE



Williams subjects



Down subjects



Task: INVENT A STORY FOR THE PICTURES



Williams subject, age 17, IQ 50

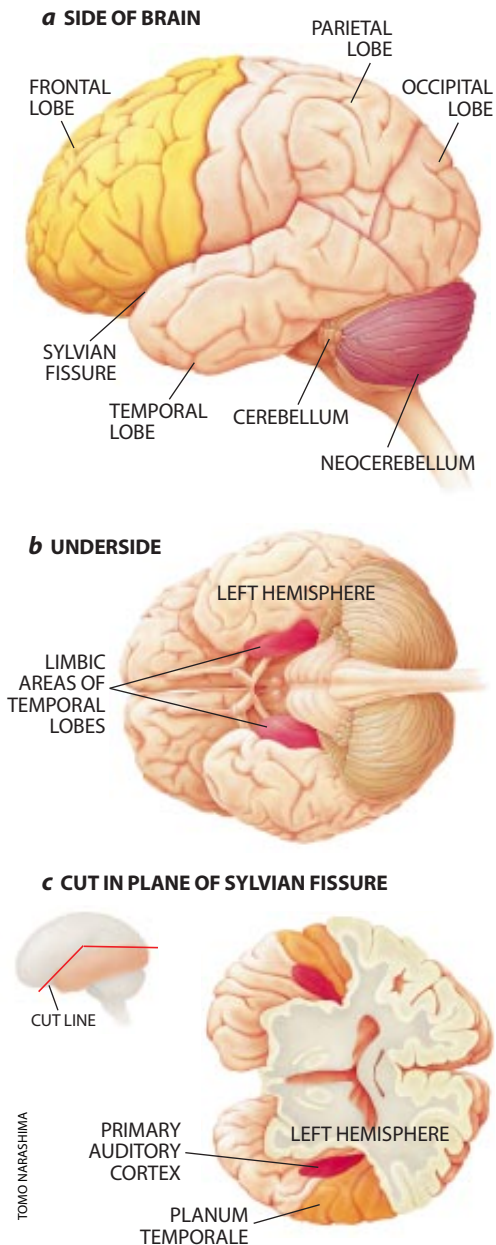
“Once upon a time when it was dark at night, the boy had a frog. The boy was looking at the frog, sitting on the chair, on the table, and the dog was looking through, looking up to the frog in a jar. That night he slept and slept for a long time, the dog did. But the frog was not gonna go to sleep. The 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.”

Down subject, 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.”

COURTESY OF URSULA BELLOGGI

COURTESY OF PENGUIN PUTNAM, INC.



BASIC ANATOMY OF BRAIN in people with Williams syndrome is normal, but the total volume is somewhat reduced. The areas that seem to be best preserved include the frontal lobes and a part of the cerebellum called the neocerebellum (a), as well as parts of the temporal lobes known as the limbic area (b), the primary auditory area and the planum temporale (c).

plies that the chromosomal defect in Williams syndrome essentially spares the left hemisphere (the region most important to language in the large majority of people) and disrupts the right (the more visual-spatial hemisphere). But the emotional expressiveness of Williams people (also thought to be a right-sided function) and at least one other

finding cast doubt on that simplistic view. Williams people recognize and discriminate among pictures of unfamiliar faces (a skill that requires the right hemisphere) remarkably well. In fact, they perform as well as adults from the general population.

Neurological Studies Add Clarity

The Salk group's examination of brains by magnetic resonance imaging and by autopsy supports the probability that the chromosomal deletion responsible for Williams syndrome alters the brain in a more complicated way. The deletion seems to produce anatomical changes (such as abnormal clustering of neurons in visual areas) that yield deficits in visual-spatial abilities. But the chromosomal defect appears to spare a network that includes structures in the frontal lobes, the temporal lobe and the cerebellum. This preserved network, then, may serve as a neuroanatomical scaffolding for the unexpectedly strong language abilities of Williams people.

To be more specific, the neuroanatomical studies indicate that the overall cortical volume in both Williams and Down people is smaller than that of age-matched normal subjects. But the volumes of individual regions differ between the two groups. For instance, the frontal lobes and the limbic region of the temporal lobes are better preserved in Williams people. The limbic system, which also includes other structures, is important for brain activities involving memory and emotions; sparing of the limbic region may help explain why Williams people are quite expressive and empathetic.

Analyses of the cerebellum uncovered further differences between the Williams and Down groups. Whereas its volume in Down subjects was small, that in Williams subjects was normal. And in Williams subjects the neocerebellum (considered to be the evolutionarily youngest region of the cerebellum) was equal to or larger than that in age-matched individuals in the general population but was reduced in Down subjects.

The finding that the neocerebellum is preserved in Williams people is particularly intriguing when placed in the context of other research. Until recently, the cerebellum was thought to be concerned primarily with movement. Yet Steven E. Petersen and his colleagues at Washington University have shown that the neocerebellum becomes active when sub-

jects try to think of a verb that fits with a given noun (such as "sit" for "chair"). Further, tests of patients with cerebellar injuries reveal deficits in cognitive function, not just in motor abilities. And anatomists report that the neocerebellum communicates extensively with a part of the frontal cortex that, in common with the neocerebellum, is larger in humans than in apes.

Given that humans have language and apes do not, some observers have proposed that the neocerebellum and the connected region of the frontal cortex evolved together to support the fluent processing of speech and may fall under the control of the same genes. The relative preservation of the frontal cortex and the enlargement of the neocerebellum in Williams people, together with the rather spared fluency in language, lend some credence to this last notion and to the idea that the cerebellum plays a part in language processing.

Recent anatomical analyses have additionally identified features that could help explain the apparent musical talent of Williams people. The primary auditory cortex (located in the temporal lobe) and an adjacent auditory region, the planum temporale (thought to be important to language as well as musicality), are proportionately enlarged in the few Williams brains examined so far. In addition, the planum temporale is normally more extensive in the left hemisphere than in the right, but in some Williams people the left region is unusually big, to an extent characteristic of professional musicians. These findings mesh well with observations by Audrey Don of the University of Windsor in Ontario, the investigator who carried out the first studies of musical ability in Williams people. She concludes that intact perception of auditory patterns may account for much of the strength in music and language seen in Williams subjects—a result that implies the related brain structures should also be intact.

Physiological probes comparing electrical activity in the brains of Williams people and others during specific tasks offer more insights into how the brain develops. In response to grammatical stimuli, for example, normal subjects show greater activity from the left hemisphere than from the right, as would be expected for language tasks. But Williams people show symmetrical responses in the two hemispheres, a sign that the typical language specialization of the left hemisphere has not occurred. Fur-

Williams Syndrome: An Inspiration for Some Pixie Legends?

Folktales from many cultures feature magical “little people”—pixies, elves, trolls and other fairies. A number of physical and behavioral similarities suggest that at least some of the fairies in the early yarns were modeled on people who have Williams syndrome. Such a view is in keeping with the contention of historians that a good deal of folklore and mythology is based on real life.

The facial traits of Williams people are often described as pixielike. In common with pixies in folklore and art, many with Williams syndrome have small, upturned noses, a depressed nasal bridge, “puffy” eyes, oval ears and broad mouths with full lips accented by a small chin. Indeed, those features are so common that Williams children tend to look more like one another than their relatives, especially as children. The syndrome also is accompanied by slow growth and development, which leads most Williams individuals to be relatively short.

The “wee, magical people” of assorted folktales often are musicians and storytellers. Fairies are said to “repeat the songs they have heard” and can “enchant” humans with their melodies. Much the same can be said

of people with Williams syndrome, who in spite of typically having subnormal IQs, usually display vivid narrative skills and often show talent for music. (The large pointed ears so often associated with fairies may symbolically represent the sensitivity of those mythical individuals—and of Williams people—to music and to sound in general.)

As a group, Williams people are loving, trusting, caring and extremely sensitive to the feelings of others. Similarly, fairies are frequently referred to as the “good people” or as kind and gentle-

hearted souls. Finally, Williams individuals, much like the fairies of legend, require order and predictability. In Williams people this need shows up as rigid adherence to daily routines and a constant need to keep abreast of future plans.

In the past, storytellers created folktales about imaginary beings to help explain phenomena that they did not understand—perhaps including the distinguishing physical and behavioral traits of Williams syndrome. Today researchers turn to Williams people in a quest to understand the unknown, hoping to decipher some of the secrets of how the brain functions. —H.M.L.



UNRELATED CHILDREN in the photograph above all display elfin facial features that clinicians associate with Williams syndrome. The depiction of an elf at the right is the 19th-century work of Richard Doyle, an uncle of the Sherlock Holmes creator.



ther, whereas normal adults generally show greater activity from the right hemisphere than the left when processing images of faces, Williams people show the opposite pattern. Such work favors the possibility that when normal developmental processes go awry, the brain often redistributes responsibilities,

forming new circuits to carry out the functions of the disrupted ones.

Research into Williams syndrome is just now taking off, but it is already helping to clarify how the brain is organized. It is also making investigators see “mentally retarded” individuals in a new light. Close study of Williams syn-

drome has shown that low IQ scores can mask the existence of exciting capacities. And it warns that other so-called mentally retarded individuals could have untapped potentials waiting to be uncovered—if only researchers, and society, will take the trouble to look for and cultivate them.

The Authors

HOWARD M. LENHOFF, PAUL P. WANG, FRANK GREENBERG and URSULA BELLUGI offer several perspectives on Williams syndrome. Lenhoff is professor emeritus of biological sciences at the University of California, Irvine, the father of a 42-year-old Williams syndrome musician and co-organizer of the Williams Syndrome Music and Arts Camp, held in Massachusetts. He is also principal investigator of a team comparing music cognition in Williams people with other populations. Wang, assistant professor of pediatrics at the University of Pennsylvania School of Medicine, studies the neurobehavioral manifestations of Williams syndrome and other genetic disorders. Greenberg, clinical consultant with the National Center for Human Genome Research at the National Institutes of Health, has worked with Williams syndrome individuals for 20 years. Bellugi is director of the Laboratory for Cognitive Neurosciences at the Salk Institute for Biological Studies. She heads a multidisciplinary team that has been examining the cognitive, neuroanatomical and neurophysiological characteristics of Williams syndrome for more than a decade.

Further Reading

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