From darkness, hope:

Robert's Program on Sudden Unexpected Death in Pediatrics (SUDP) 2017 report

> *In the harrowing months after their three-month old son Harrison* died unexpectedly in his sleep at daycare, Melanie* and Michael* were tormented by recurring questions: why did this happen to my child? Did we do something wrong? Did daycare do something wrong? Will something like this happen to our other children? Like thousands of parents devastated by SUDP, they experienced not only crushing grief and uncertainty, but feelings of guilt and fear as well. They were desperate for answers.*

Thanks to your generosity, the Robert's Program team recently has made new and exciting discoveries—revelations that further prove that SUDP has a biological basis. Led by Director Richard Goldstein, MD and Associate Director Hannah Kinney, MD, the team has:

- ✓ discovered SUDP-related brain abnormalities visible under a regular microscope
- ✓ developed an SUDP genetic panel
- ✓ discovered a possible SIDS screening tool: abnormal serotonin levels in infants' blood serum
- ✓ found additional evidence of biological basis of SUDP (including SIDS)

These revelations not only bring answers and a small measure of peace to grieving families, they bring hope for preventing future tragedies.

We are honored to share the most recent accomplishments of Robert's Program on Sudden Unexpected Deaths in Pediatrics at Boston Children's Hospital.

The role of the hippocampus in SUDP

Traditionally, pediatricians have focused mainly on the child's sleep environment when trying to reduce SUDP risk. But new research and medical-care advances have allowed scientists to discover previously undetectable, potentially lethal biological vulnerabilities in small children.

**Family members' names changed to protect their privacy.*

In one Robert's Program study, Dr. Kinney and her team discovered hippocampal abnormalities in approximately 40% of children dying from SIDS and 50% of children dying from SUDC.
These abnormalities—clearly visible under a regular microscope—include evidence of abnormal cell migration and proliferation, asymmetry, and occasionally malrotation and more. Since the hippocampus helps modulate breathing, heart rate and temperature, undiagnosed vulnerabilities like these could potentially contribute to death during sleep.

The team continues to submit grant proposals to fund further study of the hippocampus' role in SUDP. Dr. Kinney's recent proposal, "The Hippocampus and Brainstem in the Sudden Infant Death syndrome," received funding from the National Institutes of Health. With this support, the team aims to link the hippocampal findings associated with SIDS and SUDC with Dr. Kinney's ongoing work on the brainstem.

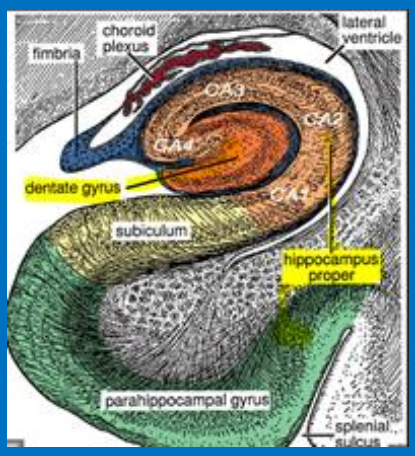
Comprehensive gene panel provides answers

As part of Robert's Program's unprecedented scientific approach to understanding sudden unexpected death, the team is also studying possible genetic factors. During its ongoing collaboration with the Massachusetts Chief Medical Examiner's Office, the Robert's Program team has developed a comprehensive gene panel for SUDP. After years of refinement, Robert's Program now provides this test for the deceased child, siblings and parents in Massachusetts families who consent to take part in the program.
The panel tests for more than 160 genes that have been implicated in sudden death—genes related to metabolic disease, cardiac disease, brain malformations, epilepsy, infectious/immunologic defense genes, and more. In July, the Massachusetts Chief Medical Examiner's Office began providing this comprehensive gene panel not just for children whose families agree to participate in Robert's Program, but for all children in the state who die suddenly and unexpectedly under the age of three.

Hippocampus 101

Due to its shape, the hippocampus takes its name from the Latin word for "seahorse."

The hippocampus includes the dentate gyrus (diagram below), the structure in which Dr. Kinney has found abnormalities in SUDP children.



> Our gene panel augments a general autopsy's findings, bringing next-century technology to the problem of SUDP.
>
> — Richard Goldstein, MD

Says Dr. Goldstein, "Our gene panel augments a general autopsy's findings, bringing next-century technology to the problem of SUDP."

The Robert's Program team is continuing to look into possible genetic variants that can lead to SUDP. Boston Children's neurologist Dr. Ann Poduri recently received a grant from Citizens United for Research in Epilepsy. She is working to identify the genetic causes of SUDP with Hippocampal Pathology, an epilepsy-related condition defined by hippocampal malformations and associated with febrile seizures.

Abnormal serotonin levels in SIDS infants' blood serum

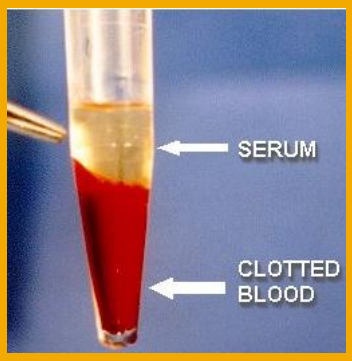
In previous work spanning more than a decade, Dr. Kinney and her team have linked SIDS with abnormal serotonin levels in the brainstem, which controls many basic functions necessary for life. Unfortunately, brainstem serotonin can only be measured at autopsy with specialized techniques.

Now, Robert's Program researchers have made a remarkable discovery. Boston Children's pathology researcher Robin Haynes, PhD, and colleagues studied 61 infants who had died from SIDS and found that 31 percent—nearly one-third—had abnormal levels of serotonin in their blood serum, the clear component of blood that contains electrolytes, hormones and any circulating drugs.

"The wonderful thing about blood serum is how easy it is to test," says Dr. Goldstein, adding, "all it takes is a simple blood draw."

This discovery brings hope that someday we'll have a screening tool to identify vulnerable infants before tragedy can strike. As a next step, the team is now exploring the direct relationship between the serotonin levels in the brainstem and those in the blood serum of SIDS infants.

A new biomarker for SIDS?



Nearly 1/3 of SIDS infants in a new Boston Children's study had abnormal serotonin levels in their blood serum.

"This raises the possibility of a forensic diagnostic biomarker—and, in the future, a screening test that could detect which babies are at higher risk of SIDS."

—Alan Michelson, MD, director of the Center for Platelet Research Studies at Dana-Farber/Boston Children's Cancer and Blood Disorders Center.

Robert's Program: an innovative translational model for SUDP

This year, the journal *Pediatrics* reported on the novel clinical approach of Robert's Program. In an article, co-authors Drs. Goldstein, Kinney and Nields (the Chief Medical Examiner of Massachusetts) described the Program's unique model in detail, allowing other programs to begin to adopt it. The article also outlined the program's first 17 cases.

Most of the detailed cases showed important neuropathological evidence of temporal lobe pathology and the contribution of genetics. The authors described what Robert's Program is finding and how it is shared with families.

Says Dr. Goldstein, "We try to improve every day as Robert's Program brings its innovation to more families."

Dr. Kinney announces her retirement

After decades of work at the forefront of SUDP research, the Robert's Program team's beloved Dr. Hannah C. Kinney has announced she will retire from her career in neuropathology, remaining involved with Robert's Program as an emeritus professor. Her day-to-day work will continue under Dr. Goldstein's leadership in the clinical and translational research areas and Dr. Robin Haynes' leadership in the lab.

Dr. Goldstein co-founded Robert's Program on Sudden and Unexpected Death in Pediatrics with Dr. Kinney, and is himself a committed and driven physician-scientist who has gained increasing national and international visibility as a SIDS expert and researcher. Dr. Haynes has worked with Dr. Kinney for 15 years, and is a creative and original scientist who has made independent contributions to SIDS research in her own right.

Robert's Program also assembles a gifted team of translational researchers who can bring new insights to the problem, especially in genomics. The promise of Dr. Kinney's efforts will also continue through Robert's Program's international research database in SIDS and SUDC.

With gratitude to her irreplaceable role in solving SUDP, Robert's Program will continue the fight to change the incomprehensible into the solvable. Your continued generosity ensures that the legacy of her important work will continue.

Thanks to you, we have hope for the future

Thanks to your support, Robert's Program work is changing minds—and approaches to SUDP—in the medical community. A sudden death that pediatricians once considered an aberration, something that "just happened" to certain children, is now being seen as an event with a biological cause.

Since Robert's Program's founding in 2012, our knowledge of SUDP has grown exponentially along with the numbers of families helped through the program's clinical limb. Thanks to your compassionate generosity, we're unraveling the mystery and providing much-needed grief support to those this tragic circumstance leaves behind.

Discovering how best to support families affected by SUDP is an integral part of Robert's Program. Dr. Goldstein is currently studying the high frequency of pathological grief—prolonged grief that interferes with daily functioning—in mothers of SIDS babies. The nature of these deaths and the lack of information about their cause make acceptance nearly impossible, he explains. His research seeks to identify which families will have the greatest difficulty coping with their loss, and to design supportive interventions to help them. "Our families are what motivates our team," says Dr. Goldstein. He adds, "Everything we do is geared toward giving them answers and preventing future families from suffering these devastating losses. Even in the face of uncertainty, we must help."

> *Melanie and Michael became involved with Robert's Program. The evaluation provided some answers—there was an infection, there were genes involved that may have contributed to the death, there was the reassurance that they had done nothing wrong.*
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> *Today, they live with the painful absence of Harrison and miss him dearly every day. However, Melanie and Michael found a measure of peace in knowing that he had been thoroughly tested for biological vulnerabilities, and that risks to other family members were evaluated, with reassuring results. Harrison now has two thriving siblings. Their family has greater confidence that unexpected tragedy is not a current threat, that there are physicians at Boston Children's Hospital available to help, and that they are not alone.*

Thanks to you, we are reaching into the darkness and emerging with hope for a future in which SUDP is only a memory. For all that you are doing to pursue this dream, thank you.