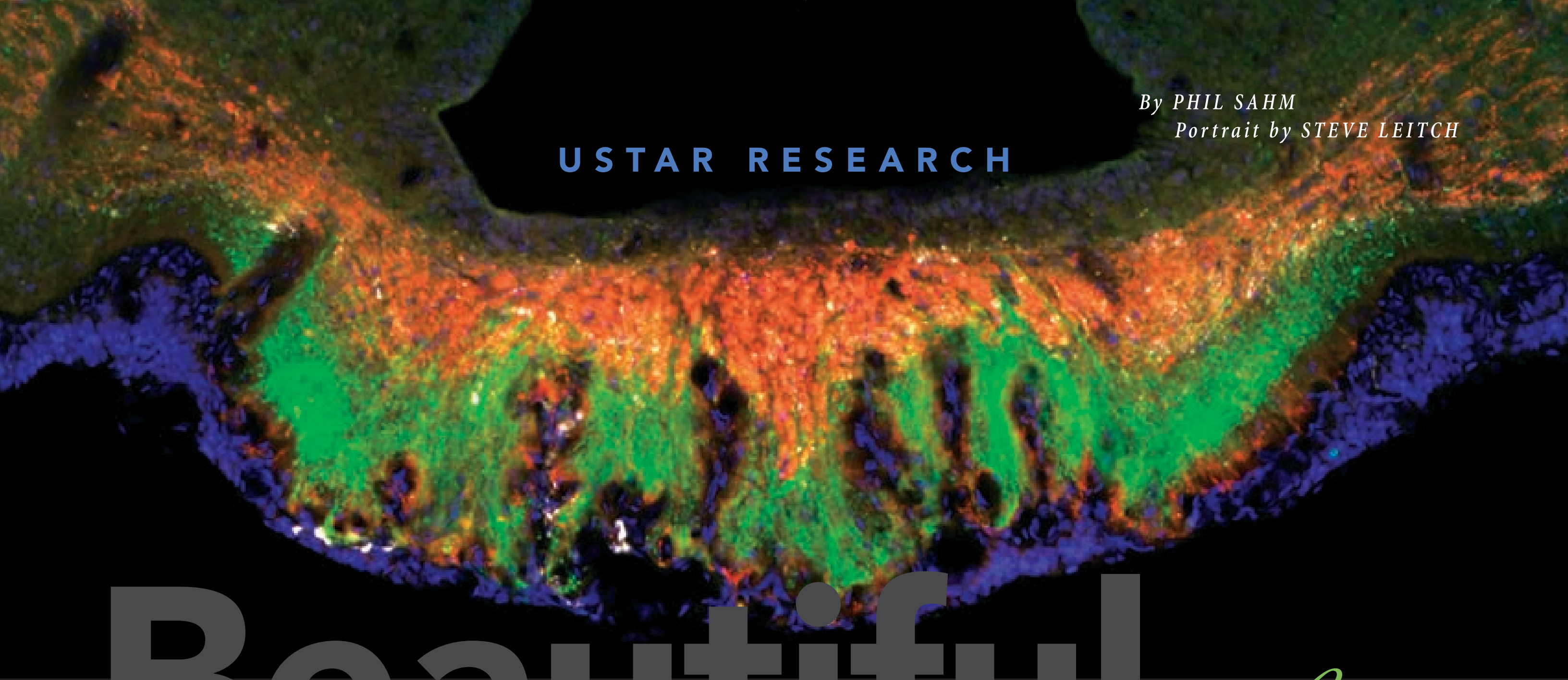

By PHIL SAHM
Portrait by STEVE LEITCH

Beautiful *Interplay:*

How Genetic Disruptions Alter Brain Structures, Which Affects Behavior

A charming 9-year-old girl with a rare genetic syndrome is helping geneticist and pediatrician Julie R. Korenberg, M.D., Ph.D., find the answers to what she has dedicated her career to understanding: the mystery and beauty of how genes influence the way people behave.

The girl has Williams syndrome, a disorder in which people are missing 25 to 28 genes on chromosome 7 and that occurs only once in every 7,500 to 20,000 live births. People with the disorder are born with serious physical and mental deficits, including cardiovascular defects and severe problems with visual-spatial perception.

Curiously, despite an average IQ of 60, children with Williams syndrome have an endearing personality trait that is the hallmark of the disorder: they are extremely outgoing and friendly, especially with strangers. Korenberg, an investigator with the University's Brain Institute and a USTAR professor of pediatrics in the School of Medicine, sums up the way these children view the world in four words: "Everybody is their friend."

Korenberg and her research colleagues at the Salk Institute for Biological Studies wrote about the unidentified girl in a study published in February. She has many distinguishing characteristics of Williams syndrome: she is physically diminutive with a round, elfin face. Her IQ of 78 is substantially lower than normal, but also 18 points higher than average for the disorder. Another subtle difference sets her apart: although charming and engaging, she doesn't run up to strangers and stare intently at them during interactions. Korenberg's study showed that the *GTF2I* gene commonly missing in Williams syndrome—but not in this girl—is associated with her less demonstrative behavior. Korenberg also showed that another gene, *GTF2IRD*—which the girl is missing—is linked to visual-spatial ability.

"Ultimately, I'm trying to understand the origins of human behavior," said Korenberg, who came to Utah from the University of California, Los Angeles, last year. "Finding this girl was very exciting. She has so much power to explain the role of genes in behavior."

Linking *GTF2I* to the girl's behavior is the pinnacle of a quest spanning more than three decades of creative investigation in which Korenberg has examined hundreds of patients with Williams and Down syndromes, and pioneered techniques and analyses to identify smaller and smaller microdeletions (losses of small parts of chromosomes) to narrow the search for single genes that affect behavior. Identifying individual genes is part of a larger goal of understanding how the disruption of genes alters the structure of the brain and its circuits, which, in turn, influences behavior. For example, she'd like to isolate the gene(s) and brain circuits that provoke anxiety, a common condition in people with Williams syndrome, and then determine if anxiety in the population at large can be traced to the same genes. Ultimately, her objective is to make a 3-D wiring diagram of the social regions of the brain.

"I'm using a multidisciplinary approach to put basic science together with cognitive science, using genetics to parse the social behavior," she explained.

Korenberg, who also directs the Center for Integrative Neurosciences and Behavior at the U of U Brain Institute, is reluctant to use the word "calling" to describe her career, but says human behavior has fascinated her for as long as she can remember. After receiving her doctorate in human genetics, she realized that that discipline was becoming the new hub of medical research and would be critical for

Julie R. Korenberg, M.D., Ph.D.

Delicate Arches

Red dye illuminates a gene product lining the inside of a coronary artery at left. The median eminence—which connects the pituitary gland to the brain—in a rat is shown on the opposite page. Green dye highlights a gene that may influence social behavior; orange and white illuminate peptides, and blue, nucleotides.

studying social behavior. She went to the University of Miami medical school to become a pediatrician, but continued her research on understanding behavior through genetics. She has studied Down syndrome for more than 30 years and Williams syndrome for more than 15.

One of the world's leading researchers in the genetics of Williams syndrome, she observed that her work has required as much creativity as insight. "At each step, we had to develop a technique to solve a different problem," she said. For example, using a technique she pioneered in the early 1990s that led to the Integrated Human BAC (bacterial artificial chromosome), Korenberg created a color-coded guide to the human genome by tagging thousands of fragments of DNA with different colors that can be seen with fluorescent light under a microscope. She then used the colored DNA fragments that were inserted into inert bacteria effectively as cloned regions of chromosomes that contain different genes. Using the colors as a guide, Korenberg was able to look for ever smaller microdeletions. Through this method, she was the first person in the world to identify fluorescent markers that spanned the entire human genome. These markers linked physical maps of chromosomes to the emerging human genome sequence.

This and other work established Korenberg as an international leader in human genetics. Her work on Williams and Down syndromes recently was published in the *American Journal of Medical Genetics, Nature, and the Proceedings of the National Academy of Sciences.* As part of the Human Genome Project, she mapped hundreds of human genes and published seminal papers on mapping and sequencing the human genome, answering basic questions about genomic structure and evolution.

Korenberg had linked *GTF2I* and *GTF2IRD1* with visual-spatial processing in earlier studies with colleagues at the Salk Institute. Both genes are transcription factors: they regulate other genes and are known to have roles in the formation of the brain and skeletal muscles. Korenberg decided to look a little deeper to further parse their roles. "We hypothesized there would be something that would tell us the difference between these two genes," she said.

A postdoctoral fellow in Korenberg's lab at the Brain Institute, Li Dai, Ph.D., searched the genomes of 17 Williams syndrome patients to find those who had retained a copy of *GTF2I* but were missing *GTF2IRD1*. Her search identified the 9-year-old girl. Subsequent behavioral tests revealed the girl's social interaction to differ subtly from most children's with Williams syndrome, while an IQ test showed her vocabulary, information processing, arithmetic, and other areas significantly higher than average for the disorder. But her ability to assemble objects or work through a maze was lower than average for people with the syndrome and substantially lower than normal.

"These differences suggested to us that *GTF2I* plays a role in social behavior, while *GTF2IRD1* contributes to visual-spatial performance," Korenberg said.

Linking *GTF2I* to social behavior is a major step, but it does not mean that it's the only gene involved, Korenberg cautions. *GTF2I* might regulate signal pathways determining the structure and function of the brain or the production of neurohormones, such as vasopressin and oxytocin. Oxytocin plays a key role in the desire to seek social interactions and trust others. But environmental factors, in confluence with genetics, undoubtedly influence social behavior as well.

Korenberg was lured to the U through the Brain Institute and USTAR (Utah Science Technology and Research) initiative—established by the Utah Legislature to promote high-tech economic development through the U of U and the state's other research institutions. At the U, Korenberg has found an ideal atmosphere for research—a highly collegial, interdisciplinary, and collaborative environment where her research and creativity can flourish.

"I was blown away by how receptive people are to new ideas," she said. "It's hard to be a creative person in a standard place."

Korenberg's creativity extends beyond the laboratory. She is a classically trained pianist and singer who likes to play songs from all genres, including musical comedies. In the past few years, she has followed another creative path by taking images from her work to make striking colored prints and photographs of the brain and heart. Last year she had the first exhibit of her art at a show in Pasadena, Calif. Turning her work into art is a natural progression for Korenberg, who sees an exquisite beauty in the mysteries of the human mind and body.

"The world is a beautiful place," she says, "and I like to do beautiful things." ◩