Generations לדורותיכם
Center for Rare Genetic Disorders
A DIVISION OF BONEI OLAM

UNRAVELING RARE GENETIC DISEASES

How Information Hidden Deep Within Our Genetic Code Can Help Create Healthy Families

When Hindy and Seth Galena returned home from Cincinnati Children's Hospital three years ago, they were lost, lifeless and childless. Their daughter, Ayelet, who suffered from a rare genetic disease affecting the immune system, known as dyskeratosis congenita, had passed away from complications after receiving a bone marrow transplant. For six months, Hindy and Seth watched their adorable little girl, who loved stickers and straws and had a smile that could light up any room of doctors, battle for her life in an intensive care unit 650 miles from their Upper East Side home. She was only two years old.

Sadly, the Galenas are not alone in their quest to have a healthy child. Nearly 30 million people in the United States, approximately half of them children, suffer from rare diseases and most cases are due to an unknown genetic abnormality. Additionally, another one in six couples face the harrowing challenge of infertility. "There were endless tears," described Seth at a Bonei Olam event in Los Angeles. "We, just kids ourselves, became mourners. We had no hope and no answers."

Then they came to **Bonei Olam**. Founded in 1999, the nonprofit organization, under the direction of its Rabbinical board, guides childless couples to the best medicine has to offer and provides extensive financial assistance allowing them to achieve their dream of parenthood. The burdensome costs of fertility treatments amounts to millions of dollars yearly paid by Bonei Olam. To date, Bonei Olam has had the privilege to take part in the birth of approximately 6,000 babies. Eight years ago, the organization formed a

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**The names in this story have been changed to protect the couples' anonymity.*

Eli Rybak, MD

"Twenty years ago, infertility was seen as a moral failure," says **Eli Rybak, MD**, a reproductive endocrinology and infertility specialist at **Reproductive Medicine Associates** in New Jersey. "Bonei Olam has been instrumental in raising awareness that infertility is a medical condition—and it is not something that warrants embarrassment or insecurity. It can be addressed and deserves the support of the Jewish community."

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sister program, **GeneArations**, its mission being to assist families facing the genetic challenge of undiagnosed disease. Unlike most undiagnosed disease programs around the world who may take years to end the odyssey of one family, GeneArations has with great Syata Dishmaya helped hundreds of these families have healthy children in its relatively short existence.

"Having spent hundreds of hours in doctors' waiting rooms, surrounded by people of all races and religions, I can tell you there is one thing that is universal across all people: a baby is a prize, a marvel and a joy to every human being," says Rabbi Shlomo Bochner, executive director of Bonei Olam, who founded the organization along with his wife, Chanie. "Our mission is to remove any barrier to bringing the dream of parenthood to childless couples."

Bonei Olam receives numerous phone calls daily from couples seeking help. Each couple is assigned a counselor who assesses their situation, proceeds to guide them to the physician best suited for their particular issue, walks them through the complexities, accompanies them to procedures when necessary and, above all, provides the finances to bring the fulfillment of their lifetime dream. At the outset Bonei Olam focused solely on helping couples struggling with infertility, over time it has evolved into a multifaceted organization providing services for high-risk pregnancies, pre and post cancer fertility as well as adoption assistance.

"**They are what to expect when you are trying to get to expecting**," Seth wrote in the couple's blog, *Ayelet Nation*. "At every step, they would tell us which doctor to call, what lab to use, what questions to ask and explain what it all meant."

"They say it takes a village to raise a child," adds Shimon Edvardson, MD, an attending physician in the neuropediatric unit at Hadassah Medical Center in Israel. "That is exactly what Bonei Olam is doing."

Joshua Klein, MD

"Bonei Olam has a sensitivity that allows them to be different things for different people the way they need it," says **Joshua Klein, MD**, a reproductive endocrinology and infertility specialist in Brooklyn. "They provide a sympathetic ear, handholding, non-judgmental advice and financial support. Most impressively, they are not only observers of advances in medicine, but they are active in moving the field forward with genetic research."

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creating families.

building eternity.

LIVING WITH RARE UNKNOWN DISORDERS

Like infertility, the concept of **GeneArations**, which helps couples with genetic disorders, grew out of a desire to help the community. Eight years ago, Rabbi Bochner was at an event when a young couple approached and **beseeched him** for help. Their three-year-old had a severe developmental delay and they suspected he had a genetic disorder.

"They told me seeing him suffer was like a 'dagger to their hearts'," says Rabbi Bochner. "But we were an infertility organization. What did I know about genetics? It quickly became clear to me that there were other young couples in need, and infertility was only a piece of the puzzle."

Many of the rare diseases that affect families remain a mystery to medical science. For years, Estee and Yisrael* battled infertility and suffered recurrent losses due to an unexplained genetic problem. Rivky and Moshe's* first child lost his fight with a disease of unknown genetic origin called Aicardi-Goutieres Syndrome (AGS), which causes severe physical and mental disability. Two of Bracha and Shmuel's* triplets were affected by an unexplained brain disease that caused them to progressively stop eating, talking and walking around their second birthday.

"The pain of not having answers is unbearable and constantly in your heart 24 hours a day," Yisrael explains. "It gets talked about every time we go into the community and see kids, neighbors or family."

"There is nothing worse for a parent than to watch their child suffer," says Bracha, who quickly transformed from a first-time mother into an advocate at physician's offices, a secretary for insurance claims and coordinator of in-home nurses and therapists. "A lot of kids with genetic diseases are cognitively fine, but physically disabled. They are trapped in their own bodies. I see videos of my daughter before she got sick—she is smiling and happily eating a peanut butter sandwich. Now, she is in a wheelchair."

Everyone is a carrier for at least one genetic disorder; and nearly half of all Ashkenazi Jews in the United States are a carrier for at least one known Ashkenazi genetic disorder. When only one parent is a carrier their children are not at risk. However, when both are carriers of mutations in the same gene, they have a 25 percent chance of having a child affected by that disease. As a result, for decades, members of the Ashkenazi Jewish community have undergone premarital genetic screening for disorders that are prevalent in their population, such as Tay-Sachs disease and Cystic Fibrosis.

Yisrael and Estee knew their dream of having a healthy child would be lost until they could identify the faulty gene—known as a mutation or variant—that affected them. "Our specialist told us finding our gene would be like looking for a needle in a haystack," Yisrael recalls. "We wondered where else we could turn."

Their answer was **Chaim Jalas**. As director of genetic resources at GeneArations, and co-director of patient services at Bonei Olam, he has helped identify and characterize dozens of rare genetic diseases that have

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prevented families from having healthy children. Most of the genes he has discovered cause debilitating neurological disease in babies. Together, with his colleagues, Chaim Halberstam and Chaim Landau, the co-directors of patient services at Bonei Olam and GeneArations, they collaborate regularly with leading scientists, physicians and genetic laboratories all over the world to help families find answers.

"When they found our gene, you would have thought it was for their own family," Yisrael recalls. "They were so excited and devoted to us. It was unbelievable."

Orly Elpeleg, MD, head of the department of genetic and metabolic diseases at **Hadassah Medical Center** in Israel says: "It is extraordinary to see this depth of knowledge and understanding in an organization." Together, she and Chaim Jalas have published nine papers in prestigious peer-reviewed medical journals identifying new genes. Recently, they discovered a mutation in the *VPS11* gene that causes hypomyelination (a defect in a protective liquid called myelin found in the spinal cord and brain) and severe developmental delays in Ashkenazi Jews, which appeared in the *Journal of Medical Genetics*.

"Bonei Olam channels all of its energy and talent for the good of people. They take one family after another, and they get things done," adds Prof. Elpeleg.

Bonei Olam's rolodex of respected researchers and clinicians around the world is part of what makes the organization so unique—and successful. Six years ago, Chaim Jalas contacted **Dr. Edvardson**, who had a reputation as a renowned neurologist, and asked if he would be willing to come to New York on a research trip to meet and document some children with rare neurologic disorders.

"I was hesitant to go at first. I did not know the organization," Dr. Edvardson describes. "I was immediately mesmerized by the work they were doing and we have had a cooperation ever since."

Dr. Klein shares a similar tale. The Harvard Medical School graduate was a resident in training when he first came to Bonei Olam's humble headquarters, their office in Boro Park, Brooklyn.

"I was thinking it would be some very simple operation run by people who were not formally trained. From the moment I walked in, I was blown away," he recalls.

"I dare to say that Bonei Olam is more up-to-date in terms of the current research and treatments available than most of the fully-trained fertility doctors out there. It was such an unbelievably impressive experience... almost to the point of being intimidating."

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John Pappas, MD

That service, says **John Pappas, MD**, assistant professor of pediatrics at New York University, who also collaborated on *SLC1A1*, is as extraordinary as the genetic coding they so often manage to unravel. "It is almost impossible to get insurance carriers to cover expensive genetic tests," he says. "Bonei Olam has stepped in for numerous families. They do an excellent job picking what tests and laboratories to use. Every time they have funded a case we have always found something significant."

DISCOVERING THE GENES THAT CAUSE DISEASE

Chaim Jalas

"Our DNA is like a cookbook that contains many recipes. If one ingredient is missing, then the cake will not taste good," explains **Chaim Jalas**. "The idea behind gene sequencing was that instead of searching for known mutations—as is done in genetic testing—scientists would be able to search the genes of families with unknown disorders and try to uncover any patterns that may explain their symptoms."

Nearly a year after Rivky and Moshe came to Bonei Olam, their gene, *SAMHD1* was also discovered. When the gene mutates, it is thought to disrupt a protein that is critical for regulating the immune system and inflammatory response in the brain and skin. Rivky says words cannot describe how grateful she is for the dedication and the financial support of Bonei Olam.

"We spent so much money on our first child, flying all over the world for physicians and therapies. Insurance covered nothing," says Rivky who supported her son on two teacher's salaries. "They are not like a doctor who gives you the cold, hard facts. You can call them anytime and they explain things 15 times until you understand it. They give you their time, they give you their money—they give you everything."

The road to identifying genes like Rivky and Moshe's that because rare disorders began more than two decades ago when a group of scientists decided to take the idea of genetic testing a step further. In 1990, they launched the Human Genome Project—an effort to identify and map all of the genes that compose human DNA.

Every person has some 22,000 genes that make them who they are. Inherited from their parents, genes are made up of DNA, which are assembled into millions of letters that contain a set of instructions, making every living creature unique.

These DNA pairs are then organized into long structures called chromosomes. From eye color and personality traits to an individual's susceptibility to develop certain diseases, genes contain a set of blueprints that tell the body how to grow and work.

But sometimes these genes are mutated causing a permanent alteration in a person's genetic code that is different from what is found in most healthy people. Mutated genes can be missing entirely, cause extra copies to appear or simply not function properly. They also range in size. Some are obvious, such as those found in Down's syndrome—which cause an entire extra copy of a chromosome to appear—while others can be as small as a missing single pair of DNA letters. Other mutations can affect multiple genes at once.

Such was the case for Dovid and Aviva. *A few months after their daughter was born, it was obvious something was wrong. She had severely low muscle tone, was uncommunicative and, not long after her first birthday, she began experiencing seizures.

"We were young, naive parents and completely on our own," explained Aviva. "The doctors dismissed us. They said they did everything they could and we should try our best with therapies."

Almost a year later, the couple was expecting a second child and they reached out to Bonei Olam for a high-risk obstetrician. Within an hour, they received a call back from Chaim Jalas. He suspected there was a genetic abnormality within the family; and if the gene could be identified, he could help them have a healthy baby.

In 1998, sequencing an entire human genome cost roughly three billion dollars. Today, that price tag has dropped to roughly $5,000 for a clinical genome. What's more, searching for these mutations has become simpler and less expensive utilizing new technology known as exome sequencing. Instead of sequencing a person's entire genome, this technique maps only the two percent of the genome thought to be the root of most mutations.

"The field has developed rapidly over the past five years," says Bryn Webb, MD, assistant professor of genetics and genomic sciences and pediatrics at the Mount Sinai Health System. "Many patients with rare diseases that could not have been diagnosed before—because they did not fit the exact clinical symptoms of a described disease—are being diagnosed now with exome sequencing."

In 2013, Chaim Jalas and Dr. Webb published a paper in *Clinical Genetics* proving a mutation on gene *COL4A3* causes Alports syndrome, a rare disease characterized by kidney failure and hearing loss that is carried by 1 in 183 Ashkenazi Jewish individuals. Without exome technology, Dr. Webb says families with this variant would still be looking for answers.

The day after Aviva and Dovid spoke with Bonei Olam, blood samples were sent to a genetics laboratory for exome sequencing. The scientists extracted the DNA from their blood and placed it onto a machine that provided a digital readout of each of the exons of 22,000 genes. First, the genes were filtered for anything that appeared too commonly in the population (this typically weeds out

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THE PATH TO A HEALTHY CHILD

Nearly a year after Ayelet passed away, the National Institutes of Health identified the gene mutation, *RTEL1*, which caused her rare disease. Seth and Hindy were thrilled. But now what? After spending two years fighting for their daughter's life, they wondered how they would find the energy to navigate the exhausting and confusing process of having a healthy child. With the heartfelt guidance and financial assistance of Bonei Olam, Seth and Hindy began their journey.

"Right before our eyes, Chaim Jalas built a practical path towards a future of having another child. The guidance was priceless. We felt empowered, like we had an inside connection to research labs and clinics. 'Chaim Jalas told me about you...' was how most new appointments started. His advice was priceless," describes Seth. "Infertility genetics are such a foreign language to so many of us and somehow Bonei Olam speaks it fluently."

Through a reproductive technique called PGD, which the couple would avoid passing on the disease to future children. Each test is individually designed for the couple. Not only does it test for the genetic mutation, but it also identifies any genetic markers that may be linked to the mutation.

After one year of partnering with Bonei Olam, a miracle arrived—a healthy son named Akiva Max. But Chaim Jalas did not stop there. He recently published an academic paper on Ayelet's mutation of the *RTEL1* gene in the *Journal of Clinical Genetics*. Since then, various laboratories have added the mutation to their genetic screening panels. Says Seth in his blog: "In other words, Ayelet's DNA, her life, with Chaim Jalas's research, will potentially save countless lives in the future."

"Bonei Olam takes a fabulous leadership role in helping these individuals," says Sherri Bale, PhD, medical geneticist and managing director of GeneDx, who works with the organization to sequence gene samples. "I only wish there were more organizations like them around."

Every day, Dr. Klein sees couples undergoing fertility treatments that decide to stop prematurely. Oftentimes, he says, these cases would have been successful if they had tried a third or fourth cycle of treatments.

"Infertility is not a linear path—you often climb and fall, climb and fall. A lot of couples

Richard Scott, MD

"Bonei Olam takes support a step further," says **Richard Scott, MD,** director of reproductive endocrinology at **Reproductive Medicine Associates** in New Jersey. "They understand the genetics of what is wrong, the basis of how we diagnose, the technical limitations, and the precision needed to obtain outcomes. Their ability to be facile with the technology makes them a more potent advocate than we see in other arenas."

run out of emotional energy, time or money," Dr. Klein says, "But when Bonei Olam is involved, they are able to provide couples with the support they need to persist. They offer a perspective the patient can relate to."

"I see a tremendous difference in the couples who have been counseled by Bonei Olam, and those who have not," adds Dr. Rybak. "They come in focused, with a game plan. One of the first things I do is ask couples if I can include their Bonei Olam counselor on our medical correspondence."

From the moment Bracha and Shmuel stepped into the Bonei Olam office, they felt understood. During their 12-year search for the gene that plagued their family, they met or exchanged emails with at least 50 physicians around the world.

"We are not the only ones in awe of Bonei Olam," Bracha says. "It is every professional we have ever met. Whenever a family calls me for advice, I say you should be grateful you only have to see one person—I had to see 50."

After Prof. Elpeleg and Chaim Jalas identified Bracha and Shmuel's gene mutation, *C20ORF7,* the couple started trying to have a healthy family with PGD. For years, they struggled and suffered through multiple losses. Bonei Olam's advisors would call them after every doctor's appointment, was always there to comfort them. They were also there to share in their joy when they finally gave birth to two healthy baby girls.

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about 95 percent of the variants). Then, the remaining genes were combed through for individual variants that looked out of place.

"It's like detective work," explains Chaim Jalas, who says families that come to Bonei Olam have a 70 percent chance of having their gene identified. "Part of our success is simply not giving up. Recently, we found a gene for a family that we first met seven years ago. That is the beauty of working for Bonei Olam. We are not on a government project where we have a deadline. We do not have to compete for funding. **No matter what it takes, or how much money it costs, we are simply here to solve the mystery."**

And they did. Within a week, Chaim Jalas discovered the little girl suffered from a mutation on the *SLC1A4* gene, which is associated with microcephaly (small head size) and developmental delays. Defects in the *SLC1A4* gene are thought to cause neurologic disease by affecting amino acids—the building blocks of proteins—from entering the brain cells. Humans need these essential proteins to survive.

"I have never met anyone quite like Chaim Jalas—he is completely self-made in terms of his expertise in genetics," says Wendy Chung, MD, PhD, director of the clinical genetics program at Columbia University, who worked with Bonei Olam to locate the gene. "He has spent countless Sundays and evenings talking to families and helping them understand very complex issues."

Once a gene mutation like Aviva and Dovid's is located, researchers also need to prove that variant actually causes disease. Each gene affects a pathway in the body that gives rise to certain functions. By examining the cells of an affected patient, often taken from the skin, scientists can see if the proteins are being disrupted in the way that the gene suggests. The best way to add further confirmation, Dr. Elpeleg says, is to find a similar patient with that variant who has the same disease.

"When we manage to find a faulty gene, not only do we provide the family with the ability to avoid birthing future children with that disease, but we also make a significant contribution to science by assigning a job for that gene," says Prof. Elpeleg.

Today, Aviva and Dovid have an option to have a healthy family—and Bonei Olam paid for all of it. "We do not even know how much the tests cost," says Aviva.

That service, says **John Pappas, MD**, assistant professor of pediatrics at NYU Langone Medical Center, who also collaborated on *SLC1A4*, is as extraordinary as the genetic coding they so often manage to unravel. "It is almost impossible to get insurance carriers to cover expensive genetic tests," he says. "Bonei Olam has stepped in for numerous families. They do an excellent job picking what tests and laboratories to use. Every time they have funded a case we have always found something significant."

LAUNCHING THE JEWISH GENOME PROJECT

Over the years, the stack of unexplained cases on the conference table at Bonei Olam has piled higher and higher. Each gene mutation they can identify has changed many lives, but it is the cases the counselors have yet to solve that keep them up at night. Despite their many successes, the team needed to do more—they wanted to find answers faster, and on a larger scale.

"The pain these families have from not knowing what disease is affecting them is unbearable," says Chaim Halberstam. "We need to help them move on and have healthy children and grandchildren."

For eight years, Chaya and Eliezer* have been working with Bonei Olam to identify several genes that have caused devastating disease and developmental delays in their three children. A few years ago, a researcher from a prestigious university called to tell them his laboratory may have located their gene. But their hope was short-lived and the gene was incorrect. Despite Bonei Olam's tireless efforts, they too have yet to find a solution for the family.

"There have been a lot of ups and downs. Our situation would seem to be hopeless. Any academic institution would have given up on us by now, but Bonei Olam continues to search," says Eliezer who is hopeful they will find an answer someday. "There are no honors given out for anonymous research like this, and yet they continue to work nonstop and travel all over the world to help families like us. Bonei Olam is in our corner and not being alone gives us hope. They do not give up. So we do not give up."

Oftentimes, the Bonei Olam team would find a variant in a gene and have an inkling it was suspicious, but they did not know how often it appeared in the general healthy population. For all they knew, many Ashkenazi Jews could carry what appeared to be an odd variant. The counselors knew the answer to finding the exception could be found by looking at the rule: healthy Jewish individuals.

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"Of the 22,000 genes that have been identified, scientists still do not know what about 75 percent of them do," explains Dr. Edvardson. "There are hundreds of thousands of normal gene variants—some people have blue eyes, others have brown. These normal variants need to be known before we can point to a true mutation."

In 2015, Bonei Olam received approval from an Institutional Review Board (IRB)—an independent ethics committee that monitors biomedical research—to launch the Jewish Genome Project. The goal of the research study is to build a database of genetic information for at least 1,000 healthy people of Ashkenazi Jewish descent. By having this repository, scientists can learn more about the genetic differences that may predict whether a person is at risk for disease. Other databases of this kind have helped inform other ethnicities about genetic defects that are prevalent within their heritage.

The genetic information, which will be analyzed in partnership with the Broad Institute of Massachusetts Institute of Technology (MIT) and Harvard University. The data will be anonymized and shared publicly on a gene sharing website known as the Exome Aggregation Consortium (ExAC). This will allow a physician across the world with an Ashkenazi Jewish child suffering from unexplained symptoms to consult the database and compare the patient's genetic profile with a healthy control group. Eventually, Bonei Olam plans to conduct similar studies of other Jewish ethnicities.

Dr. Pappas says the project will also help explain how common genetic conditions are in the population. "If we know that 5 in 1,000 people have this particular mutation, it helps inform where to allocate your resources to help the community. This is extremely helpful not only for people of Ashkenazi Jewish origin, but also for the general population" he says.

"We have a lot of reference data that is of European ancestry but not Jewish ancestry," explains Dr. Chung. "There are genetic differences that are unique to the Ashkenazi community, but are not mutations per se. We need good reference data to understand which variants are unique differences and which are mutations. This will allow us to diagnose families more efficiently."

"An Ashkenazi Jewish control population is the best way to quickly identify more diseases," agrees Dr. Bale. "When we find a mutation, we can look at our control group of 1,000 individuals. If the variant has never been seen, we know it is more likely to be the real thing. Right now, we simply do not know what is normal."

The Jewish Genome Project will also help connect families who are dealing with the same afflictions. Part of the beauty of Bonei Olam's work is that once a new gene is identified, they may also be able to identify other unsolved cases where children suffer from a similar set of symptoms.

For ten years, Rochel and Mordechai* traveled the world searching for a genetic answer to the medical riddle that caused neurologic disease, autism and seizures in their three children, and took the life of their eldest child. When they finally came to Bonei Olam, Chaim Jalas not only located the gene, SLC35A3, but also linked the mutation with two other unsolved cases. The findings, published in the Journal of Medical Genetics, demonstrated that a mutation on the SLC35A3 gene was associated with autism spectrum disorder, epilepsy and arthrogryposis (joint malformation).

"It is often a relief for families to know that they are not alone," says Dr. Edvardson. "They can ask other families about the natural history of the disease and what complications they are looking at."

Thanks to Bonei Olam's dedication, Rochel and Mordechai's two living children, who are now teenagers, can be tested for the mutation before they get married. The organization offers genetic counseling to help educate families about how a gene may affect their extended family and is always available to the family's Rav to communicate and explain the circumstances. In many cases it may be critical to test those family members to verify if they carry the mutation thereby avoiding more affected children Chas V'sholom.

"I often speak with couples about the importance of sharing this knowledge with their family members," says Andria G. Besser, BEd, MS, CGC, head of genetic counseling at Bonei Olam. "Since it can be difficult for families, when given permission, we will call on their behalf and explain all of the information."

Bonei Olam is recruiting healthy Ashkenazi Jewish adults to participate in the Jewish Genome Project. Each volunteer must provide consent, fill out a brief questionnaire regarding personal and family medical history and provide a DNA sample by having their blood drawn. Since the goal of the research study is to learn information about normal variants that will help patients in the future, participants will not receive medical care or benefits. In addition, volunteers will not receive any information about what genetic diseases they may carry.

"I would not wish what I went through upon anyone," says Aviva, who hopes her community will enroll in the study. "This is the easiest way to help people and ensure another family never has to go through these challenges."

HOW YOU CAN HELP GENETIC RESEARCH

In a few cases, genetic information has also been used to help treat children already affected by devastating neurologic diseases. However, Bonei Olam advisor Chaim Landau cautions families that this takes time. For example, the gene for cystic fibrosis was identified in 1989, but it took 26 years for a gene-based drug to be approved by the Food and Drug Administration.

Dr. Edvardson believes this idea, known as gene therapy, which involves replacing a faulty gene with a corrected one that is designed in the laboratory, will be a realistic option in the future. But it will only be possible if the mutation has been identified.

For example, many mutations prevent the neurotransmitters—chemicals in the brain that tell the heart to beat and lungs to breathe—from communicating properly. If scientists understand what the mutation is affecting, there may be a therapeutic way to stimulate, or someday even replace, that function.

"Gene therapy, which is still yet to come, is our last ray of hope for these children," he says. "Right now, for many, all we do is offer symptomatic relief."

CREATING MIRACLES:

ONE FAMILY AT A TIME

More than 6,000 families have built a better world with the support of Bonei Olam. When Rivky and Moshe watch their healthy son—who recently started grabbing toys and babbling—they feel like first-time parents again. "We marvel at his antics," she describes. "I love to make him laugh and hear his giggle. Every day he does something new." Aviva and Dovid applaud their energetic son every time he destroys their clean apartment. Hindy and Seth say it is a relief to be a normal family when they bring their son—who is now walking and talking—to the doctor for a well visit.

Someday, Hindy and Seth will tell him about the amazing little girl who carved a path for him—and the organization that made it all possible. "They are able to uncover the trauma, the hidden pain of being alone and helpless, and search for a path forward," he says. "Only leaders like Rabbi Bochner and Chaim Jalas are able to look you squarely in the eye with such love and say, 'This trauma is our trauma. This miracle is our miracle. We are going to create together.'"

Listing of most prestigious genetic medical journals recently published, that credit Bonei Olam's executive staff members **Chaim Jalas, Chaim Shia Halberstam, Chaim Landau** amongst others, in solving and identifying rare and troublesome Jewish Ashkenazic genetic mutations.

CLINICAL GENETICS
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Short Report

A founder mutation in *COL4A3* causes autosomal recessive Alport syndrome in the Ashkenazi Jewish population

Webb BD, Brandt T, Liu L, Jalas C, Liao J, Fedick A, Linderman MD, Diaz GA, Kornreich R, Thiagalingam H, Mehta L, Edelmann L. A founder mutation in *COL4A3* causes autosomal recessive Alport syndrome in the

BD Webb[a,b,†], T Brandt[a,†], L Liu[a], C Jalas[c], J Liao[a], A Fedick[d], MD Linderman[e],

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Short Report

A founder mutation in the *TCIRG1* gene causes osteopetrosis in the Ashkenazi Jewish population

Anderson SL, Jalas C, Fedick A, Reid KF, Carpenter TO, Chirnomas D, Traff NR, Ekstein J, Rubin BY. A founder mutation in the *TCIRG1* gene

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Developmental defects

ORIGINAL ARTICLE

Two novel CCDC88C mutations confirm the role of DAPLE in autosomal recessive congenital hydrocephalus

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ABSTRACT
Background Human congenital non-syndromic

hydrocephalus can be divided into syndromic (two-thirds of cases) and non-syndromic (a third)

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A founder mutation in the *MPL* gene causes congenital amegakaryocytic thrombocytopenia (CAMT) in the Ashkenazi Jewish population

Chaim Jalas [a], Sylvia L. Anderson [b], Tova Laufer [b], Kristina Martimucci [b], Alex Bulanov [b], Xie Xie [b], Josef Ekstein [c], Berish Y. Rubin [b,*]

Molecular Genetics & Genomic Medicine

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ORIGINAL ARTICLE

Carrier frequencies of eleven mutations in eight genes associated with primary ciliary dyskinesia in the Ashkenazi Jewish population

Anastasia M. Fedick[1,6], Chaim Jalas[3], Nathan R. Treff[1,2], Michael R. Knowles[4] &

CLINICAL REPORT

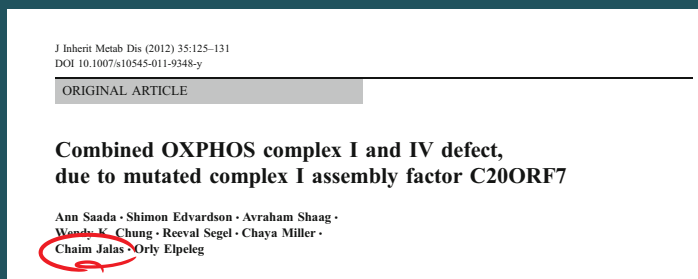
AMERICAN JOURNAL OF medical genetics PART A

A Deleterious Mutation in the *LOXHD1* Gene Causes Autosomal Recessive Hearing Loss in Ashkenazi Jews

S. Edvardson,[1]* C. Jalas,[2] A. Shaag,[3,4] S. Zenvirt,[3,4] C. Landau,[2] I. Lerer,[3,4] and O. Elpeleg[3,4]

[1]Pediatric Neurology Unit, Hadassah, Hebrew University Medical Center, Jerusalem, Israel

[2]Ronel Olam, Center for Rare Jewish Genetic Disorders, Brooklyn, New York

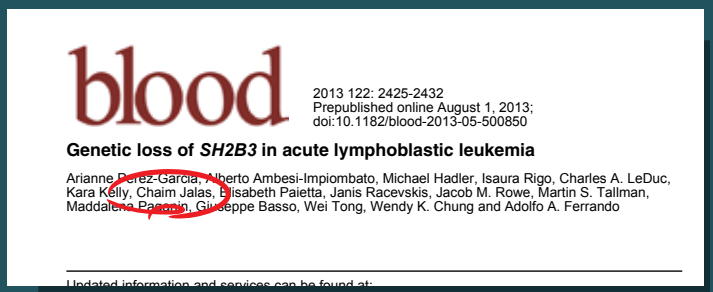


J Inherit Metab Dis (2012) 35:125–131
DOI 10.1007/s10545-011-9348-y

ORIGINAL ARTICLE

Combined OXPHOS complex I and IV defect, due to mutated complex I assembly factor C20ORF7

Ann Saada · Shimon Edvardson · Avraham Shaag · Wendy K. Chung · Reeval Segel · Chaya Miller · Chaim Jalas · Orly Elpeleg



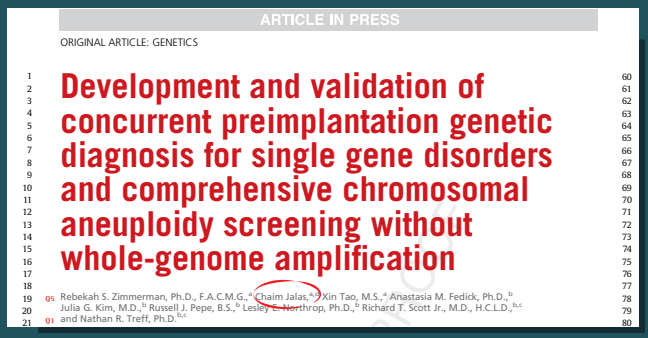
blood

2013 122: 2425-2432
Prepublished online August 1, 2013;
doi:10.1182/blood-2013-05-500850

Genetic loss of *SH2B3* in acute lymphoblastic leukemia

Arianne Perez-Garcia, Alberto Ambesi-Impiombato, Michael Hadler, Isaura Rigo, Charles A. LeDuc, Kara Kelly, Chaim Jalas, Elisabeth Paietta, Janis Racevskis, Jacob M. Rowe, Martin S. Tallman, Maddalena Paganin, Giuseppe Basso, Wei Tong, Wendy K. Chung and Adolfo A. Ferrando

Updated information and services can be found at:

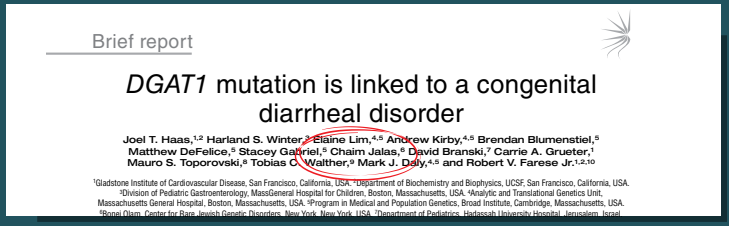


ARTICLE IN PRESS

ORIGINAL ARTICLE: GENETICS

Development and validation of concurrent preimplantation genetic diagnosis for single gene disorders and comprehensive chromosomal aneuploidy screening without whole-genome amplification

Rebekah S. Zimmerman, Ph.D., F.A.C.M.G.,* Chaim Jalas,[a,b] Xin Tao, M.S.,[a] Anastasia M. Fedick, Ph.D.,[b] Julia G. Kim, M.D.,[b] Russell J. Pepe, B.S.,[b] Lesley E. Northrop, Ph.D.,[b] Richard T. Scott Jr., M.D., H.C.L.D.,[b,c] and Nathan R. Treff, Ph.D.[b,c]

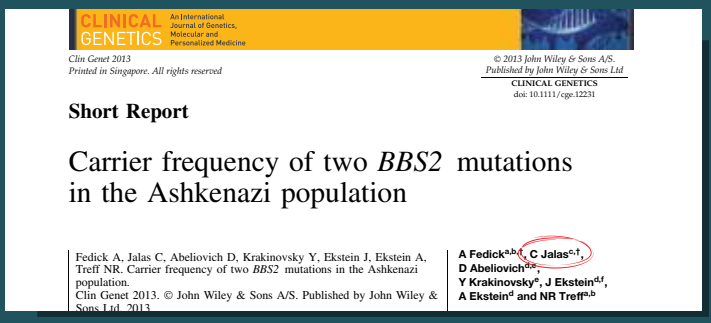


Brief report

DGAT1 mutation is linked to a congenital diarrheal disorder

Joel T. Haas,[1,2] Harland S. Winter,[3] Elaine Lim,[4,5] Andrew Kirby,[4,5] Brendan Blumenstiel,[5] Matthew DeFelice,[5] Stacey Gabriel,[5] Chaim Jalas,[6] David Branski,[7] Carrie A. Grueter,[1] Mauro S. Toporovski,[8] Tobias C. Walther,[9] Mark J. Daly,[4,5] and Robert V. Farese Jr.[1,2,10]

[1]Gladstone Institute of Cardiovascular Disease, San Francisco, California, USA. [2]Department of Biochemistry and Biophysics, UCSF, San Francisco, California, USA. [3]Division of Pediatric Gastroenterology, MassGeneral Hospital for Children, Boston, Massachusetts, USA. [4]Analytic and Translational Genetics Unit, Massachusetts General Hospital, Boston, Massachusetts, USA. [5]Program in Medical and Population Genetics, Broad Institute, Cambridge, Massachusetts, USA. [6]Ronel Olam, Center for Rare Jewish Genetic Disorders, New York, New York, USA. [7]Department of Pediatrics, Hadassah University Hospital, Jerusalem, Israel



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doi: 10.1111/cge.12231

Short Report

Carrier frequency of two *BBS2* mutations in the Ashkenazi population

Fedick A, Jalas C, Abeliovich D, Krakinovsky Y, Ekstein J, Ekstein A, Treff NR. Carrier frequency of two *BBS2* mutations in the Ashkenazi population.
Clin Genet 2013. © John Wiley & Sons A/S. Published by John Wiley & Sons Ltd, 2013

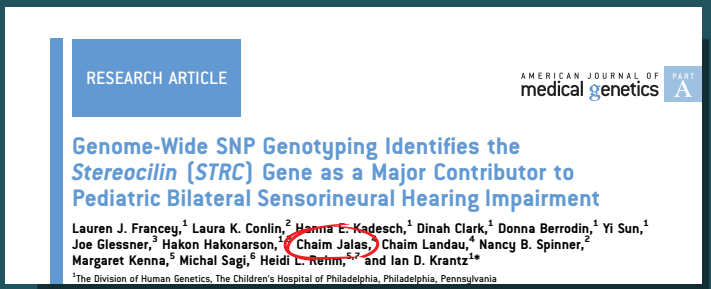
A Fedick[a,b], C Jalas[c,†], D Abeliovich[d,§], Y Krakinovsky[e], J Ekstein[d,f], A Ekstein[d] and NR Treff[a,b]

Research

Original Investigation

Association Between Missense Mutations in the *BBS2* Gene and Nonsyndromic Retinitis Pigmentosa

Elia Shevach, BSc; Manir Ali, PhD; Liliana Mizrahi-Meissonnier, MSc; Martin McKibbin, FRCOphth; Mohammed El-Asrag, MSc; Christopher M. Watson, PhD; Chris F. Inglehearn, PhD; Tamar Ben-Yosef, PhD; Anat Blumenfeld, PhD; Chaim Jalas, BSc; Eyal Banin, MD, PhD; Dror Sharon, PhD



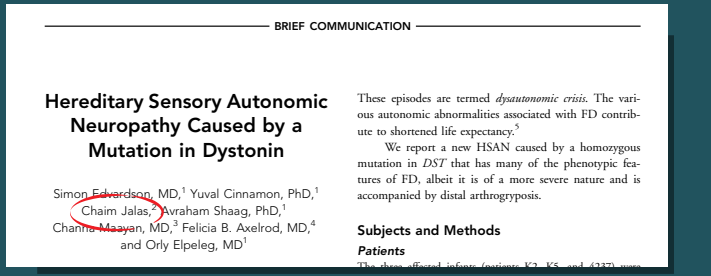
RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Genome-Wide SNP Genotyping Identifies the *Stereocilin* (*STRC*) Gene as a Major Contributor to Pediatric Bilateral Sensorineural Hearing Impairment

Lauren J. Francey,[1] Laura K. Conlin,[2] Hanna E. Kadesch,[1] Dinah Clark,[1] Donna Berrodin,[1] Yi Sun,[1] Joe Glessner,[3] Hakon Hakonarson,[1,3] Chaim Jalas,[4] Chaim Landau,[4] Nancy B. Spinner,[2] Margaret Kenna,[5] Michal Sagi,[6] Heidi L. Rehm,[5,7] and Ian D. Krantz[1]*

[1]The Division of Human Genetics, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania



BRIEF COMMUNICATION

Hereditary Sensory Autonomic Neuropathy Caused by a Mutation in Dystonin

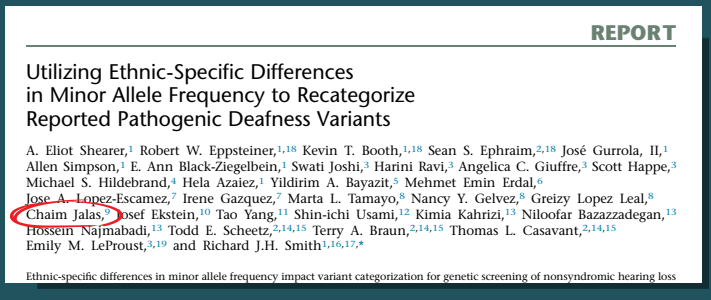
Simon Edvardson, MD,[1] Yuval Cinnamon, PhD,[1] Chaim Jalas,[2] Avraham Shaag, PhD,[1] Chanita Maayan, MD,[3] Felicia B. Axelrod, MD,[4] and Orly Elpeleg, MD[1]

These episodes are termed *dysautonomic crisis*. The various autonomic abnormalities associated with FD contribute to shortened life expectancy.[5]

We report a new HSAN caused by a homozygous mutation in *DST* that has many of the phenotypic features of FD, albeit it is of a more severe nature and is accompanied by distal arthrogryposis.

Subjects and Methods

Patients

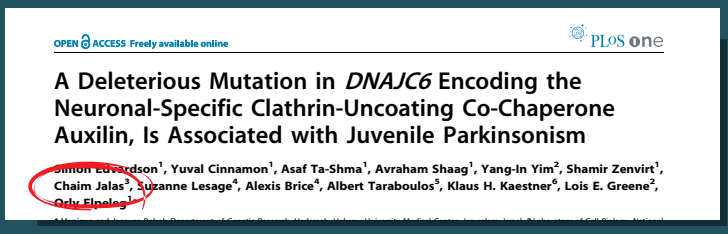


REPORT

Utilizing Ethnic-Specific Differences in Minor Allele Frequency to Recategorize Reported Pathogenic Deafness Variants

A. Eliot Shearer,[1] Robert W. Eppsteiner,[1,18] Kevin T. Booth,[1,18] Sean S. Ephraim,[2,18] José Gurrola, II,[1] Allen Simpson,[1] E. Ann Black-Ziegelbein,[1] Swati Joshi,[3] Harini Ravi,[3] Angelica C. Giuffre,[3] Scott Happe,[3] Michael S. Hildebrand,[4] Hela Azaiez,[1] Yildirim A. Bayazit,[5] Mehmet Emin Erdal,[6] Jose A. Lopez-Escamez,[7] Irene Gazquez,[7] Marta L. Tamayo,[8] Nancy Y. Gelvez,[8] Greizy Lopez Leal,[8] Chaim Jalas,[9] Josef Ekstein,[10] Tao Yang,[11] Shin-ichi Usami,[12] Kimia Kahrizi,[13] Niloofar Bazazzadegan,[13] Hossein Najmabadi,[13] Todd E. Scheetz,[2,14,15] Terry A. Braun,[2,14,15] Thomas L. Casavant,[2,14,15] Emily M. LeProust,[3,19] and Richard J.H. Smith[1,16,17,*]

Ethnic-specific differences in minor allele frequency impact variant categorization for genetic screening of nonsyndromic hearing loss



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PLOS one

A Deleterious Mutation in *DNAJC6* Encoding the Neuronal-Specific Clathrin-Uncoating Co-Chaperone Auxilin, Is Associated with Juvenile Parkinsonism

Simon Edvardson[1], Yuval Cinnamon[1], Asaf Ta-Shma[1], Avraham Shaag[1], Yang-In Yim[2], Shamir Zenvirt[1], Chaim Jalas[3], Suzanne Lesage[4], Alexis Brice[4], Albert Taraboulos[5], Klaus H. Kaestner[6], Lois E. Greene[2], Orly Elpeleg[1]*

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