The Clinical Roya Kabuki Program – Year 5 Report

Patient-centered research

Since last year's report, more families have volunteered to participate in research made possible by your wonderful support. As you know, every individual who shares a medical history or provides a sample for analysis contributes to the knowledge about Kabuki syndrome. This is vitally important for such a diverse condition that affects multiple body systems and causes a wide variety of symptoms. The more we learn, the more we can improve the daily lives of patients with Kabuki syndrome worldwide.

- Total index patients consented to research 166 (up from 143)
- Total participants consented to research 419 (up from 388)
- Families in genetic clinic 91 (up from 73)
- Families in neuropsychology clinic 54 (up from 47)

In 2022 we launched the Kabuki Syndrome Patient Registry in collaboration with All Things Kabuki and the National Organization for Rare Disorders (NORD). The registry allows us to collect additional data for our natural history study—a comprehensive exploration of Kabuki syndrome to identify demographic, genetic, environmental and other variables that correlate with the disease and its outcomes. With more patients involved in the natural history study, we can better plan and recruit for multicenter clinical trials and develop recommendations for patient-driven standards of care.

Neuropsychology clinic: Research and support

Regular neuropsychological testing is crucial for assessing the developmental progress of children with Kabuki syndrome. Normally conducted in clinic by an expert administrator, the tests measure areas of cognitive function including reasoning, visual-spatial processing and working memory. The assessments are often time-consuming and tiring for the patient. So how can these tests be administered in the setting of a global, multicenter clinical trial, where researchers will need to use them to gauge a therapy's effectiveness? Benjamin Goodlett, PhD, attending psychologist in the Division of Genetics and Genomics, leads the neuropsychological testing for kids in the Roya Kabuki Program, and he decided to study this question to prepare for clinical trial readiness.

In his study, Dr. Goodlett examined the feasibility of using computerized cognitive assessments in comparison to traditional paper and pencil tests in children with Kabuki syndrome. If successful, these tests could eliminate the need for a highly trained administrator and be offered to speakers of any language. His team is analyzing the data and intends to publish the results later this year.

Education and advocacy

Over the past year we continued building connections in the Kabuki community and raising awareness of Kabuki syndrome, two important aims of our program. In May, Dr. Gussoni expanded the Roya Kabuki Program's "The More You Know" webinar series with a session on muscle hypotonia in Kabuki syndrome. These webinars offer easy-to-understand information on topics of interest to people affected by Kabuki syndrome and are available on royakabuki.org. A new session about the Kabuki syndrome patient registry is being planned for 2023. Outside of the series, an

informational webinar hosted by Boston Children's Social Work Department focusing on transition planning for teenagers with intellectual disabilities was made available to the Kabuki syndrome community in December.

For the first time since 2019, the Boston Children's Eversource Walk was held in person in June 2022 and Team Kabuki Friends was delighted to be there. 47 participants raised close to $10,000 for the Roya Kabuki Program's community support and outreach efforts. At the 2022 Kabuki Syndrome Foundation virtual conference, Dr. Bodamer provided an overview of research initiatives at Boston Children's, and Dr. Gussoni presented her research on muscle hypotonia with Rachel Gottlieb, program coordinator for the Roya Kabuki Program. Gottlieb also joined Dr. Bodamer and Rene King, CEO of All Things Kabuki, in a poster presentation on Kabuki syndrome at the 2022 NORD summit.

Advances in the laboratory

Mouse mutations and muscle function

As you may recall, Dr. Gussoni has been studying mice with mutations to the KMT2D gene—one of the two genes currently known to be responsible for causing Kabuki syndrome. Like human patients, these mice carry the mutation in every cell in their bodies. Her important findings on the effects of this mutation on muscle tissue were featured in last year's report.

These studies helped Dr. Gussoni obtain funding from the National Institutes of Health (NIH) to acquire two more mouse colonies: one that allows her to examine organ-specific KMT2D mutations, and, for the first time, one in which she can investigate organ-specific mutations to KDM6A, the other gene recognized as a cause of Kabuki syndrome. By inducing these mutations just in the muscle tissue, Dr. Gussoni can learn exactly how they affect muscle function; compare the two mutations for similarities and differences, which will inform care of patients; and possibly identify drug targets. She will then be able to use human samples collected through the Roya Kabuki Program's clinical research efforts to validate her findings.

Understanding the disease, pinpointing targets

People with Kabuki syndrome experience such a wide range of symptoms because their gene mutation can trigger changes to multiple biological pathways—the molecular mechanisms that lead to normal or disordered functioning. In mouse studies, Dr. Bodamer's lab analyzed pathways in the brain, the spleen, the liver and in muscle to locate molecular activity that causes defects and may be amenable to treatment. Using the same cutting-edge analysis on human blood samples, Dr. Bodamer's team found some unexpected pathways affected by Kabuki syndrome that also may respond to therapeutics. These results are forthcoming in Human Molecular Genetics.

Maxwell Heiman, PhD, a principal investigator in the Division of Genetics and Genomics, continued his work with C. elegans thanks to a grant from the Rosamund Stone Zander Translational Neuroscience Center (TNC) at Boston Children's. As you know, your generosity gave the Heiman lab the resources it needed to develop a worm model of Kabuki syndrome that fluoresces when levels of KMT2D and KDM6A are lowered (as they are in human patients). During the past year, Dr. Heiman used the TNC grant to prepare the C. elegans for drug-screening readiness. When therapeutics intended to elevate production of the Kabuki proteins eventually are tested in these models, a reduction in fluorescence would indicate effectiveness.