The Clinical Roya Kabuki Program – Year 6 Report

Progress for patients with Kabuki syndrome

The Roya Kabuki Program is touching more lives than ever, providing healing and hope to families affected by Kabuki syndrome. In the clinic and in the lab, Olaf Bodamer, MD, PhD, and his team of caregivers and scientists dedicate themselves to these families. Their goal is unwavering: to ensure that every patient with this rare genetic condition is healthy, happy and thriving.

Growth in the Kabuki clinic

Over the past year, 32 new families enrolled in the Roya Kabuki Program and volunteered to participate in research. To help meet the needs of Boston Children's growing Kabuki community, Dr. Bodamer recruited Aya Abu El Haija, MD, to serve as clinical co-director of the Roya Kabuki Clinic and join him in working directly with patients and families. An attending physician in the Division of Genetics and Genomics and an instructor of pediatrics at Harvard Medical School, Dr. Haija is an expert in genetic disorders, vascular anomalies and various tumor predisposition syndromes.

Now, Drs. Bodamer and Haija are beginning to enroll patients in the Kabuki Syndrome Outcome Measures and Biomarkers Consortium (KSOC). The KSOC is a collaborative clinical-trial readiness study led by the Kabuki Syndrome Foundation to develop three potential outcome measures for Kabuki syndrome over the next two years. Participating patients with genetically confirmed Kabuki syndrome will provide blood and urine samples, undergo neuropsychological testing and complete an electroencephalogram (EEG), giving researchers vital data that can be used to measure efficacy of pioneering treatments.

One of just four institutions included in the KSOC, Boston Children's is leading efforts to find promising biomarkers in participants' blood and urine samples through the use of metabolomics.

Metabolomics breakthrough in the Bodamer lab

When the body breaks down food during metabolism, it produces small molecules known as metabolites. Metabolomics is the study of all metabolites in a biological specimen.

Outside of the KSOC, the Bodamer lab analyzed metabolites in blood and urine samples from patients with the two main types of Kabuki syndrome, KS1 and KS2, as well as in healthy controls. The team found a large number of significantly altered metabolites between KS1 patients and controls, and identified a metabolite that showed meaningful change in both KS1 and KS2 patients. These findings were presented in an abstract at the 2023 annual meeting of the American Society of Human Genetics, and a paper on this work has been submitted for publication. Running metabolomics on the specimens obtained through the KSOC will allow Dr. Bodamer to validate the biomarker in a larger and more diverse population— and then translate it into a tool that may be used in future Kabuki syndrome clinical trials.

The path to drug discovery

Dominant loss-of-function variants in KMT2D and KDM6A are associated with Kabuki syndrome. The Bodamer lab has been pursuing small molecule compounds with the potential to increase KMT2D or KDM6A expression and to restore the downstream effects on different pathways. After

conducting high-throughput screening of thousands of small molecules, Dr. Bodamer has identified several drug candidates that show efficacy in Kabuki syndrome cell lines. Additional pre-clinical validation in patient-derived cell lines is ongoing, and encouraging results may lead to future testing in different Kabuki syndrome model organisms.