INTERNATIONAL KLEEFSTRA SYNDROME FAMILY & SCIENTIFIC CONFERENCE

FEBRUARY 4, 2021

Hosted by IDefine, Boston Children’s Hospital Translational Neuroscience Center, Radboud University Medical Center, and KleefstraSyndrome.org
Dear collaborators and guests,

Welcome! We are grateful for the opportunity to bring together patients with Kleefstra Syndrome (KS), our community of caretakers and organizers, doctors, and researchers in the spirit of collaboration at this first International Kleefstra Syndrome Family & Scientific Conference. We have no doubt that the conversations started and relationships built today will change the course of KS treatment and the way we think about treating intellectual disabilities around the world.

When we launched IDefine this summer, we knew we were filling a gap that we had sensed between the experts on this rare disease and the incredible strength of the active KS community that provided such valuable support in the wake of our children’s diagnoses with this rare genetic condition. We had a hunch that focusing the incredible power and determination of patients and those supporting their care to participate in research efforts in meaningful ways — doing the parts that we can do to leave medical experts to their work — would produce some incredible results. Turns out, we were right.

In less than a year, we have funded the Kleefstra Syndrome Clinic at Boston Children’s Hospital, bringing together experts from around the world, including Dr. Kleefstra and her dedicated team from Radboudumc, convened spaces for families to seek advice and learn directly from experts on the forefront of KS research. We have built a network of partners and volunteers whose dedication and skills know no limits — and we are just getting started.

We are thrilled for the chance to come together at this inaugural International Kleefstra Syndrome Family & Scientific Conference and for the opportunities that this new year holds for us to unlock and activate the limitless potential of each and every person who makes up this incredible community.

We are stronger together.

Here’s to a great conference,

Andy, Darrick, Eric, Geoff, and Mason

IDefine Founders
CONTENTS

3 Welcome Letter
5 About Kleefstra Syndrome
6 About IDefine
7 About KleefstraSyndrome.org
7 About Kleefstra Syndrome Clinic at Boston Children’s Hospital
9 Conference Schedule
10 Speakers + Topics
19 Follow on Social Media
20 Our Beautiful KS Family
22 Boston Children’s Hospital Specializes in Treating Kleefstra Patients
   The story of Darrick and Tiffany Reed, and their daughter Brianna.
24 Paging Jeff Bezos
   How Mason Harrell and Geoff Rhyne are teaming up to take on KS.

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KleefstraSyndrome.org
Kleefstra Syndrome (KS) is a rare genetic condition that affects development and involves many body systems.

People with Kleefstra Syndrome usually have distinct facial features, developmental delay, intellectual disability, low muscle tone (hypotonia), and communication difficulties. Kleefstra Syndrome is caused by a mutation in a gene called EHMT1 or the deletion of a specific region of chromosome 9 that includes EHMT1.

Kleefstra Syndrome was named in 2010 for Dr. Tjitske Kleefstra who, along with her research team at Radboudumc Center of Expertise in Nijmegen, the Netherlands, identified the genetic cause of a set of characteristics in a so far unknown syndrome, honing in on the EHMT1 gene as the cause of intellectual disabilities in patients with a consistent group of characteristics, including distinctive facial features, low muscle tone, and Autistic-like behavior, among others.

Given the relatively recent discovery of the causative factor in the set of symptoms that is KS, there is still much to learn about how best to treat patients. To date, roughly 500 patients have been diagnosed with KS, and the process for obtaining a diagnosis can be difficult depending on the medical expertise available in a given area. However, with the power of an active and committed KS community of families, scientists, and doctors pushing for continued research and, ultimately, a cure, this is changing.

Dr. Kleefstra and her team at Radboudumc, along with US-based Kleefstra Syndrome expert Dr. Siddarth Srivastava and the team at Boston Children's Hospital's Translational Neuroscience Center, continue to study KS and possible treatments, including potential drug therapies.

The scientific community sees KS as a gateway to understanding the mechanism behind other intellectual disabilities stemming from genetic causes. There is much hope that what is learned to improve care and outcomes in the KS community will improve care for all patients with intellectual disabilities.

While there is still much to learn and much work to do, exciting new avenues of research continue to open to help us better understand and manage Kleefstra Syndrome. Those diagnosed with KS can, in general, expect to lead a long and purposeful life.

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ABOUT IDEFINE

IDefine is a US-based organization whose mission is to discover life-changing treatments and, ultimately, cures for those with intellectual disabilities stemming from genetic disorders.

Founded by parents seeking better answers for their children diagnosed with Kleefstra Syndrome, IDefine is built on the premise that we are stronger together.

Idefine exists to facilitate collaboration between the active community of KS patients and their families and medical experts to accelerate research efforts toward more effective treatments for KS.

Realizing that Kleefstra Syndrome presents an excellent model to further understand mechanisms of intellectual disabilities and epigenetic regulation, IDefine sees their focus on KS as just a beginning. In time and through continued collaboration, IDefine hopes that their work will offer invaluable insight into treatment and cures for others with intellectual disabilities.
ABOUT KLEEFSYNDROME.ORG

KleefstraSyndrome.org is a UK-based charity dedicated to fostering a supportive community for individuals and families affected by Kleefstra Syndrome. Founded in 2008 by parents seeking answers in the wake of their child’s diagnosis with this rare condition, this volunteer-led organization has grown rapidly to become the international hub for KS families to connect and share resources, experiences, and information. Over the past 12 years, KleefstraSyndrome.org and their dedicated team of volunteers have supported thousands of individuals — patients, caretakers, siblings, and others — in navigating life with a Kleefstra Syndrome diagnosis. By creating spaces for the KS community to interact through forums, classes, online events, and workshops, KleefstraSyndrome.org has built the foundational community from which new connections and efforts toward furthering research, drug development, and improving treatment for KS can grow.

ABOUT KLEEFSYNDROME CLINIC AT BCH

The Kleefstra Syndrome Clinic and Neurogenetics Program at Boston Children’s Hospital are dedicated to the comprehensive care of children and adolescents with Kleefstra Syndrome and many other genetic disorders. Their team of nationally recognized experts is also a leader in basic and clinical research and partner with leading organizations to provide the best possible treatments to patients.

The Kleefstra Syndrome Clinic was partially funded through direct donations from the KS community. IDefine’s summer fundraiser to “Kickstart the Kleefstra Clinic” brought in over $75,000 in contributions to cover the start-up costs of the clinic in just four weeks.

The establishment of this clinic marks an important step in creating a global hub for the latest KS research, and it will serve as a model for other KS clinics to be established around the world. The goal is to make the best care available to every KS patient and to strengthen our knowledge base about this rare genetic condition.

KS NATURAL HISTORY STUDY ON REGRESSION

KS patients age 13 or older are invited to participate in an international study led by Dr. Kleefstra and funded by the Netherlands Organization for Health Research and Development (ZonMw). Since the initial identification of the causative EHMT1 gene of KS, Dr. Kleefstra and her team became aware that patients might experience dramatic loss of skills and quality of life which were very hard to rectify. In treating KS patients at the Radboudumc clinic, Dr. Kleefstra and team recognized a halt of developmental regression and even a spectacular reversal in some patients treated with the antipsychotic Olanzapine. Based on these results and a related thesis study by Dr. Karlijn Vermeulen, it was hypothesized that patients can recover from these dramatic events if recognized and treated in time. To gather more evidence to support this hypothesis, the present natural history study was designed. This study is led and coordinated by the Radboudumc team with participating centers at Boston Children’s Hospital and Manchester Centre for Genomic Medicine.

For more information, contact:
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Help Us Investigate the Natural History of Kleefstra Syndrome

At Boston Children’s Hospital, we are conducting a research study for individuals ages 13 years and older who have been diagnosed with Kleefstra Syndrome. The goals of this research are to study the natural history of Kleefstra Syndrome and determine best practices for treating the mental health challenges such as psychosis and behavioral regression that can be associated with Kleefstra Syndrome.

Who can participate in this study? Anyone genetically diagnosed with Kleefstra Syndrome (EHMT1 deletion or pathogenic variant) that is 13 years of age or older.

How long will the study last? This will be a four-year natural history, observational study. You will be asked to visit Boston Children’s Hospital at least four times during the study or you may participate through a yearly virtual study visit.

What will participants do during this study?
- Participant/caregiver will need to sign our informed consent form which will provide details of the study and ensure everyone’s understanding.
- Participants will have behavioral and cognitive testing, physical exams, and blood tests (for safety).
- Parents/caregivers will answer questions about the participant’s behavior and medical history.
- If a participant shows clear signs of psychosis or a deterioration in behavioral functions, we may ask the participant to come in additional times.

This is an international study. Patients and their caregivers will be seen at the Radboud University Medical Center, Manchester Centre for Genomic Medicine, or Boston Children’s Hospital. If you are interested in participating in this important study, please contact Jacqueline.Drew@childrens.harvard.edu.
INTRODUCTION AND WELCOME
10:00 am – 10:10 am  Professor Mustafa Sahin + Geoff Rhyne

PRESENTATIONS
Moderator – Dr. Maya Chopra
10:10 am – 10:25 am  Professor Tjitske Kleefstra – Overview: The Journey of Kleefstra Syndrome
10:30 am – 10:50 am  Dr. Siddharth Srivastava + Dr. Anne O’Donnell – Kleefstra Syndrome: Neurodevelopmental Concerns and Latest Molecular Updates
10:55 am – 11:20 am  Dr. Joost Kummeling – Mapping & Tackling the Development and Psychiatry in Kleefstra Syndrome
11:25 am – 11:40 am  Dr. Joyce Geelen – Growth in Children with Kleefstra Syndrome
11:45 am – 12:00 pm  Professor Annette Schenck – Kleefstra Syndrome: A Hidden Metabolic Disorder?

BREAK 12:00 PM – 12:10 PM
Moderator – Dr. Siddharth Srivastava

TANDEM TALK
12:10 pm – 12:40 pm  Tandem Talk – Dr. Nadif Kasri + Dr. Liz Buttermore – Harnessing the Potential of Stem Cells to Understand Kleefstra Syndrome + The Promise of iPSCs: Patient Driven Research for Rare Neurodevelopmental Disorders

BREAK 1:40 PM – 2:00 PM

DISCUSSIONS
Moderators – Kira Dies + IDefine
2:00 pm – 2:20 pm  Family-Led Discussion – Main Issues as Presented by Parents
2:20 pm – 2:40 pm  Fundraising Priorities

EXPERT PANEL Q & A
2:45 pm – 3:15 pm  Moderator – Dr. Meera Modi

CONCLUSION
3:20 pm – 3:30 pm  Dr. Maya Chopra – The KS International Consortium

FAMILY DEBRIEF
3:30 pm – 4:00 pm

*All times are US Eastern Standard Time (EST).
MUSTAFA SAHIN, M.D., Ph.D.
Professor of Neurology, Harvard Medical School

Dr. Mustafa Sahin received his ScB degree from Brown University and his M.D. and Ph.D. from Yale University School of Medicine. He completed a pediatrics residency at Children’s Hospital of Philadelphia and child neurology residency at Boston Children’s Hospital. He did his postdoctoral research training in Developmental Neurobiology at Boston Children’s Hospital. Dr. Sahin has established and directs the Multidisciplinary Tuberous Sclerosis Program at Boston Children’s Hospital. He has received numerous awards, including a Spinal Muscular Atrophy Foundation/AAN Young Investigator Award, the 2005 Young Investigator Award from the Child Neurology Society, and a 2009 John Merck Scholar Award. In 2013, Dr. Sahin established the Translational Neuroscience Center at BCH, which aims to expand treatment options for nervous system disorders.

The research in the Sahin laboratory is directed at understanding the cellular mechanisms of neuronal connectivity and its relationship to neurological dysfunction. His research centers upon tuberous sclerosis complex (TSC) and spinal muscular atrophy (SMA) — two neurological disorders whose genetic basis is well understood but whose cell biology remains unknown. His lab has generated several lines of evidence showing that TSC/mTOR pathway plays crucial roles in axon specification, guidance, myelination, and regeneration. These experiments support the notion that neurological defects in Tsc-deficient mice can be blocked by postnatal mTORC1 inhibition and led to the design of a clinical trial directed by Dr. Sahin in patients with TSC, investigating the effect of an mTORC1 inhibitor on neurocognition. Dr. Sahin was integral in establishing a Tuberous Sclerosis Complex Clinical Research Consortium, including principal investigators from five premier TSC clinics, culminating with an NIH Autism Center of Excellence award to the Consortium with Dr. Sahin as the overall PI: Early Biomarkers of Autism in Infants with Tuberous Sclerosis Complex (TSC), NCT01780441, currently ongoing. Dr. Sahin also directs a NIH U54 grant-funded consortium, Rare Disease Clinical Research Network for Developmental Synaptopathies, which focuses on known genes associated with autism and intellectual disabilities (mutations in Shank3, TSC and PTEN).

“\nThe research in the Sahin laboratory is directed at understanding the cellular mechanisms of neuronal connectivity and its relationship to neurological dysfunction.”
Tjitske Kleefstra is a full professor in clinical genetics and psychopathology in rare syndromes at Radboudumc Center of Expertise in Nijmegen, the Netherlands. Professor Kleefstra aims to perform strong interdisciplinary work to improve both diagnostics health care and research dedicated to genetic neurodevelopmental disorders. During her thesis studies, she identified in 2005 the gene EHMT1 causative for what is now known as Kleefstra Syndrome.

The Journey of Kleefstra Syndrome
Since the introduction of so-called next-generation genetic technologies, the number of diagnosed cases with Kleefstra Syndrome has increased tremendously. Knowledge on the genotypes and phenotypes is gradually growing. The aim now is to establish an international clinical guideline and Professor Kleefstra will discuss this in more detail during the conference.

Key Abbreviations and Definitions
NGS: Next-generation sequencing
WES: Whole-exome sequencing

What Does This Mean for My Child?
Deletions and EHMT1 mutations are genetically different and, depending on the deletion size, more severe (physical) problems might be expected. However, looking at the different EHMT1 mutations and small deletions so far reported, the phenotype spectrum is highly variable. Recurrence risk for other children in the family is usually low, but be aware of mosaicism and chromosomal translocations.

Dr. Maya Chopra is a clinical geneticist with expertise in rare genetic disorders, currently serving as Director of Translational Genomic Medicine at the Translational Neuroscience Center (TNC), Boston Children’s Hospital (BCH). Dr. Chopra obtained her specialist qualifications in Australia as a Paediatrician through the Royal Australasian College of Physicians, and Clinical Genetics through the Human Genetics Society of Australasia. Following her specialist qualifications, Dr. Chopra has held clinical, research and leadership positions at the Royal Prince Alfred Hospital (Sydney), Shanghai First Maternity and Infant Hospital (Shanghai), and the Imagine Institute of Genetic Diseases (Paris). Through these international experiences, she has gained extensive experience in the evaluation and diagnosis of patients with rare genetic diseases in a range of healthcare systems, together with an expertise in rare variant interpretation, gene curation, and clinical bioinformatics. In her current role with the TNC, Dr. Chopra is the genomic expert for translational research into neurodevelopmental disorders, including for the BCH KS Clinical and Research Program.

The Kleefstra Syndrome International Consortium
We are delighted to be launching the Kleefstra Syndrome International Consortium, with the support of the BCH ICCTR (International Center for Clinical and Translational Research). The Consortium will work together to:

1. Develop a network of dedicated KS experts internationally
2. Evaluate and collaboratively contribute to ongoing translational research efforts for KS
3. Share data, resources, and expertise in order to better understand KS
4. Develop and publish best practice consensus guidelines to lift the standards for our centers and for all practitioners who see individuals with KS
5. Work collaboratively to establish KS cohorts for clinical trial readiness

Key Abbreviations and Definitions
Consortium: An association of two or more organizations or individuals with the objective of participating in a common activity or pooling resources and expertise for achieving a common goal.

What Does This Mean for My Child?
International collaboration is absolutely essential in order to better understand — and eventually develop interventions for — Kleefstra Syndrome. The Kleefstra Syndrome International Consortium, supported by the ICCTR, will harness the power of collective expertise to work toward the common goal of improving the lives of individuals with KS.
SIDDHARTH SRIVASTAVA, M.D., Ph.D.

Dr. Siddharth Srivastava is a pediatric neurologist at Boston Children’s Hospital specializing in neurogenetics. His research involves studying different genetic causes of neurodevelopmental presentations — such as autism, intellectual disability, cerebral palsy, and developmental regression — using the multimodal approach of gene discovery, cognitive/behavioral phenotyping, and biomarker identification. At Boston Children’s Hospital, he provides care to children in a variety of neurodevelopmental and neurogenetics clinics. He takes part in the Developmental Neurogenetics Program, which specializes in the diagnosis and management of genetic disorders associated with neurodevelopmental disabilities. Within this program, he sees patients in the Boston Children’s Hospital Kleefstra Syndrome Clinic, whose goals include optimizing long-term neurodevelopmental outcomes and coordinating specialty care across multiple disciplines.

“International collaboration is absolutely essential in order to better understand — and eventually develop interventions for — Kleefstra Syndrome.”

ANNE O’DONNELL-LURIA, M.D., Ph.D.

Anne O’Donnell-Luria is an Assistant Professor in Pediatrics at Harvard Medical School who leads a research group at Boston Children’s Hospital and the Broad Institute of MIT and Harvard. She co-leads the Broad Center for Mendelian Genomics and the Rare Genomes Project focused on discovering novel disease genes and finding genetic diagnoses for undiagnosed individuals. She is a practicing clinical geneticist in the Kleefstra Syndrome Clinic and the EpiChroma Clinic at Boston Children’s Hospital (BCH) where she partners with other clinicians to manage children and adults with Mendelian chromatin disorders, including Kleefstra Syndrome.

Kleefstra Syndrome: Neurodevelopmental Concerns and Latest Molecular Updates

This talk from a child neurologist/neurodevelopmental disability expert and a clinical geneticist will provide an overview of neurodevelopmental concerns seen in Kleefstra Syndrome. It will cover the latest updates and open questions in our understanding of the mechanisms of EHMT1 dysfunction as it relates to the symptoms of Kleefstra Syndrome.

Key Abbreviations and Definitions

KS: Kleefstra Syndrome
NDD: Neurodevelopmental disorders
ASD: Autism spectrum disorder
ID: Intellectual disability
WEGS: Whole epigenome sequencing

What Does This Mean for My Child?

International collaboration is absolutely essential in order to better understand — and eventually develop interventions for — Kleefstra Syndrome. This Consortium, supported by the ICCTR, will harness the power of collective expertise to work toward the common goal of improving the lives of individuals with KS. There is a spectrum of neurodevelopmental issues seen with Kleefstra Syndrome, but there are multiple approaches to dealing with these challenges. Our understanding of the mechanisms of Kleefstra Syndrome is expanding, but there is more to learn, and there are increasing opportunities to engage in research on Kleefstra Syndrome.
JOOST KUMMELING, M.D.

Joost Kummeling is a medical doctor and Ph.D. student working under the supervision of Prof. Dr. Tjitske Kleefstra. He obtained his master’s degree in 2018 after doing research on the cognitive functioning of people with GHB addiction and after completing an internship at the Human Genetics Department at the Radboud University Medical Centre in Nijmegen. His field of interest is neurodevelopmental disorders, and his main focus is mapping and treating the neuropsychiatric problems that can occur in people with Kleefstra Syndrome.

Mapping and Tackling the Development and Psychiatry in Kleefstra Syndrome

Kleefstra Syndrome (KS) is a rare genetic disorder caused by a defect of the EHTM1 gene. Many patients with KS experience psychiatric problems, which are often hard to diagnose and treat. Professor Kleefstra’s team set up a follow-up study to map out and monitor the well-being of people with KS. In addition, they want to evaluate the efficacy of the well-known anti-psychotic drug Olanzapine in people with KS who are experiencing psychotic episodes.

Key Abbreviations and Definitions

Psychosis: A serious mental disorder characterized by thinking and emotions that indicate the person experiencing them has lost contact with reality.

Regression: A return to a former or less developed state.

Adaptive functioning: How well a person handles common demands in life and how independent they are compared to others of a similar age and background.

Neuropsychiatry: The branch of psychiatry that investigates the links between mental illness and organic disease of the brain.

What Does This Mean for My Child?

• Psychiatric problems in people with KS are common, but may present atypically (making the right diagnosis may be difficult because of this).
• Sleep disturbances are also common and may be followed by regression.
• Parents can experience a lot of stress, so don’t forget to take care of yourself.
• There are many relevant patient/support groups to be online.
• A guideline to substantiate care in people with KS is being developed.

DR. JOYCE GEELEN, M.D., Ph.D.

Dr. Joyce Geelen is a paediatrician specialising in developmental medicine and genetic disorders. In her outpatient-clinic in the Amalia Children’s Hospital in Nijmegen, The Netherlands, she takes care of children with rare genetic neurodevelopmental disorders. She also works in the multidisciplinary team at the Centre of Expertise for Rare Genetic Neurodevelopmental Disorders, where she sees children of all ages with Kleefstra Syndrome. As a paediatrician, she evaluates all the aspects of their development and health.

Growth in Children with Kleefstra Syndrome

Dr. Geelen and her team have performed a retrospective data analysis among 49 patients with Kleefstra Syndrome. The present study is the first report on gender specific length, weight, and BMI curves for Kleefstra Syndrome. They report observed differences in growth compared to the normal population. Most notable is a higher reported likelihood to develop childhood obesity.

Keywords
Height
Weight
Growth chart
Obesity

What Does This Mean for My Child?

Health professionals and parents of children with Kleefstra Syndrome should be aware of specific growth patterns and the increased risk of obesity. More research is needed for the cause of the obesity and how to influence it.
Annette Schenck studied biotechnology at Berlin’s University of Technology, Germany. In 2003, she obtained her Ph.D. and an award for the best thesis of the year from the University Louis Pasteur, Strasbourg, France, for her work on the molecular basis of Fragile X Syndrome. Her postdoctoral research at the Max Planck Institute for Cell Biology & Genetics in Dresden, Germany unraveled the function of a novel endocytic organelle. In 2007, Professor Schenck successfully competed for a tenure-track research fellowship from the Radboud University Medical Center in Nijmegen, the Netherlands to establish her independent research line systematically investigating the molecular, cellular, and developmental basis underlying intellectual disability disorders. In 2008, she was awarded a VIDI grant from the Netherlands Organization for Scientific Research (NWO), promoted to Assistant Professor, and tenured. In 2009, she was promoted to Associate Professor. In 2020, Professor Schenck was awarded a VICI grant — NWO’s most prestigious personal career award. She was promoted to full Professor, and elected a member of the Academia Europaea. Professor Schenck has worked on Kleefstra Syndrome for more than a decade.

Kleefstra Syndrome: A Hidden Metabolic Disorder?
For more than a decade, Professor Schenck’s group has studied the function of the highly conserved EHMT/G9a family of Euchromatin Histone methyltransferases in the fruit fly Drosophila as a model. Her presentation focuses on two important findings that they have made. First, their early work demonstrated that flies lacking EHMT/G9a show different learning and memory deficits and identified the genes that it controls. Motivated by their observation that EHMT/G9a regulates key genes/molecules that are acutely required for learning and memory formation, not only for brain development, Professor Schenck’s group attempted to reactivate the gene by a genetic trick, specifically in adult flies, after finishing development. They found that the flies in which they reactivated EHMT/G9a show normal learning. Second, among the genes regulated by EHMT/G9a, they also found many involved in cellular stress and immune response. Their data turned out to be predictive: flies lacking EHMT/G9a are susceptible to various stress cues, including oxidative stress and virus infection (also a kind of stress for the organism). They found that, surprisingly, this is not because so-called stress resistance programs, which are in charge to eliminate the experienced stress, do not properly work. Flies lacking EHMT/G9a can activate these programs and do not show increased damage as can be induced by the stress. Instead, they die from an enormously overactivated, energy-demanding stress response and altered metabolism, together exhausting quickly available energy (sugars; needed for a rapid response to stress) within a short time. They found the same signature in several publicly available gene expression dataset on EHMT/G9a-deficient cells that have been generated in presence of different stresses. They propose that Kleefstra Syndrome is a so far unappreciated, hidden metabolic disorder that can get “out of balance” upon different stress challenges. They also propose that regressive periods as observed in Kleefstra Syndrome may result from environmental challenges such as infection, and cause metabolic switching with subsequent acute energy crisis in the brain. It is important to test this hypothesis and investigate how such an energy crisis can be counteracted. Interestingly, Olanzapine, which appears to interfere with regressive periods, acutely increases blood sugar levels and accelerate fat metabolism, which can be predicted to be beneficial based on their hypothesis. They are currently trying to establish an integrated consortium of patients, clinical and fundamental researchers to push their understanding of metabolic dysregulation in Kleefstra Syndrome further. They also plan to test a larger number of drugs for their ability to improve cognitive functions such as learning in the Kleefstra Syndrome fly model, to identify novel intervention strategies.

What Does This Mean for My Child?
Although Professor Schenck’s group conducts their research using an evolutionary distant organism, they have been able to collect data which argue that it may be possible to improve cognitive functions postnatally in individuals with Kleefstra Syndrome. Their identification of metabolic dysregulation in Kleefstra Syndrome is supported by data from mammalian studies on the EHMT/G9a family. Both raise further hope that the course of the disease is improvable. They need to work hand in hand to push their understanding and these developments forward.
ASSOCIATE PROFESSOR
NAEL NADIF KASRI, Ph.D.

Nael Nadif Kasri studied biochemistry at the KU Leuven (Belgium), followed by a Ph.D. (2000 – 2004) in molecular biology at the KU Leuven with Prof. Dr. Humbert de Smedt. During his Ph.D. thesis, Professor Kasri studied the role of Ca2+ and calmodulin in the regulation of IP3Rs. After his Ph.D., Professor Kasri worked as a postdoctoral researcher (2005 – 2010) in the lab of Prof. Dr. Linda van Aelst at Cold Spring Harbor Laboratory, where he studied the role of RhoGTPase signaling in excitatory synapses in the hippocampus. In 2010, Professor Kasri moved to the Netherlands and started his independent research group at the Radboud Medical Centre, where he is part of the Donders Institute for Brain, Cognition and Behaviour. In 2011, he received the Hypatia Fellowship and Marie Curie reintegration grant. The focus of his research is to understand the synaptic basis of neurodevelopmental disorders using in vitro human models and in vivo mouse models.

Harnessing the Potential of Stem Cells to Understand Kleefstra Syndrome

Professor Kasri will discuss the recent efforts to better understand the disease etiology of KS. In this study, they used skin cells from KS patients to generate stem cells. These stem cells have the unique ability to generate any cell type in the body. They used these stem cells to generate “neurons,” the main cells residing in the brain. Doing so, they studied the difference between neurons from KS patients and non-affected people. They grew these neurons on “smart dishes” allowing them to “listen” when, with who, and how often these neurons talk to each other. They found that neurons from KS patients were talking to each other in a different way. Further investigation showed that some proteins that are important for the communication between neurons were different in KS neurons, including an important protein — the NMDA receptor. Subsequently, they used this information to restore normal neuron communication. Although they are very excited about the current findings, they absolutely want to emphasize that currently this study only has been performed on “neurons in a dish” and therefore is only a first, but important step into KS research. It still has to be defined to what extent this “dish phenotype” is relevant to any of the brain phenotypes (features) in the KS patients. The Nijmegen team will conduct further studies in a whole organism (mice) to test the safety and efficacy of their new strategy.

Key Abbreviations and Definitions

hiPSC: Human-induced pluripotent stem cells
MEAs: Micro-electrode arrays

What Does This Mean for My Child?

Using a stem cell-derived model for Kleefstra Syndrome, they are getting a better idea of how neurons are behaving differently in KS patients. This is an important first step that will allow them to test new strategies to try to correct what is going wrong.
ELIZABETH BUTTERMORE, Ph.D.

Dr. Elizabeth (Liz) Buttermore is a Scientific Program Manager for the Translational Neuroscience Center (TNC) at Boston Children's Hospital (BCH) as well as one of the Assistant Directors of the Human Neuron Core. She earned her BS in Biochemistry and Molecular Biology from the University of Richmond in 2006 and her Ph.D. in Neuroscience from the University of North Carolina in 2012. From there, Dr. Buttermore completed her postdoctoral training in the lab of Dr. Clifford Woolf at BCH, where she developed protocols for differentiating stem cells and skin cells into pain-sensing neurons and used those neurons to develop screens for painful neuropathies. Since 2016, Dr. Buttermore has utilized her background to establish the phenotyping service within the Human Neuron Core at BCH, helping researchers advance their science through functional, morphological, and transcriptomic analyses. Recently, Dr. Buttermore has also taken on the role of Scientific Program Manager to help develop and guide new stem cell-related projects within the TNC at BCH.

The Promise of iPSCs: Patient-Driven Research for Rare Neurodevelopmental Disorders

Drug discovery in neuroscience faces many unique challenges, including access to the central nervous system through the blood brain barrier and a complex biology and circuitry that is still being defined. In order to overcome these challenges to identify treatments for neurodevelopmental disorders, such as Kleefstra Syndrome, scientists need better preclinical data. One requirement for improved preclinical data is a robust model system. Recent advances in stem cell technology have allowed for the creation of stem cells from patient skin or blood cells, called induced pluripotent stem cells (iPSCs). These patient-derived iPSCs can then be differentiated into neurons to model how a patient mutation causes changes in neuronal function compared with a healthy control neuron, followed by testing of therapeutics for reversal of these in vitro phenotypes. This strategy has already successfully transitioned from the bench to the clinic for amyotrophic lateral sclerosis (ALS). In their hands, they have demonstrated that rapamycin, an mTOR inhibitor, can reverse in vitro phenotypes in Tuberous Sclerosis Complex (TSC) patient iPSC-derived neurons. Rapamycin has also been shown to improve seizures, at least in the first year of treatment, in patients with TSC mutations. Therefore, they believe that these model systems can be used to screen for and identify novel therapeutic targets for neurodevelopmental disorders.

Key Abbreviations and Definitions

iPSCs: Induced pluripotent stem cells
Stem Cells: Cells that have the ability to become other cell types
Differentiation: The transformation of cells from one cell type to another, for example, differentiating stem cells into neurons
In vitro: In a culture dish
Phenotypes: Characteristics of cells that give information about the healthy or function of those cells
Preclinical data: Data obtained in a research setting that is necessary for making the decision to test a treatment option in the clinic

What Does This Mean for My Child?

For Kleefstra Syndrome, the more information they can gather about what makes patient iPSC-derived neurons different from control neurons will allow for translating this research to therapeutics. They currently know there are a few cellular phenotypes related to EHMT1 mutations, but it is not clear how this translates to Kleefstra Syndrome patients with larger deletions. Once they have a better understanding of how neurons from different Kleefstra Syndrome patients are the same and how they differ, then they can develop screens to improve these cellular phenotypes with the goal of identifying a target or therapeutic for this patient population.
KIRA A. DIES, SCM, CGC
Co-Director, Clinical Research and Regulatory Affairs Service

Ms. Dies received a Master of Science degree (ScM) in Genetic Counseling in 2003 from the Johns Hopkins Bloomberg School of Public Health. She is board certified by the American Board of Genetic Counseling and a licensed genetic counselor in Massachusetts. Her experience includes establishing a new clinic, the Comprehensive Brain Malformation Program, at Boston Children’s Hospital and coordinating research on the genetics of brain malformations and cognitive disorders. She also previously coordinated multi-site research and family resources for the non-profit Autism Consortium. Ms. Dies currently manages clinical research programs in Neurogenetics and provides clinical genetic counseling for patients in the Neurology department. She is also adjunct faculty at the Boston University School of Medicine Genetic Counseling graduate program and is a coordinator of the Research Seminar Series, aiding in the development of student thesis projects. She serves on the Board of Directors for the CureSPG47 advocacy organization and on the Professional Advisory Board for the Tuberous Sclerosis Alliance.

MEERA MODI, Ph.D.
Director of Preclinical Research, Translational Neuroscience Center
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Dr. Modi is a research scientist focused on drug discovery in neurodevelopmental disorders. She is currently a Principal Associate in the Department of Neurology at Boston Children’s Hospital and Harvard Medical School. She holds a Ph.D. in Neuroscience from Emory University, where her work focused on the development of novel assays for screening prosocial therapeutics. She completed a postdoctoral fellowship in Pfizer’s Neuroscience Research Unit during which she characterized a novel animal model of autism and served as a biology lead for autism drug discovery. At Boston Children’s Hospital, her work is focused on identifying translational biomarkers in stem cell models, mouse models and human subjects. To this end, she oversees the Human Neuron Core and the Translational Neurophysiology Core in providing preclinical and clinical EEG based measures of neurological disease and pharmacological interventions in academic and industrial collaborations. Her team is currently engaged in the characterization of stem cell derived neurons from patients with Kleefstra Syndrome.
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When Darrick and Tiffany Reed of Olathe, Kansas received their daughter Brianna’s Kleefstra Syndrome diagnosis in early 2018, they immediately began searching for information about the disorder. There wasn’t much to be found, and as far as they could tell, Brianna was the only diagnosed case in the state of Kansas.

When they visited leading healthcare providers in Kansas City, they were simply presented with information they had already found on their own via Google searches. No doctor they saw had ever heard of Kleefstra Syndrome, much less treated a patient with it.

The lack of available knowledge and the feeling of isolation compelled the Reeds to seek connection with other Kleefstra parents around the world, and eventually, for Darrick to become a founder of IDefine earlier this year.

Perhaps IDefine’s biggest accomplishment in its short history is the partnership with the Translational Neuroscience Center at Boston Children’s Hospital (BCH) to create the Kleefstra Syndrome Clinic.

In October, the Reeds flew to Boston with Brianna for her first in-person appointment with Dr. Siddarth Srivastava, AKA Dr. Sid, a pediatric neurologist at BCH, who is helping to create the KS Clinic.

“It was an excellent experience across the board,” said Darrick. “Families that have not had a chance to speak with a KS Specialist will likely learn a great deal. Dr. Sid broke down the science, discussed treatment programs moving forward, how to effectively parent a child with Kleefstra, and about access to resources that are currently out there.”

During their two-and-a-half-hour appointment, they also met with Drs. Anne O’Donnell, the associate director of the Broad Center for Mendelian Genomics, who has a Kleefstra Syndrome-specific research project, and Dr. Maya Chopra, director of Translational Genomic Medicine.

All Kleefstra families are encouraged to visit Boston Children’s Hospital, if it’s feasible for them. In the midst of the COVID pandemic, regulations have been lifted to allow first visits with Dr. Sid to occur virtually rather than in person. However, insurance coverage varies by provider. Dr. Sid and his team will work with families to file the necessary paperwork.

“Aside from the benefit to the individual families, there’s benefit for the KS community, as well,” said Darrick. “As much as we can support Dr. Sid in seeing as many Kleefstra patients as possible, that helps his team aggregate clinical data. This will allow for the COE to look at the natural history of KS patients and then to use that information for the build-out of additional research programs to find new treatments and a cure, so it’s ultimately a win-win.”

It’s been two-and-a-half years since Brianna’s diagnosis and the Reeds are still not aware of another case of Kleefstra Syndrome in Kansas. However, thanks to IDefine and Boston Children’s Hospital, they finally have some answers and they know that they’re not alone in the fight.

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Standing in his neighbor’s yard, Harvard-educated, double board-certified MD, Mason Harrell wept. His neighbors cried, too.

“It was the best Christmas morning ever,” Mason recalls. “We went outside for a walk, and Eleanor fell in the yard. Usually, she’d cry until you help her stand up or scoot herself to an object to pull herself up — not that time.”

Mason is a veteran who’s been called upon by elite organizations, including the World Health Organization and the Massachusetts Institute of Technology. He’ll tell you that Christmas morning was one of the most amazing moments of his life.

“For the first time, Eleanor, my two-year-old daughter, pushed herself off of the ground — on her own,” he beams. “It was a wish come true.”

Eleanor has Kleefstra Syndrome (KS), a rare genetic disorder that negatively impacts physical and intellectual abilities. Her EHMT1 gene is compromised. It regulates many genes, affecting all organ systems, especially the brain.

“A genetic cause of delays is not something that gets better,” Mason explains. “My biggest fear is that she’ll regress during puberty, to the extent that she’ll become catatonic. That’s a possible effect of KS.”

Her diagnosis sent Mason into a pretty bad depression. He couldn’t do the things he needed to, like learning about KS. He couldn’t read through his tears. His best friends helped him review the literature. Once he pulled himself together, he started networking.

“I knew it was time for me to do something,” Mason said. “We went to Europe to speak with Dr. Kleefstra. I needed to talk to the expert and ask what I could do to help.”

Dr. Kleefstra directed Mason to Geoff Rhyne, another father to whom she’d recently spoken. One LinkedIn message connected the two. They joined forces with a Ph.D. biomedical scientist at Illumina and three other fathers to create the nonprofit IDefine, committed to identifying life-changing treatments and cures for those with rare genetic disorders.

“We want our children to define their own futures; that’s why we named it IDefine,” Mason clarifies. “If we can restore their intellectual disability to what it should be — that can happen.”

Within the first months, they raised almost $200,000. Still, millions more are needed to find a cure for intellectual disability and autism.

“We’re using KS as a model syndrome to solve intellectual disability, to correct the code,” details Mason. “Partnering with the world’s top experts, including Harvard-affiliated Boston Children’s Hospital, we believe it’s possible within our lifetime.”

To accelerate the process, Mason and Geoff sent an email to Jeff Bezos to get Amazon to offer a round-up purchase option on Rare Disease Day, Feb. 28. The co-founding fathers posted on social media asking for help in getting Jeff to read the email, counting on the degrees of separation.

“It’s like writing an email to Santa Claus,” Mason grinned. “We know it will take helpers to get Jeff’s attention. We know it sounds crazy, but we believe if we all work together, we can change the world.”

Visit IDefine.org for more information and to learn how you can help.

By Jackie Gutierrez
Dr. Mason Harrell and his daughter, Eleanor, need your help. Mason lives in Coronado with his wife, Rossella, and daughters, Eleanor (center) and Celine.

Photo: Jackie Lynn Photography
jackielynnphoto.com
We are jumpstarting our Kleefstra Syndrome program in partnership with IDefine to accelerate research for the condition. Your experience with Kleefstra Syndrome is important and can help researchers advance treatments for your community. We welcome all patients and caregivers.

**SHARE YOUR JOURNEY TO POWER PROGRESS**

**JUMPSTART NEW RESEARCH FOR YOUR RARE DISEASE**
Your (or your loved one’s) medical records contain clues that can lead to new treatments.

**SPEED UP DEVELOPMENT OF TREATMENTS**
Using cutting-edge tech, we analyze your community’s data to improve trial design and chances of success.

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**BE PART OF MULTIPLE RESEARCH EFFORTS, WITHOUT LEAVING HOME**
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