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A Hunt for Genes That Betrayed a Desert People

By DINA KRAFT

HURA, Israel — In a sky blue bedroom they share but rarely leave, a young sister and brother lie in twin beds that swallow up their small motionless bodies, victims of a genetic disease so rare it does not even have a name.

Moshira, 9, and Salame, 8, who began life as apparently healthy babies, fell into vegetative states after their first birthdays.

Now their dark eyes stare enormous and uncomprehending into the stillness of their room. The silence is broken only by the boy's sputtering breaths and the flopping noise his sister's atrophied legs make when they fall, like those of a rag doll, upon the mattress.

"I cannot bear it," said the children's father, Ismail, 37, turning to leave the room as his daughter coughs up strawberry yogurt his wife feeds her through a plastic syringe.

The sick children are Bedouin. Until recently their ancestors were nomads who roamed the deserts of the Middle East and, as tradition dictated, often married cousins. Marrying within the family helped strengthen bonds among extended families struggling to survive the desert. But after centuries this custom of intermarriage has had devastating genetic effects.

Bedouins do not carry more genetic mutations than the general population. But because so many marry relatives — some 65 percent of Bedouin in Israel's Negev marry first or second cousins — they have a significantly higher chance of marrying someone who carries the same mutations, increasing the odds they will have children with genetic diseases, researchers say. Hundreds have been born with such diseases among the Negev Bedouin in the last decade.

The plight of the community is being addressed by an unusual scientific team: Dr. Ohad Birk, a Jewish Israeli geneticist, and two physicians, Dr. Izzeldin Abuelaish, a Palestinian from the Gaza Strip, and Dr. Khalil Elbedour, himself a Bedouin from Israel.

They work together in the southern Israeli city of Beersheba at a genetics center with two neighboring branches, the Genetics Institute of Soroka Medical Center and the Morris Kahn Human Molecular Genetics Lab at Ben-Gurion University of the Negev.

Dr. Birk heads both institutions, which work to identify the mutant genes that cause these diseases. In the last two years, the center has identified eight mutant genes not previously associated with a disease, as well as dozens of new mutations in other genes that were already associated with diseases.

The findings are passed on to interested families who are given premarital genetic counseling and prenatal testing. More than 20 couples chose to end pregnancies over the past year, after doctors diagnosed in the fetuses terminal diseases that usually kill within the first few years of life.
But there are risks. In a small, closed society in which secrets are hard to keep, there is the danger of stigmatizing carriers and their families, subsequently lowering their chances for marriage should word get out that a genetic disease runs in the family.

The researchers try to minimize that risk by approaching families confidentially through their family doctors and offering them discreet testing, even in their own homes. Extensive genetic counseling is provided before and after testing. Results are given only in person by genetic counselors who walk individuals and families through the science and emotions of the process.

The researchers are also working closely with local Muslim leaders to spread a message about the benefits of genetic testing.

Many of the diseases among the Bedouins are not only rare but extremely severe. One such disease is aplasia cutis, in which babies are born with no skin on their skull. Some babies are born with neurological-spastic diseases and die within a few months. Other inherited conditions are blindness and severe mental retardation.

In a Bedouin tent camp south of Beersheba, Omar, 11, lives with an especially rare disorder known as "congenital insensitivity to pain with anhidrosis." Children with this disorder become their own worst enemies, burning and maiming themselves without feeling a thing.

Omar's body is covered with scrapes and bruises, and his left leg was amputated below the knee — a result of a septic infection that set in after he hurt himself. His mother, who like several others interviewed asked not to be identified for fear of being stigmatized, fears he will hurt or even kill himself if left alone, so she carries him constantly around the steep, rock-strewn slopes. But it is exhausting, and she also has to care for her 11 other children.

"He is glued to me," she said. "I am very supportive of testing so people won't suffer the way I have suffered."

The Beersheba research team seeks to identify the mutant genes behind such diseases through genetic linkage analysis, in which the genomes of affected and non-affected family members are scanned at 10,000 known points of variation using powerful Affymetrix chips.

Once researchers home in on the area where the defective gene is housed, the region is sequenced to find the specific mutant gene.

"It's very satisfying to be able to tell families" that the gene causing a particular illness has been identified, said Dr. Elbedour. Of course, he cautioned, it is not easy for families to receive the news that they carry a risky gene, and the knowledge is not a cure. But it can be a step toward prevention.

Identifying the disease-related genes may help researchers design drug therapies. The Israeli lab is working to do so. "We are actually finding pathways and the molecular basis for diseases," Dr. Birk said.

The team is focusing on Mendelian diseases, the relatively rare type caused by disorder in a single gene. But Dr. Birk said the research might also help the team members find genes that combine to cause more common problems like diabetes, epilepsy, asthma and obesity.

The findings on Mendelian disease could be used by the major Bedouin populations in neighboring Egypt, Jordan and Saudi Arabia with similar gene mutations. But so far, Dr. Birk said, scientists in those countries have refused offers to collaborate.

"It's so essential and basic that we should be working together," he said. "It's funny. The only Middle Eastern people we are collaborating with are the Palestinians."
The cooperation sometimes falters. On a recent morning an exasperated Dr. Abuelaish stormed into Dr. Birk's office. He was furious that Israeli soldiers at the crossing from Gaza into Israel had made him wait two hours to pass through and then asked him to take off his shirt to make sure he was not wired with bombs.

Still, Dr. Abuelaish declares, "Medicine does not know borders."

Dr. Abuelaish, who works as an obstetrician and a gynecologist in the Jabalia refugee camp in Gaza, is one of the few Gaza Palestinians permitted to enter the country since Israel's recent withdrawal from Gaza, traveling to Beersheba once a week.

An estimated 140,000 Bedouins live in the Negev desert in the south of Israel bordering Gaza. Some of the families the researchers are studying have branches in both the Negev and Gaza.

One of the lab's breakthroughs was solving the genetic puzzle that caused members of three extended families to be born without eyes. One of the families was in Gaza, another in the Negev, and one was a Jewish family of Syrian-descent living in Jerusalem.

One member of the Gaza family is Ramzi Abu Aljidian, 24, who like his sister has eyelids but no eyes underneath them. He is pleased his family's participation in the research was fruitful.

"We want to prevent such cases in the future," said Mr. Abu Aljidian, who added that his condition persuaded him not to marry within the family. Mr. Abu Aljidian married a woman who is not a relative, and the couple have two normal, healthy children.

Dr. Abuelaish is the lab's connection to Gaza. A specialist in fetal medicine, he meets with families who have a history of genetic diseases, collects blood samples and draws up the detailed family trees of his patients.

"People need help, and we try to help them," he said. Access to the modern facilities in Israel is essential for his patients in Gaza because there are no genetic labs there.

In Beersheba, Dr. Abuelaish shows Dr. Birk a collection of X-rays he took of a brother and sister from Gaza who suffer from phocomelia, in which their limbs are short and twisted.

"That's his hand," said Dr. Abuelaish, pointing to a 6-year-old boy who has three oversized fingers on one hand, two on the other. Like his older sister, he has legs that are only a few inches long. The two get around in wheelchairs that they roll down the dusty streets of their refugee camp.

The children, like many of the Gazans, do not have permission to enter Israel. Dr. Abuelaish must therefore document the clinical side of the cases as thoroughly as possible and take that documentation — together with blood samples and photographs — back to Israel.

The lab was sponsored by Morris Kahn, an Israeli philanthropist, and was championed by the acting president of Ben-Gurion University, Rivka Carmi, a genetics professor herself, specifically to research genetic diseases among the Bedouins. Its research has helped establish Israel as an important center for the study of genetic diseases among inbred peoples.

One of the main challenges facing the researchers is how to reach out to the people affected in a culturally sensitive way.

Bedouins are known for their pride and privacy, and illness is associated with weakness and a loss of family honor. The stigma of disease causes some families to balk at the idea of testing.

Muslim religious leaders have been drafted to help educate the members of the group about genetic problems, speaking out about the dangers of marrying relatives and increasing awareness...
of genetic testing and counseling. The imams also let families know that under Islam a woman can abort a fetus up to four months for health reasons.

"We are trying to convince people that to do a test is in their best interest," said Jomah al-Zodeah, 36, an imam in the Bedouin town Rahat. He and his two wives, cousins from either side of his family, recently had their blood tested by Dr. Elbedour.

Mr. Zodeah knows the toll of genetic disease; several children in his own extended family have died young.

Among the genes the Israeli genetics lab has identified is the one that caused Moshira and Salame's devastating disease. For years the children's parents, cousins who are both carriers of the gene that causes the illness, struggled over the decision of whether or not to have more children.

Just over two years ago they decided to take a chance. They had a baby girl who is free of the disease. Now pregnant again, their mother, Gazia, 30, was able for the first time to receive a prenatal test that determined the fetus she is carrying is indeed healthy. In her modern and immaculate home, Gazia has just finished feeding Moshira and Salame a liquid lunch through a plastic syringe. She muses on the better lives genetic research might bring.

"I hope everyone will have healthy children," she said.