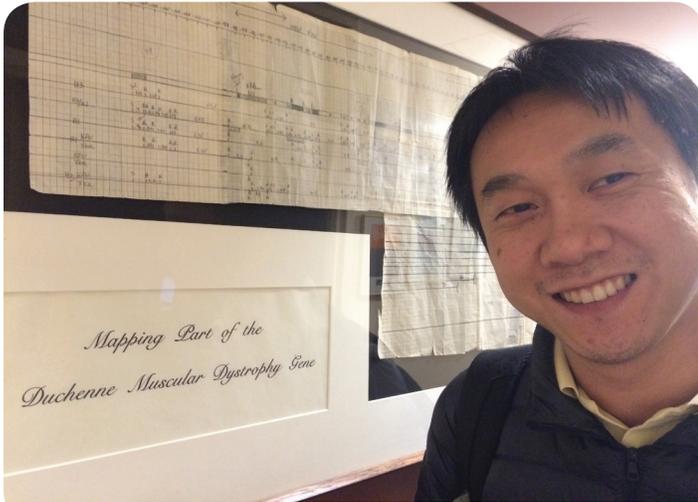# Improving the Diagnosis of Neuromuscular Diseases

Development grant jointly funded by the AANEM Foundation and the Muscular Dystrophy Association (MDA) was awarded in 2016 to fund the following project.



Dr. Lek, mapping of the first muscle disease gene, DMD, Kunkel Lab, Boston Children's Hospital.

## Improving the Diagnosis of Neuromuscular Diseases

**Monkol Lek, PhD**
**Massachusetts General Hospital,**
**Boston, MA**

A development grant jointly funded by the AANEM Foundation and the Muscular Dystrophy Association (MDA) was awarded to Monkol Lek, a postdoctoral fellow at Massachusetts General Hospital in Boston. Dr. Lek was awarded $119,746 over two years to improve the diagnosis rate of rare muscle diseases.

Dr. Lek recently shared his thoughts on his research and this award:

### Summarize your research:

The main goal of my research project is to improve the diagnosis rate of rare muscle diseases. Currently the diagnosis rate using exome sequencing is approximately 40%. In this research project, we take two approaches to improve the diagnosis rate. Firstly, whole genome sequencing allows us to detect variants in regions outside of the protein coding regions (i.e. exome). The other approach is sequencing RNA extracted from muscle biopsy, which allows us to observe the consequences of difficult to interpret variants on gene expression and splicing. Both approaches have improved our ability to detect potential disease-causing variation but the challenge also remains in the interpretation. The last aim of this project is to provide resources to the community to improve the interpretation of rare variants discovered in our patients.

### What spurred your interest in this type of research?

I was diagnosed with limb girdle muscular dystrophy in my early 20s. At the time there was very limited information on my disease, why it was so hard to find the disease-causing gene and if there was any treatment. I went back to University and then research to contribute to all three of these areas. It took over a decade to find my disease causing gene, TCAP/Telethonin, and I didn't want other patients to wait that long as I can empathize with the frustration of not knowing.

### You were first author on a research paper in *Nature* last summer – "Analysis of protein-coding genetic variation in 60,706 humans" – how does this work relate to this project?

The *Nature* paper details a resource called the Exome Aggregation Consortium (ExAC) data set, which summarizes the genetic variation from over 60,000 individuals including Europeans, Africans, East Asians, Latinos, and South Asians. The resource was a major collaborative effort of analysts and computation biologists at the Broad Institute and senior scientists around the world, which took approximately two years to develop. The mutations we discover in muscle disease patients should be rare, as the muscle diseases are rare themselves. This comprehensive and diverse resource has allowed us to better determine the frequency of potential disease causing mutations discovered in our muscle disease patients. We have used this resource to aid in the diagnosis of all our rare muscle disease patients that have been exome sequenced. The resource can be accessed via the ExAC browser (http://exac.broadinstitute.org), which since its release in October, 2014, has been visited over 7 million times by the research community.

### How will this award help you in your research?

This award allows me to dedicate my research efforts to the genetic diagnosis of the most difficult muscle disease cases. It will also allow me to explore novel approaches and technologies, while building strategic collaborations necessary for the next stage of my career as an independent investigator. I'm very grateful for the support of AANEM/MDA and their investment in young scientists.

### What else would you like to share with AANEM members?

For neurologists, never to be satisfied to tell patients each year that there is no treatment available for their disease. For researchers, to know patients are extremely grateful for your dedication and hard work. Lastly, for patients and their families, to contribute to the efforts the best way they know how. I was told when I was diagnosed to leave the research to the experts and was glad I never listened!