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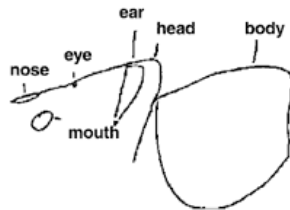
Music, the Brain, and Williams Syndrome*Rare disorder offers insight into the genetic basis of cognition*By **Brendan A. Maher**

Gloria Lenhoff is a 46-year-old lyric soprano singer who has performed with such diverse groups as the San Diego Master Chorale and members of Aerosmith. She can sing nearly 2,500 songs in more than 25 languages, reportedly in a perfect accent. She even has perfect pitch.

But the rest of her world is not perfect. Gloria is affected by a rare genetic disorder called Williams syndrome. With an IQ of about 55, Gloria literally cannot subtract three from five or make change for a dollar. But what she and others with her affliction share is music. Innately connected, they often have an astute grasp of music's technical aspects—the beat, rhythm, tone, and timbre.

Identified more than 40 years ago, Williams syndrome results from non-homologous recombination during gametogenesis that deletes about 20 genes on one copy of chromosome 7.¹ Characteristics of Williams syndrome include pixie-like features—upturned nose, small chin, protrusive ears—as well as stunted growth, heart problems, poor visuospatial cognition, sensitivity to loud noises, a gregarious personality, and an average IQ of about 60. Many of these individuals have difficulty with the simplest of mental and physical tasks, but some abilities, especially verbal skills, appear to be spared. Classified by some as a nonverbal learning disability, this syndrome allows speech and language aptitude that far exceeds their other cognitive functions. A Williams-afflicted person, for example, couldn't scribble more than a few lines to depict an elephant but could describe one in expressive, almost lyrical detail. "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," said a patient in an experiment conducted by Ursula Bellugi, director, Laboratory for Cognitive Neuroscience at the Salk Institute for Biological Studies.¹

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Elephant Drawing

The dissociation between language and spatial cognition in Williams syndrome is evident in this contrast between the drawing and verbal description of an elephant by an 18-year-old with Williams syndrome.

To some, perhaps the most striking distinction is the extraordinary connection that these people have with music. All exhibit a strong affinity for music, and while their attention span for many tasks is fleeting, they will spend hours listening to or making music. Research is scarce, but some evidence shows a high incidence of perfect pitch, and an uncanny sense of rhythm among this group.^{2,3} One boy with Williams syndrome was taught to tap a complicated 7/4-time rhythm with one hand while keeping 4/4-time with the other.⁴

Some researchers will not use the word "savant," but all admit that a connection with music exists, and that it and the other anomalies in this syndrome might help to

further knowledge about disease and how the brain develops and works.



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Lessons from the Heart

Genetic discoveries of Williams syndrome began at the heart. "We were interested-still are interested-in obstructive vascular disease," says Mark T. Keating, Howard Hughes Medical Institute investigator and professor of cell biology at Harvard Medical School. One such disease, supravalvular aortic stenosis (SVAS), exists in many Williams syndrome patients but also occurs in otherwise healthy patients. For the latter, this genetic disorder results from a defective copy of the *ELN* gene that encodes for elastin, a substance that comprises about half of the dry weight of arteries. While conducting linkage analysis and fluorescence in situ hybridization (FISH), Keating, then at the University of Utah, and his team traced Williams syndrome to a de novo deletion of *ELN* on Chromosome 7. They discovered that the responsible microdeletion at 7q11.23, unseen without FISH, included about 2 million base pairs that were flanked by highly duplicative chromosome regions.¹ Using FISH to identify the deletion region has reigned as a diagnostic tool for Williams syndrome, although work done by Stephen Scherer at Toronto's Hospital for Sick Children department of genetics and genomic biology, recently uncovered a 1.5 million-base pair inversion of the deletion area that occurs in roughly 5 percent of Williams patients.⁵ Scherer says, "There's this fallacy that you have to have the deletion to have the disease," which can cause health insurance problems. In 30 percent of these cases, the parents were found to have the inversion without the clinical manifestations of Williams. This inversion increases the likelihood of unequal crossing over and may be a mechanistic explanation for the Williams deletion.

Genes in the usual deletion region include the *Drosophila* homologue, frizzled (*FZD3*), syntaxin 1A (*STX1A*), replication factor C2 (*RFC2*), the gene encoding for LIM-kinase 1 (*LIMK1*). Rare partial deletions, smaller than the typical 2MB standard, exist, and the varying degrees of Williams syndrome characteristics they produce offer important insight in connecting cognitive function and genetics.

Individuals with a deletion that included only *ELN* and *LIMK1* had the heart problems and the impaired visuospatial constructive cognition associated with Williams syndrome, but no other symptoms. It's believed, says Keating, that *LIMK1*'s role in cytoskeletal control and actin formation is responsible for developmental deficiencies in the posterior parietal cortex. Though work from a UK lab refutes this evidence,¹ examining those rare cases of partial deletions and the traits they produce can lead to previously unconsidered gene-brain connections. "For instance," says Colleen A. Morris, professor of pediatrics, University of Nevada School of Medicine and clinical collaborator with Keating, "most children with Williams syndrome have anxiety, but anxiety is also common in the general population. Might there be a gene within the Williams deleted region that is important in the general population in terms of anxiety?"

It's a story that will continue to unfold as new technology becomes available. Eric Green, director, NIH Intramural Sequencing Center, presented six previously unreported genes in the deletion area at the American Society of Human Genetics meeting in October. His lab has been studying the deleted region in humans and 11 other non-human vertebrates. "In primates," Green says, "this is a very complicated region with these large duplicated blocks. In lower vertebrates it's not so complicated and it's not duplicated." The evolutionary implications of this have incited Green to study this gene dense region on chromosome seven, "in everything from chimpanzees on down to pufferfish."

The Language of Music

Anecdotal evidence of an intimate connection with music, a great memory for songs, and the kind of auditory finesse that can discern the differences between vacuum cleaner brands, has followed Williams people for some time, but little evidence has been published. Neuropsychologist Audrey Don, now at the children's therapy unit at Good Samaritan Hospital in Seattle, was one of the first to explore the relationship. "Cognitively, kids with Williams syndrome are better with verbal skills. Their word knowledge and use of words is better than their nonverbal type of

thinking," she says.

She administered a simple musical test of tones and beats to people with Williams syndrome and a control group matched for vocabulary level. She found that musical ability matches verbal ability and was higher than the Williams' children overall cognitive abilities.² Their parents, providing further survey information, reported an extremely strong and emotional connection with music. A lullaby tape, says Don, made one infant cry. When the child was older, she was asked why she wept; the child said the songs were too sad.

An impromptu study conducted at the Williams Syndrome Music and Arts Camp in Massachusetts' Berkshire Mountains gave another inkling into this particular peak of Williams cognition. The experimenters asked eight children to imitate clapped rhythms. They performed as well as normal, musically trained students who were matched to their mental age of five to seven years.³ But, the professional musicians that coded the responses qualified the mistakes of Williams subjects as "wrong in an interesting way."³ They often missed the exact sequences, but creatively kept within the realm of the time signature, much like a jazz musician will jam. The Williams subjects were three times as likely as controls to offer what the researchers called "creative completion" to the test rhythm when giving an incorrect response.

Howard M. Lenhoff, professor emeritus, School of Biological Science, University of California, Irvine, recently completed a study linking Williams syndrome to a higher incidence of absolute or perfect pitch, a condition that normally occurs in one out of 10,000 people in Western populations; these people often study music from a very early age. In numerous trials, five musically trained Williams subjects, including Lenhoff's daughter, Gloria, displayed near-ceiling levels of absolute pitch.² Of the subjects, which represent about 1/1000 of the Williams population, four could read music and name notes, a rare ability in Williams people. Gloria, says Lenhoff, was the only one unable to read music and had to be taught, but she still performed within the acceptable range of absolute pitch. Lenhoff chose a nonrandom sample of subjects because of their ability to name notes. While criticized for choosing outliers, he says, "If you look for the average, you'll find the average."

The age at which these participants began to study music raises other questions. It's commonly accepted that to develop perfect pitch, one has to study music before age six, yet all of the subjects, save one, started after this critical period. Lenhoff predicts that this period is extended in those with the syndrome. "The open window gets jammed," he says, "It's open in extended years, and I think into adulthood." Lenhoff and others hypothesize that this open window may be critical for language acquisition in early years, but in normal populations it often fades with disuse-somewhat less often, incidentally, in populations that speak tonal languages such as Mandarin or Vietnamese.²

Back to the Brain

The cognitive strengths and weaknesses of these people have given support to the existence of multiple intelligences,³ and a number of neurological studies are beginning to uncover the connections between function and brain. Comparative magnetic resonance imaging (MRI) studies between Williams and Down patients uncovered a different profile of development. While the frontal cortex of all these individuals is smaller than that of a normal person, those with Williams syndrome have a volume proportionate with the rest of the brain, while in Down syndrome it is reduced. In both the neocerebellum, believed to be the most recently evolved part of the brain, and Heschl's gyrus, an area within the primary auditory cortex, size is even comparable to that of normal subjects.¹

The neocerebellum, originally thought to be involved in movement, has many anatomical connections with the frontal cortex, says Paul P. Wang, assistant professor of pediatrics in child development and neurology at Children's Seashore House, University of Pennsylvania Children's Hospital. "I think we're not ready to make any earth-shattering conclusions, but it gives us some clues as to what these areas of the brain may be important for," says Wang, who is involved in studies on phonological working memory-a kind of short-term memory for sounds.

Whether innately gifted in music or not, Williams people display a unique set of cognitive and physical symptoms that could further aid in other research areas, from cardiovascular disease to the very root of how genetics translate into ability. Yet, studies of the connection between music and Williams syndrome offer a creative outlet and method to reach out to this population. "For these kids the emotional engagement really pulls them. Music encourages something of normalcy and fulfillment," says Don. Morris speaks of counseling families to use music to instruct and for its calming effect.

Though she worries that some parents might be disappointed if their child is not quite the musical prodigy, she speculates about what could be learned. "[Music] is one of the things that's found in all cultures and in all forms. So I think that it's a basic human characteristic. If there is a genetic component to that, then that is absolutely fascinating."

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Mixing Science and Parenting

For more than 40 years, Howard M. Lenhoff studied the enzyme kinetics of the freshwater hydra. An accomplished enzymologist, Lenhoff's strict adherence to the "grind and find" tactics of his field earned him an impressive publication record on the nitty-gritty molecular mechanics of this model organism. But two years ago, at age 70, Lenhoff switched research gears to study cognitive neuroscience. The reason: Lenhoff's daughter, Gloria, suffers from Williams syndrome.

Gloria was born in 1955. Says Lenhoff, "It was pretty obvious when Gloria was an infant that she was handicapped mentally and physically." For 34 years, her parents grieved, believing that an oxygen deficiency at birth had caused her problems.

They didn't learn the truth until years later. Her condition was identified by cardiologists in the late 1950s and early 1960s, but Gloria wasn't diagnosed with Williams syndrome until 1989. As Lenhoff learned more about the disorder, he attended gatherings of researchers and physicians who were investigating various aspects of Williams. "I harassed them year after year," he says, "asking that they investigate the many anecdotal reports of musical talent made by parents and teachers. Finally, one said, 'Why don't you do it?'" Having taken an early retirement from the University of California, Irvine, Lenhoff used the time to convince the National Science Foundation to award him a small, high-risk grant for the study. The results of this study were published this past summer.¹

Still, the parent in him presides. Even though Gloria is living safely in a Methodist-run community for handicapped people, Lenhoff and his wife worry about her future. They recently moved to Oxford, Miss., to be near her. Says dad: "We just want to make sure that everything is all right for her before we die."

-Brendan A. Maher
H.M. Lenhoff et al., "Absolute pitch in Williams syndrome," *Music Perception*,
18[4]:491-503, 2001.

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