THE CAMPAIGN FOR
Mass General

MassGeneral Hospital
for Children℠

Understanding UBTF

Improving the quality of life for those living with UBTF as we move toward treatments

January 2022

Massachusetts General Hospital is one only a handful of academic medical centers implementing gene therapy treatments for both children and adults, while exploring a range of potential therapeutic strategies for ultra-rare diseases, including Upstream Binding Transcription Factor (UBTF). Led by Florian Eichler, MD, Mass General's combination of research and patient care harnesses the expertise of clinician-scientists, geneticists, biologists, biostatisticians and others, all in an effort to explore multiple opportunities to improve the quality of life for individuals with ultra-rare neurological diseases while pursuing promising treatments and potential cures.

Thanks to the support of Cure UBTF, Dr. Eichler and his collaborators are making significant progress in their efforts to better understand UBTF and develop treatments. Your generosity has allowed Dr. Eichler and his team to advance two areas of study and the progress is outlined below.

Natural History of UBTF: Understanding when individuals reach, or just as importantly, fail to reach, particular milestones in their neurological development can provide critical measurements of changes in function caused by UBTF, allowing translational scientists to create more targeted interventions. One dozen patients filled out surveys that were analyzed by Amanda Nagy, MD, a neurology resident at Mass General.

In parallel with this patient-reported information, Anoopum Gupta, MD, PhD, who leads the Laboratory for Deep Neurophenotyping at Mass General, is piloting the use of wearable devices that use machine learning to measure balance, movement and coordination over a three-month period. This pilot study is gathering information from three patients, but we are hopeful that this tool's passive collection of data, gathered remotely, will make it easier for more patients to participate. In addition to measuring a loss of function, we also hope to use these tools to measure the effectiveness of treatments to show they are successful.

Gene Therapy: Support from Cure UBTF has also been used to advance our studies of potential gene therapies to correct the UBTF gene. We are working on a potentially exciting collaboration with N-Lorem, the non-profit subsidiary of Ionis Pharmaceuticals, which is developing an antisense oligonucleotide (ASO) to correct the UBTF gene. We have harvested skin fibroblasts and are comparing them directly to kidney cells that have undergone gene editing by Ben Kleinstiver, PhD at the Mass General Center for Genomic Medicine, and team. Dr. Kleinstiver, an expert in the realm of gene editing, has been able to

create kidney cells that carry the UBTF gene defect that is present in humans. The goal of these experiments in cell cultures is to find biomarkers pertinent to patients affected by UBTF, as well as have model systems to assess future therapies. For instance, it will ensure the ASO corrects UBTF and reduces or eliminates DNA breaks. These in vitro tests also track the behavior of the ASO to make sure it is safe and there are no off-target effects. Additionally, in vitro models will allow us to screen drug libraries to find medications that could be beneficial to patients with UBTF gene defects.

Looking ahead: The support of Cure UBTF is allowing Dr. Eichler to build a rich infrastructure with collaborators both within Mass General Brigham and across the country, as well as with industry. This infrastructure allows a larger, diverse collection of investigators, working across specialties, to take on the problem from different angles. By pursuing more than one potential solution, we will move more quickly toward the most effective treatments and cures.

In the coming year or two, Dr. Eichler hopes to seed several more projects to explore more opportunities. In collaboration with Dr. Kleinstiver, Dr. Eichler will undertake gene editing to correct the UBTF gene defect in previously created kidney cells and patient fibroblasts. Working with collaborators in the Ataxia Unit and Physiatry Department at Mass General, we will explore new devices to support neurological performance and coordination in UBTF patients, thereby preparing for future clinical trials with ASOs and other compounds. Our goal is to intervene earlier, before functionality is lost, and test effective ASO and other gene-modifying strategies that can repair UBTF and prevent the loss of movement for children with UBTF.

Thank you for your partnership.