For most of us, snacking is a bad habit. For Melissa Moss, a Californian with a rare genetic disorder, it's a matter of life and death. A chromosomal abnormality known as Prader-Willi syndrome has cursed her with both an insatiable appetite and a metabolism so slow that she gains weight eating just 1,600 calories a day.

Moss, an articulate 28-year-old, used to steal leftovers from cafeteria trays when she was in elementary school, or even pick scraps off the floor. Now that she’s an adult, food is never far from her mind. She spends hours every day counting calories, weighing and reweighing foods, and figuring out, down to the last half pretzel, how much she can eat. Her 1,300-calorie-a-day diet of yogurt, fruit, fat-free turkey sandwiches, and diet TV dinners is spartan and monotonous, but it has kept her slender, and alive. Untreated, most people with the syndrome become obese by their teenage years and are dead by adulthood, killed by heart disease, diabetes, or other conditions. Some have died from gorging until their stomachs actually burst.

Cruel as it is, Prader-Willi could prove to be important to scientists trying to understand the complex biology of appetite. Researchers are trying to determine exactly how the syndrome's genetic abnormalities spur the appetite. If they succeed, they could not only help treat the roughly 20,000 Americans afflicted with the syndrome but also help explain how the rest of us eat—and why so many of us eat too much.

Eating may seem basic, but the whole process, from feeling hungry to finally pushing away from the table, is controlled by elaborate and largely mysterious circuitry between brain and gut. Scientists have identified more than 250 genes and at least 40 neurochemicals that regulate metabolism and appetite, but it’s clear that in humans, social cues are at least as powerful as biological signals. The study of metabolism and appetite, one appetite researcher wrote, is like "a few small islands of scientific
understanding surrounded by a vast sea of uncertain phenomena."

The neurobiology of eating, according to one model, begins when positive signals flow from the mouth through the cranial nerves to the brain. Dopamine and opioids are then released that create a sense of pleasure. At the same time, hormones are released that begin to curb the appetite. As more food goes down the hatch, the belly begins to expand. That triggers messages back to the brain to slow down eating. The small intestine also provides feedback as specific nutrients set off neurological and hormonal signals that say "I'm full."

So where, exactly, does hunger come from? The obvious answer is that the brain initiates the sensation to get more energy and nutrients. But Ralph Norgren, a behavioral scientist at Pennsylvania State University, says researchers can't find a day-to-day correlation between how much we eat and how much energy we expend. It's only when the numbers are tracked over the course of a week that a strong relationship becomes clear. "It doesn't happen in an individual meal or during a day, but it does happen, and it's very precise," he says. Increase the time frame even further to an evolutionary scale and the relationship grows more obvious. William Zipf, a pediatric endocrinologist and Prader-Willi expert at Ohio State University, says, "All our traits were designed to find food, take in food, store food. That's what we needed to survive 30,000 years ago." Inside every thin person, in other words, is someone who feels he's more likely to survive if he eats more.

Prader-Willi could prove a guide to this uncertain terrain because its origins are so specific. Unlike most genetic diseases, the syndrome is rarely inherited. Instead, it is caused by a random accident during egg, sperm, or embryonic formation that either deletes or muffles dozens of genes along a stretch of chromosome 15. Ten of the genes, when disrupted, have been linked to the characteristics of Prader-Willi. In addition to ravenous appetites, Prader-Willi patients have weak muscles, slow metabolisms, small hands, feet, and genitals, and a distinctive triangular mouth. They are often short and very fair, and they tend to have significant learning disabilities. Compulsive behaviors—skin picking, repetitive questioning, and a need to collect and rearrange objects—are common. They can also be very stubborn. (Melissa, luckily, has milder symptoms than most.) Many also have remarkably good memories, and some have an unusual talent with jigsaw puzzles.

Scientists now believe that the same genes that are disrupted in patients with those symptoms are also involved in the function of the hypothalamus, one of the most ancient parts of the brain. The hypothalamus mediates hormonal responses and controls metabolic systems such as heart rate, body temperature, and growth. It has also been fingered, by appetite researchers, as the central switching station for the neural circuitry that controls eating. The overeating, however, does not begin at birth. "It's almost as if [in Prader-Willi patients] this part of the brain that controls eating is turned off in the first couple of years," says Merlin Butler, a cytogeneticist and pediatrician at Children's Mercy Hospital in Kansas City. "And then once it's turned on,
it never gets turned off again."

But are people with the syndrome always hungry, or do they simply never feel full? William Zipf has seen a child eat more than 25 chicken salad sandwiches during an hour-long study and then ask for lunch, suggesting that those with the syndrome never feel satiated. Other scientists say the problem lies with a hyperactive appetite. But Moss says that she doesn't always feel hungry. "I don't know if I ever really feel full, though," she adds.

Meanwhile, researchers are taking a closer look at the neurochemicals associated with appetite and metabolism. At the University of Florida College of Medicine in Jacksonville, pediatric geneticist Daniel Driscoll recently launched a project to look for abnormal levels of leptin, ghrelin, and neuropeptide Y in the blood and cerebrospinal fluid of Prader-Willi patients and other obese children. Leptin and ghrelin are both hormones that have powerful systemic effects on eating and metabolism. When injected into the hypothalamus of a rat, neuropeptide Y has been shown to induce overeating immediately.

A good deal of recent appetite research has also focused on the role of the brain's pleasure centers. Some of the same neurochemicals involved in eating seem to underlie drug addiction, says Norgren. Cocaine and heroin, for instance, increase dopamine levels in the brain. "Eating preferred foods does exactly the same thing," Norgren says, "from the same parts of the brain." Travis Thompson, director of the Institute for Child Development at the University of Kansas Medical Center, believes that the neurotransmitter gamma-aminobutyric acid is somehow involved in producing the obsessive-compulsive behaviors. Several genes involved in manufacturing one of the receptors for the neurotransmitter lie on the chromosome that is altered in Prader-Willi patients. More telling, Thompson has found that Prader-Willi patients have three times as much of the neurotransmitter in their blood as those without the syndrome.

Given that this neurotransmitter inhibits dopamine in the brain, it's possible that people are simply chasing the pleasure of a full stomach. "Clearly, in Prader-Willi, some switch that's on goes off, or one that is off goes on," Driscoll says. "Nobody knows. That's the Holy Grail. You find that out, and it gives you a window right into the house of obesity—a view right into the dining room itself."