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## BATTLING FOR A CURE; [SPORTS FINAL Edition]

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**Full Text** (2237 words)

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JACOB SONTAG

6, RYE, N.Y.

Shortly after her son Jacob Sontag was born in 1996, Jordana Holovach began to feel that something wasn't quite right.

"When I started hanging out with other moms, I noticed something was a little different," remembers the Rye, N.Y., mother, now 34. "At 2 months, I began to get concerned that he wasn't lifting his head. He had started smiling and was really alert, but I was concerned that he wasn't holding up his head."

A series of tests and misdiagnoses followed. Finally, Jacob's father went in for genetic testing to rule out certain diseases. In fact, Holovach had already undergone a prenatal screening - both parents are Ashkenazi Jews, a group prone to certain hereditary diseases - but the geneticist had failed to test for one genetic mutation in particular: Canavan disease. A test for it was just becoming widely available.

A BIG LAUGH AND RADIANT SMILE

"I start researching all the diseases that we were ruling out," recalls Holovach. "I get to Canavan and I'm like, 'Oh, please, God.' I remember calling my mother in the middle of the night because it was too upsetting to sleep. You'd hope this was a nightmare and you'd wake up and this would all go away."

It didn't go away. Eventually diagnosed with Canavan disease, Jacob Sontag is now 9 years old and cannot walk, talk, sit up or do just about anything else that other 9-year-olds regularly accomplish. He eats through a feeding tube, accompanying his meals with daunting medications like Topamax, Baclofen, Clonopin, lithium carbonate and others.

What he can do is laugh and smile widely, a grin that could light up several city blocks, let alone a room. "When people meet Jacob, they become magnetized by him and his smile," says his mother.

Canavan is caused by a mutated gene that inhibits production of an enzyme called aspartoacylase. This enzyme normally breaks down N- acetyl aspartate (NAA), an acid in the brain; without the enzyme, NAA levels are allowed to build up and eat away at the myelin - better known as the "white matter" - that serves as the protective layer around nerve paths in the brain and spinal cord.

The NAA eats away the myelin, and the nervous system eventually shuts down. Canavan children rarely live to their fifth birthday.

The genetic mutation is most common among Ashkenazi Jews (those of Eastern or Central European descent); approximately 1 in 40 are carriers. If both parents have the trait, a child has a 25% chance of developing Canavan disease.

KITCHEN AS CURE CENTER

There are approximately 1,000 Canavan patients in the U.S. at present. The rarity of this disease and other leukodystrophies - disorders affecting the myelin, such as Krabbe or Pelizaeus- Merzbacher disease - has made research and funding from the government and pharmaceutical companies scarce at best. That's why Holovach founded the nonprofit foundation Jacob's Cure in 2000.

"People can see where their money is going, they don't see great administrative costs. I don't have an office in Manhattan - this is Jacob's Cure center here," says Holovach, motioning to her kitchen table.

Jacob Sontag is still alive primarily because of the foundation's funding of the work of Dr. Paola Leone, an Italian neuroscientist who has been researching myelin disorders for a decade. Leone first met Jacob in 1996, shortly after performing a first-of-kind gene therapy trial in New Zealand on two American girls suffering from Canavan disease.

"There was an increase in white matter in the brain and the children did better neurologically," says Leone of the first trial. The girls, now 9 and 10, are "doing well - for what a disease like Canavan means."

Holovach heard about the trial when Jacob was 6 months old. "All I wanted to do was get in my car and drive to Yale and wait for Paola to come to work the next day," she remembers. "It was the longest night of my life because I couldn't sleep and I couldn't get on the phone."

But Leone, at Yale at the time, was out of funding and preparing to close shop. "I said, 'When's the next gene therapy? I'm in,'" recalls Holovach. "She said, 'Sorry, we're shutting down our lab, we don't have any more funds to work on this.' I said, 'No, no, no, I don't think you heard me. Whatever you need, I'm going to get for you.'"

Holovach has been battling for funding and clinical trial approval ever since, any way she can. There has been testimony before Congress. Meetings with Sens. Hillary Clinton and Chuck Schumer. Television appearances. A much-publicized shouting match with a Yale geneticist in the university's hospital lobby.

Much has been accomplished. Leone was awarded the first-ever National Institute of Health (NIH) grant for viral gene therapy, where the gene is delivered inside a nonpathogenic virus and injected into six regions of the brain (formerly, a fat molecule was used for delivery into the ventricles; Jacob also received two such treatments).

Leone will soon publish the viral clinical trial results, which she says show "anything but failure." Jacob was one of the trial's 10 patients.

Now, the battlefield has shifted to stem cells. Currently at Robert Wood Johnson Medical School in New Jersey, Leone and others believe the greatest hope for Canavan and similar myelin disorders lies in using both stem cell and gene therapies.

"It's therapy for repopulating the brain," says Leone. "If the brain is missing cells or has cells that are no longer working, it's cell replacement. Sometimes, you have to use both." The gene therapy, which Leone calls a "prerequisite," lowers NAA levels in the brain, which then allow the stem cells to generate new white matter.

#### COMBINED APPROACH BEST

Leone does not work with embryonic stem cells - the subject of nationwide debate over the last few years - and instead uses fetal stem cells derived from abortions performed because of a health risk to the mother. An Italian colleague, Dr. Angelo Vescovi, and others have published results on using such cells to repopulate the brain and grow white matter in animals with multiple sclerosis, a disease also affected by myelin deterioration.

At the University of Rochester Medical School, Dr. Steve Goldman was recently able to use human neural stem cells to restore nerve function in mice born without any myelin at all. "The cells migrated throughout the brain and the brain stem, and formed normal myelin," reports Goldman. "The brain looked substantially remyelinated - much improved from the standpoint of the brain anatomy." Much of the lab work was performed at New York Presbyterian Hospital-New York Weill Cornell.

Goldman says that to his group's surprise, stem cells derived from adult brain tissue were better at making new myelin than those from aborted fetuses. Regardless of the efficacy of the various sources, Goldman agrees that using both genes and stem cells holds promise. "There are a number of diseases like Canavan's that will likely require combined approaches," he says.

## A RESEARCH VACUUM

Despite such promising results, obstacles continue to arise. The day before Jacob's ninth birthday, the NIH denied Leone's grant application for basic research on the Canavan animal model for the next five years.

"A year and a half of work, so much data, so many animals' lives - it's a huge turndown," says Leone, her head-shaking almost visible over the phone. "This used to be the country of resources and opportunity, but it's turning out not to be anymore for young and creative investigators." Holovach is equally angry. "What are they doing to protect their investment?" she asks, referring to past NIH funding. "Are they just going to stand by and watch the lab shut down?"

Leone, who has already had to move labs three times in the last eight years, is considering relocating overseas to continue her work.

"She's put her career on the line to do what she wants to do, which is cure disease and make science applicable to the patients," says Holovach. "If she has to leave the country, I'll be devastated. It would be such a great, great loss to lose such a scientist. My government is doing things so wrong."

Time, Jacob's worst enemy, ticks on. His NAA levels will begin to drop again without further treatment. But his mother tirelessly refuses to quit.

"I'm equipped to sleep three hours a night," says Holovach. "I'm not equipped for a life without Jacob."

'WE NEVER KNEW HE HAD A DISEASE.'

## OMAR ODEH

### 6, CHATTANOOGA

It is unbearable enough for an infant to show signs of illness right from birth. It is perhaps even harder, however, to watch a child flourish for years - and then suddenly crumble seemingly out of nowhere.

"He developed just like a normal kid, he walked and talked - he even knew his alphabets," says Saussan Odeh, of her son Omar, now 6. "We never knew he had a disease."

When Omar was 2, Odeh and her husband, who live in Chattanooga, Tenn. (they declined to be photographed for this article), noticed he was tripping and falling down frequently. A neurologist soon diagnosed Omar with metachromatic leukodystrophy (MLD), a debilitating hereditary illness that affects myelin like Canavan disease.

At ages 5 and 6, Omar suffered violent seizures. "The seizure really cut off his speech," says Odeh. "After the seizure, he just could say 'water,' 'Mommy' or 'Daddy.' After the second time he had a seizure, he couldn't say any of those."

Bone marrow therapy for MLD can cost upwards of \$250,000 for a single treatment, and is notoriously risky. Omar is also too old for such operations to be effective. So Odeh, 25, stays home with her son now while her husband, Ashraf, works at a beauty-supply store.

Aside from giving Omar his daily doses of anti-seizure medication, his mother feels increasingly helpless.

"We're just trying to hang on," she says. "It's very, very hard. I would do anything for my son."

'THERE'S A VERY LOVING, DETERMINED LITTLE PERSON INSIDE THAT WE HAVE TO HELP GET OUT.'  
HUNTER KELLY

### 8, BUFFALO

Former Buffalo Bills quarterback Jim Kelly and his wife, Jill, realized that something was wrong with their son Hunter on the way home from the hospital after his birth in 1997.

"As soon as we walked through our door, he began to act very uncomfortable and cry all the time," remembers Jill Kelly. "That persisted for the first few months of his life. He was irritable constantly. He was arching his back and acting like he was in pain. He never held his head up, he never reached any of the milestones that newborns have in the first few months."

While Jim Kelly had overcome plenty of obstacles playing with the Bills, they paled in comparison with the ones that his family would now face with their son. Hunter's symptoms began to worsen; one doctor thought he might have cerebral palsy. But when Hunter began having seizures, they paid a visit to a neurologist at Children's Hospital in Buffalo.

"She just said, 'I'm going to take some blood and test for leukodystrophies.' Of course, we didn't know what that was," remembers Jim. "We had never heard of it. I went home that day and checked on the Web for these things."

"I was pretty confident, but two weeks later, our neurologist called us into her office and our pediatrician was there. She sat us down and told us the diagnosis and that it was Krabbe disease. We were devastated, to say the least."

Like Canavan, Krabbe disease is a rare neurodegenerative ailment affecting the myelin, or white matter, of the brain. Also similar to Canavan is the eventual complete neurological breakdown of patients - and a life expectancy of only a few years.

Within a week, their son was using a feeding tube. "Hunter wasn't able to swallow. It took us, like, an hour to give him just an ounce of formula," says Jim. "We almost waited for him to die."

"She told us there's no cure, there's nothing anyone is doing. So we just left it at that, even though here we're thinking, 'Wait, this is Jim Kelly, we can do stuff.' But there was nothing, which is why we started the foundation."

The nonprofit institution Hunter's Hope has raised close to \$4 million so far to fund Krabbe research and treatment options. Much of the money raised has gone toward umbilical-cord blood transplants, a procedure that, although somewhat risky, has shown promising results in Krabbe patients who are only a few months old. Several hundred such cord blood transplants are performed annually.

Hunter, meanwhile, turned 8 on Valentine's Day. He shares his birthday with his dad, who retired from the NFL at the end of the 1996 season. Jill says both she and her husband are impressed every day with Hunter's cognitive abilities and progress.

"Every single person that works with Hunter is amazed," she says, beaming. "He blinks once for yes. He's been trying to pull his head forward. There's a very loving, determined little person inside that we have to help get out."

#### **[Illustration]**

Caption: CHET GORDON HOPEFUL: Jacob Sontag and his mother, Jordana Holovach, are awaiting the results of the clinical trial in which he participated. SABINA PIERCE FRUSTRATED: Despite promising results, Dr. Paola Leone faces funding obstacles. BRODY WHEELER PROACTIVE: Jim and Jill Kelly with son Hunter.

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