NEWS

Friendly Faces and Unusual Minds

Working with a rare set of individuals who have Williams-Beuren syndrome but still show normal intelligence, scientists are trying to tease out what happens in this neurodevelopmental disorder—and shed light on the brain's normal function

To outsiders, a Williams-Beuren Syndrome (WS) convention can seem like a large family reunion. The 200 or so affected individuals who gather for the 3-day biannual event look similar to one another in many ways, although they are not related. Their upturned noses, wide mouths, and small chins give them an elflike appearance—the reason this rare genetic condition, found in 1 out of 7500 people, is also called elfin face syndrome. What's perhaps most striking is the conventioneers' lack of social inhibition. "You walk into the hotel lobby, and they surround you and start talking to you even though you are a perfect stranger," says Karen Berman, a psychiatrist at the National Institute of Mental Health (NIMH) in Bethesda, Maryland.

This excessive friendliness is just one indication that the brains of people with WS work a bit differently from typical brains. In another odd example, WS individuals are incapable of putting together the simplest of puzzles, owing to their inability to visualize an object as a set of parts. That impairment, known as the visuospatial construction deficit, also makes it difficult for them to judge distances and to negotiate stairs. More broadly, even though most people with WS have little difficulty using language and in some cases have notable musical talent, general intelligence tests usually show them to be mentally retarded.

The uniform and well-defined cognitive features shared by those with WS have convinced some researchers that the disorder offers a window into the genetic basis of the human mind. Since the discovery in the early 1990s that the syndrome is caused by the deletion of a tiny section of one copy of chromosome 7, researchers have attempted to identify the roles that the different genes within that section play in the development and functioning of the brain. The broader goal of these efforts has been to learn how cognitive and behavioral features arise from specific genetic traits and their interplay with the environment.

Cognitive window. Most individuals with Williams syndrome share distinctive facial features (*above*) and the same set of physical and mental impairments. The disorder is caused by the deletion of a segment of one copy of chromosome 7, including the *elastin* gene.

These efforts are beginning to pay off. Researchers have drawn links between the genes absent in WS, structural and functional abnormalities in certain brain regions, and cognitive deficits that are the hallmarks of the disorder. Some of the gene-brain-behavior links have subsequently been confirmed in mouse models, and scientists have uncovered neurodevelopmental pathways that are disrupted by the deletion of WS genes. Taken together, these findings "have been invaluable in understanding how relatively subtle developmental defects can have a significant impact on neurological function," says Dennis O'Leary, a neurobiologist at the Salk Institute for Biological Studies in San Diego, California. The work, he adds, opens the door to explaining how genes work through the brain to make us who we are.

The neural connection

Although other physicians may have come across earlier cases of the disorder, British physician J. Williams was the first to identify it in a 1961 paper that described children with a unique set of facial, cognitive, and heart defects. A second research group, led by German cardiologst Alois J. Beuren, independently identified the syndrome the following year, adding excessively social behavior to its list of characteristics.

As a step toward understanding how genes contribute to the cognitive profile in WS, researchers have sought to determine the neural mechanisms that underlie signature traits of the illness. One challenge they have faced is the mental retardation of most people with WS, which makes it difficult to perform many experimental tasks testing cognition. Karen Berman, along with NIMH neurologist Andreas Meyer-Lindenberg, psychologist Carolyn Mervis of the University of Louisville, Kentucky, and others, got around that hurdle by assembling from around the world 13 volunteers with WS who had both the chromosomal deletion and the cognitive deficits characteristic of the syndrome but showed normal overall intelligence.

In one set of experiments, the researchers had the volunteers perform two tasks aimed at elucidating the visuospatial construction deficit. In the first, they asked the individuals whether two pieces of a puzzle presented on a computer screen could fit together to form a square. In the second, volunteers had to determine whether images presented one after the other were located at the same height on the screen. Comparing the functional magnetic resonance images (fMRI) of the WS group with those of healthy controls, the researchers found that the WS individuals showed significantly lower neuronal activity in a part of the brain used by the spatial processing pathway of the visual system.

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In contrast, the people with WS showed normal brain activity along the neural pathway responsible for identifying objects, which may explain why they seem to have little difficulty in recognizing faces or other visual material.

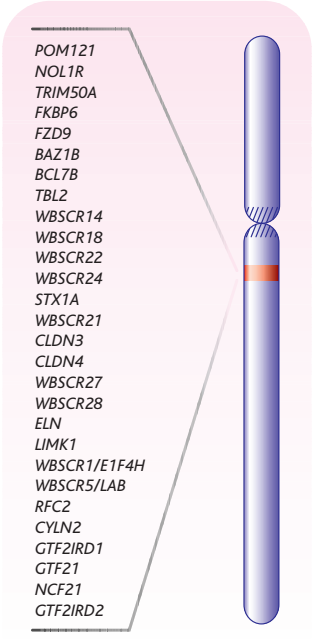
Using MRI scans to examine structural details of WS-affected brains, the researchers found an abnormally low density of nerve tissue adjacent to areas where activation was weak during the two tasks, suggesting that this region was not contributing its fair share of input to the spatial processing stream. This anatomical flaw—in the fold separating the parietal and occipital lobes (parietooccipital sulcus)—was a likely basis for the visuospatial construction problem in WS patients, Berman and her colleagues concluded last year in a report in *Neuron*. The researchers have now followed up by analyzing the geometry of the fold; they reported in the 24 August *Journal of Neuroscience* that it was significantly shallower in the WS volunteers than in controls. And in the 1 July *Journal of Clinical Investigation*, the group reported other studies on the same set of patients that revealed structural and functional abnormalities in the hippocampal region, which offers a possible explanation for long-term memory impairments and other cognitive deficits in WS.

To some WS researchers, the normal intelligence of the volunteers in the NIMH-led studies presents a problem. "What's vexing is that their IQ makes them unrepresentative of the general population of WS patients, and yet that very feature makes them good experimental subjects," says Allan Reiss, a psychiatrist at the Stanford University School of Medicine.

Meyer-Lindenberg rejects such skepticism. The WS people his team recruited showed the same visual deficits as mentally retarded WS patients, which means they were not able to circumvent their defective neural mechanisms while performing the assigned tasks. "If we'd had a negative finding—that is, if the volunteers had performed as well as the controls, we could have suspected that their intelligence was helping them to somehow compensate for their handicap. But to find eye-popping abnormalities and still ascribe that to the IQ difference between them and the general WS population, we'd have to make up some very convoluted reasoning," he says.

Despite this disagreement, Reiss and his colleagues have come up with some of the same results. In one experiment, Reiss's team compared brain scans of 43 WS individuals with characteristically low IQs to those of 40 healthy subjects and found low densities of nerve tissue in certain regions along the spatial processing pathway. In another study, the researchers looked at fMRI scans of 11 patients who were asked to determine whether faces presented on a computer screen were gazing at or away from them. (This was a simpler task than the ones used by Berman's group.) Not only were the people with WS slower in their responses than controls, but they also showed significantly less activity in their primary and secondary visual cortices while performing the task, Reiss and his colleagues reported in *Neurology* last year.

Decoding the brain. NIMH's Karen Berman and Andreas Meyer-Lindenberg are studying 13 WS individuals with normal intelligence.



Missing. In all, 28 genes have been identified in the chromosome 7 region deleted in typical WS cases.

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A faulty template

Pinpointing the neural underpinnings of cognitive deficits in WS is only one piece of the puzzle. Another is linking genes to those anatomical and functional defects. Even though the chromosomal deletion in WS encompasses just 28 known genes—a very small number given that thousands of genes are involved in brain development—isolating their specific contributions to the cognitive aspects of the disorder is a complex problem. "These genes could be interacting among themselves and with other genes in a ridiculous number of ways," says Julia Korenberg, a molecular geneticist at the Cedars Sinai Health System in Los Angeles, California.

Researchers have attempted to narrow the list by studying a few people who have shorter deletions on chromosome 7 than is seen in individuals with WS and yet show some of the same cognitive characteristics. For example, in a study published online by *Science* this week (www.sciencemag.org/cgi/content/abstract/1116142), a British-American team led by May Tassabehji, a medical geneticist at the University of Manchester, U.K., adds to the evidence that a gene called *GTF2IRD1* plays a role in the visuospatial deficit. The researchers identified a 4.5-year-old girl with a chromosome 7 deletion that included this gene but excluded many of the other candidates. The report centers on how the gene's loss may explain the girl's WS-like facial features, but the researchers note that she also has serious problems with spatial navigation

In some of the earliest work using this partial-deletion strategy, reported in 1996, Mervis and geneticist Colleen Morris of the University of Nevada, Las Vegas, identified a gene called *LIM kinase 1* as a strong candidate to explain the visuospatial construction deficit. (The group also used the technique to identify a gene that codes for elastin as a contributor to the vascular and heart defects in WS.) But the *LIM kinase 1* story is confusing: Researchers have identified individuals missing one copy of the gene who show none of the WS cognitive defects.

Studies in recent years have implicated other genes within the cluster of 21 for the visual deficit, two prominent ones being *GTF2IRD1* and *Gtf2i*, both identified by Korenberg in collaboration with the Salk Institute's Ursula Bellugi and others. Findings from other partial-deletion cases have thrown two more genes to the mix: *frizzled 9* and *cycln2*.

Mouse models are helping sort out the roles of the different candidates. In work reported in *Neuron* 3 years ago, for example, Zhengping Jia of the University of Toronto in Canada and his colleagues knocked out the *LIM kinase 1* gene in mice and demonstrated

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that the animals had poor synaptic function and memory. Neurons in these mice had inadequate dendritic spines, the protruding tendrils on the surface of a nerve cell that help form excitatory synapses.

And in experiments described in the June issue of *Development*, clinical neurologist Samuel Pleasure of the University of California, San Francisco, and his colleagues found that mice lacking one or both copies of the *frizzled 9* gene ended up with fewer-than-normal neurons in their hippocampus, due to a surge in programmed cell death in that region. The gene defect significantly hampered the animals' spatial learning abilities.

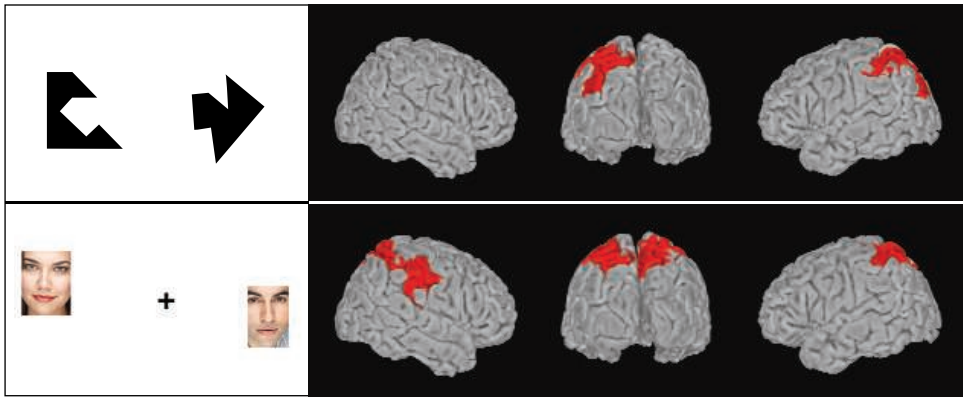
Brain autopsies of WS patients are also shedding light on the disorder's visual problem. Surveying the molecular landscape of one such brain, Harvard neurologist Albert Galaburda and his colleagues found an abnormally low expression of *Gtf2i* in the peripheral visual cortex and superior parietal regions. In earlier WS autopsies, the same group had discovered that the neurons in the dorsal parietal cortex—a part of the spatial processing system—were larger and stubbier than normal, suggesting that they had not been patterned correctly during the brain's development. "It's possible that *Gtf2i* lies in the pathway of certain dorsal patterning genes, and its low expression is selectively detrimental to neuronal development in the dorsal parietal cortex," speculates Galaburda, whose group presented the work at the Society for Neuroscience meeting last year.

So which of these half-dozen genes actually underlies the syndrome's visuospatial construction deficit? "I don't think anybody would want to get into a contest about whose gene is more important," says Pleasure. "The likely scenario is that multiple genes are responsible. This may be a more well-defined syndrome than other genetic disorders, but it's still quite complicated."

Afraid of none

A video clip running on Berman's desktop computer provides a vivid illustration of the excessively social nature of people with WS. The video shows an 18-month-old girl with the disorder interacting with a normal 5-year-old boy who's sitting on the floor. She walks up to within a few inches of him and peers into his face with great intensity. When the boy starts to get uncomfortable after a few seconds and turns his head, she shifts position to continue staring at him from up close. Even after he stands up and begins bouncing a basketball on the floor, she doesn't relent.

Despite such social fearlessness, WS patients typically display high levels of nonsocial anxiety, such as fear of heights. Berman and her colleagues have sought to tease apart the neural basis of this paradoxical behavior by asking their normal-IQ WS volunteers to perform two tasks. In the first, the researchers presented them with an image of a face showing anger or fear and, a few seconds later, two other faces simultaneously. They were then asked to pick which of the latter faces bore the same emotion as the first. The second task required a similar kind of matching—only, instead of faces, the images presented on the computer were of fear-provoking scenes such as a boat sinking or a house burning. As a control task, the volunteers had to match one of two geometrical shapes to a shape shown earlier.



Spatial challenge. While performing a square-completion task (*top*) and a location task (*bottom*) in the NIMH-led study, individuals with WS showed lower than normal activity (red) in brain regions lying along the spatial processing pathway.

Comparing fMRI scans taken during these tasks, the researchers found significant differences between the WS group and a control group in the activation of the amygdala, a brain region known to regulate people's fear response. For the task involving threatening faces, the amygdala in the WS individuals was much less active. In contrast, while performing the second task, using scenes rather than faces, these volunteers showed higher amygdala activation than did the controls. The researchers also found that during either task, the orbitofrontal cortex (OFC) was less active among the people with WS than in controls, while the medial prefrontal cortex (MPFC) was more active. Berman says the findings, reported in the August issue of *Nature Neuroscience*, fit nicely into a model of social cognition in which amygdala function—and therefore fear response—is regulated by both the OFC and MPFC. She notes that her group has documented a structural abnormality in the OFCs of WS individuals, which may explain their low fear response to faces.

A complete account of the cognitive problems in WS must include the role of the environment in mediating the syndrome's effects, researchers stress. That role could be especially important for social cognition, says Ralph Adolph, a cognitive neuroscientist at the California Institute of Technology in Pasadena. "Since the genes influence social behavior very early on in WS individuals, their unusual social behavior in turn is likely to construct an abnormal social environment—that is, other people will socially interact with a WS child differently than with a child without the syndrome," he says. "I think we can certainly draw a link between genes and cognition, as long as we realize that the link is very complex and always brings in the environment in its mediation."

Evidence that more than genes governs the cognitive abilities of those with WS comes from findings that "individuals with the same classic WS deletion vary considerably in their visuospatial construction ability, although almost all show a significant deficit," says Louisville's Mervis. "On average, individuals who have a parent who is good at drawing are themselves better at drawing than are other individuals with the same deletion; this is likely due to a transaction between genes from outside the deleted region and the environment. Children in these families may well have more opportunities to draw, in addition to having better adult models of how to draw."

Nobody expects that there's a simple, straight line connecting genes to the mind, says Reiss, who along with his colleagues is planning a longitudinal study of children with WS. Such work, he hopes, will shed light on both the genetic and environmental pieces of the puzzle. "We have the possibility of unraveling how genes and environmental moderators shape cognition and behavior," he says. "Now that is really exciting stuff."

—YUDHIJIT BHATTACHARJEE

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