The Roya Kabuki Program at Boston Children's Hospital
YEAR 2 REPORT

Year 2 (7/18-8/19)

We are pleased to share the progress of the Roya Kabuki Program as we embark on our third year of advancing research and clinical outcomes in the Kabuki syndrome community. Our researchers aim to define the individual presentation of the disease—the clinical phenotype and its natural history—and pave the way for the design of a clinical trial that tests the efficacy of novel drugs and treatments. We have received indispensable feedback from families of children diagnosed with Kabuki syndrome, and worked with various collaborators in the field who all share a common goal: to improve care for the Kabuki syndrome community.

The Clinical Roya Kabuki Program

The multidisciplinary team that manages individuals with Kabuki syndrome of all age groups at Boston Children's Hospital has been expanded to include the following specialties: Cardiology (Dr. Mansfield), Endocrinology (Dr. Kremen), ENT/ORL (Dr. Kenna), Immunology (Dr. Yee), Neuropsychology (Dr. Goodlett), Nutrition (Dr. Viau), Ophthalmology (Dr. Fulton) and Orthopedics (Dr. Matheney). Each patient with Kabuki syndrome can be evaluated by these "Kabuki Champions" following an individual needs assessment. All patients are seen by the core Genetics team (Drs. Bodamer and Knoll and by the genetic counselor Mrs. Rashid) for in-depth review of medical and family histories, physical exam, clinical phenotyping and discussion of challenges and open questions. The family will be provided with an "action grid" that summarizes the pertinent findings and recommendations of the Kabuki care team. This allows for seamless coordination of follow-up with the local care teams if and when needed.

Patients who have been seen in clinic are eligible for follow-up through telehealth, which has been established and used for Kabuki syndrome since September 2018.

Parent Advisory Board

In September 2019, a Parent Advisory Board was established with the intention of engaging directly with the needs and interest of the patient community. We recruited 6 dedicated parents from our clinical and research community. The members of the Parent Advisory Board provide guidance during bi-annual conference calls, provide input and direction in allocating community outreach funds raised by the Roya Kabuki Program, and act as liaisons for patient families in the Kabuki community in their local areas.

The Scientific and Outreach Projects

Natural History Study

There are 56 (research consented) families with genetically confirmed Kabuki syndrome enrolled in the Natural History Study, which addresses nutrition, growth, muscle function, hearing, balance, speech, neurodevelopment and quality of life. Patients with molecularly confirmed Kabuki syndrome are assessed using a systematic, tiered, phenotyping approach focused on organ systems. The goal is to identify disease-specific patterns that inform us about the underlying disease mechanism and health outcomes, and prepare for clinical trial readiness. In addition, we have started to partner with the Department of Ophthalmology (Dr. Anne Fulton) to dissect the eye phenotype of Kabuki syndrome using the data collected through the Natural History Study. In collaboration with the National Taiwan University Children's Hospital in

Taipei (Dr. Joyce Tsai), similar efforts are underway to define the renal and genitourinary phenotypes in Kabuki syndrome.

Collaboration with Chinese Institutions

A successful scientific and clinical collaboration between the Roya Kabuki Program and two University Children's Hospitals in Shanghai and Shenzen has been established. Since its inception, 12 patients with Kabuki syndrome have been identified. The plan forward is to establish a telehealth clinic for Kabuki syndrome and related conditions between our institutions and to expand this collaboration to other hospitals in China and South East Asia. Our first experience has been summarized and submitted for publication to the American Journal of Medical Genetics (see under publications).

Identifying new genes causing Kabuki-like syndrome

The Roya Kabuki Program uses next generation sequencing technologies in patients with a clinical diagnosis of Kabuki syndrome and no variants in known Kabuki genes to help identify additional disease genes, which will broaden the molecular spectrum and increase the diagnostic yield.

Generating cell lines for in vivo studies

Cell lines (Epstein Barr Virus (EBV) transformed lymphoblasts and primary fibroblasts) from patients with genetically confirmed Kabuki syndrome are generated for the study of molecular and cellular mechanisms that underlie the syndrome. These cell lines are important resources for in-vitro studies of drug interaction and drug screening.

Mutations in two genes—*KMT2D* and *KDM6A*—have been identified as cause for the clinical manifestations. They are known to work together to regulate gene expression; findings relative to one will most likely shed light on the other. We have generated a total of 31 EBV transformed lymphoblast and 11 primary fibroblast cell lines from Kabuki patients and their family members (14 EBV transformed lymphoblast lines). Eight EBV transformed lymphoblast and 4 fibroblast lines were generated from confirmed *KMT2D* patients and another 5 EBV transformed lymphoblast and 2 fibroblast cell lines originated from *KDM6A* patients. The genotypes of the remaining cell lines have not been confirmed yet. We have also generated three primary cell lines from skeletal muscle of *KMT2D* patients.

The quest for a biomarker for Kabuki syndrome

The identification of a biomarker (metabolites, peptides/proteins, methylation and gene expression pattern) specific to disease activity in Kabuki syndrome is critical for the understanding of cellular mechanisms and clinical trial readiness. A biomarker can be used in addition to clinical endpoints, to evaluate therapeutic efficacy.
Toward that end, the Roya Kabuki Program, has entered collaborations with the Broad Institute of MIT and Harvard, Takeda Pharmaceutical Ltd., and other researchers to employ an array of different methods for biomarker identification.

Muscle phenotype in Kabuki syndrome

To better understand how hypotonia develops in patients with Kabuki syndrome and what tissues

are affected (muscle or nervous tissue, or both), we have obtained and studied skeletal muscle samples of three KMT2D patients.

Patient outreach activities

April 2019 - Boston Marathon
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June 2019 - Boston Children's Annual Eversource Walk: Team Kabuki Friends
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July 2019 - All Things Kabuki Family Conference
|
October 23, 2019 - Kabuki Day

Patient recruitment

The newest version of the study protocol was approved by the BCH Institutional Review Board (IRB) on July 11, 2019. It was updated to include neuropsychological evaluations in collaboration with Takeda Pharmaceuticals Ltd. and muscle impedance testing. The program will continue to facilitate transferring all enrollments prior to the July 10, 2018, date (Manton protocol) into our own Roya Kabuki protocol. All newly recruited families enroll directly into the current protocol.

	Individuals (index, siblings, parents, etc.)	Families
In Contact	525	206
Consented	313	124

- 206 families have been in contact with the Roya Kabuki program since September 2017 with 49 of these families initiating contact since December 2018.
- 201families have been consented to the research protocol.
- 201 blood samples, 199 urine samples have been collected, processed and stored.
- 14 patients with KS have provided tissue samples. We have received muscle tissue from 3 KS patients.
- 14 index patients have had neuropsychological evaluations through this research study.

Internet presence

Roya Kabuki Program website (www.royakabuki.org)
BCH Internal Kabuki Website (www.childrenshospital.org)
Bodamer Lab Website (www.bodamerlab.org)

Publications (members of Roya Kabuki Program in bold)

Carapito R et al, **Hung CY**, **Bodamer O**, Chelly J, Isidor B, Bahram S. ZMIZ1 variants cause a syndromic neurodevelopmental disorder. Am J Hum Genet 2019; 104:319-330.

Rosenberg CE, **Daly T, Hung C, Hsueh I**, Lindsley AW, **Bodamer O**. Prenatal and Perinatal History in Kabuki Syndrome. Am J Med Genet 2019 (accepted).

Wang Y et al. **Bodamer O**. The phenotypic spectrum of Kabuki Syndrome in patients of Chinese descent. Am J Med Genet 2019 (submitted).

Romeo-Luperchio T, Applegate CD, **Bodamer O**, Bjornsson H. Haploinsufficiency of KMT2D is sufficient to cause Kabuki syndrome. J Med Genet 2019 (submitted).

Berry K, Hoffman D, **Hung CY**, Adam M, **Bodamer O**. Kabuki Syndrome- a disorder of transcriptional regulation. Lancet 2019 (in preparation).

Tellier A, Julio L, Hung CY, Bodamer O. Animal models in Kabuki Syndrome. Expert Opinion Drug Discovery 2019 (in preparation).

Daly T, Roberts A, Yang E, Mochida G, **Bodamer O**. Holoprosencephaly in Kabuki Syndrome. Am J Med Genet 2019 (in preparation).

Lectures and presentations:
Keynote: Kabuki syndrome. Beijing Children's Hospital Summit, China. January 2019

Collaboration is key

Boston Children's is deepening the understanding of Kabuki syndrome and moving the world closer to the solutions children need to lead healthier lives. While chemical screens and genomic analyses are challenging for rare disorders because of the small number of patients, we are making progress thanks to the support of the Kabuki community.

We are also building a collaborative environment on a global scale. Working with researchers, clinicians, and patient family groups will allow us all to reach our goal of improving outcomes in the Kabuki syndrome community sooner, together.

We deeply appreciate the community's enthusiastic and steadfast support in our quest to find new treatments for Kabuki syndrome. We look forward to sharing the next update.