NBIAcure NEWSLETTER

- JUNE 2018 -

Team Member Spotlight

Dr. Randy Woltjer is a neuropathologist who has been working as part of the NBIAcure team for ten years! When asked how he became interested in neuropathology, Randy will begin by telling you about a patient he saw as a medical student while completing his rotation in internal medicine.This patient was being treated for leukemia, but while in the hospital she also developed acute congestive heart failure caused by the buildup of too much fluid. Randy knew that normally this problem was easy to notice early, as patients are weighed daily and any weight gain is suggestive of fluid buildup. Wanting to understand why her weight gain had gone unnoticed, Randy started to investigate. It turned out, this patient had been weighed on three separate scales, and the slight differences between the scales masked the weight she had been gaining.

Randy tells this story to illustrate how he wants to get to the bottom of problems, rather than just managing disease and symptoms. This pushed Randy to explore the field of pathology as a way to understand what causes diseases and ultimately how to cure them. He started out as a pathologist in cancer research, and through a somewhat serendipitous connection between genes in cancer and genes in Parkinson's disease, Randy started to familiarize himself with brain diseases. Eventually, Randy took a fellowship as a neuropathologist and received a grant to study neurodegenerative diseases of the brain. This grant took Randy to the University of Washington, and finally to OHSU, where Dr. Hayflick first approached him to help with PKAN research.

In addition to being a dedicated member of the NBIAcure team, Randy runs the Oregon Brain Bank (OBB). The OBB has two missions, to give families diagnoses of brain diseases and to help and promote research. Many brain diseases, such as Alzheimer's, cannot be diagnosed with genetic testing, and often times the only way to give a true diagnosis is through brain autopsies. It can also be difficult to identify bio-markers without examining the brain. Past donations are the reason researchers were able to find the presence of abnormal protein deposits in neurons of PKAN patients. Brain donation is often a very difficult decision for families to make. However, donating can be a way for our loved ones to continue to help find a cure even after death. Any NBIA tissue donations to the OBB would be studied at OHSU by Dr. Hayflick and Dr. Woltjer.

Life of a skin biopsy

Many of you have already given us this type of sample, but for those who haven't, a skin biopsy is a procedure where Dr. Hayflick removes a small piece of skin about the size of a pencil point. Here is what we do with the sample next.

First the tissue piece is washed and digested with two enzymes at 37 degrees celsius

Second, the tissue is attached to a culture plate

Next, the plate is filled with nutrients for the cells to "eat"

Then we wait for the cells to "crawl" out of the tissue piece until they eventually cover the entire plate

Once the cells have crawled out, we perform research experiments with them

Some cells are frozen in liquid nitrogen and can be used in research for decades to come

"All of us families appreciate all of you more than you'll ever know. We love all of you for your hard work."
-NBIA Family

"You've given our family hope. Thank you."
-NBIA Family

"We believe in you!"
-NBIA Dad

Thank you to everyone who has donated, and for all your kind words of support. Our whole team truly appreciates it!

CoA-Z Update

One of the companies who was testing multiple methods to produce CoA-Z has finalized a process for making large quantities of the compound! They are now moving forward with making a large batch for safety and purity testing.

Is BPAN the Most Common NBIA Disorder?

No one can say exactly how many people in the world have a NBIA disorder, but we can guess based on how many people have been diagnosed so far. Today, PKAN is the most common type of NBIA disorder, closely followed by PLAN and BPAN. However, overall numbers are not the entire story and there are three main factors that are contributing to a recent rise in BPAN diagnoses.

Discovery of the *WDR45* Mutation

PANK2 gene mutations were discovered to be the cause of PKAN in 2003. Three years later the PLAN gene, *PLA2G6,* was discovered and ten years later mutations in the *WDR45* gene were determined to be the cause of BPAN. Sequencing an individual's DNA and finding a mutation in a specific gene is the most accurate way to give someone a diagnosis of NBIA. Doctors have only been able to make genetic diagnoses of BPAN for five years, instead of twelve to fifteen for PLAN and PKAN. However, most diseases are never diagnosed with genetic testing and only rely on clinical features. In other words, doctors can examine a patient and give them a diagnosis. However, this can be especially difficult in BPAN.

Clinical Features of BPAN

Individuals with BPAN are usually brought to see a doctor when they are young due to characteristics such as broad developmental delay, repetitive or even autistic behavior, and seizures. Unlike the symptoms of PKAN, these clinical features are common among a number of diseases, making it very difficult for doctors to diagnose. Additionally, the presence of brain iron accumulation on MRI may not show up until early adulthood for many individuals with BPAN. In comparison, people with PKAN have very distinct, "eye of the tiger" MRI patterns from a young age, making PKAN an easier disease to diagnose clinically. Once clinical features of a suspected genetic disease, such as PKAN or BPAN, are identified, a gene panel can be ordered. This is a genetic test of a few genes that are likely to have mutations based on the patients symptoms. The recent addition of the *WDR45* gene to seizure pannels has lead to an increase in early BPAN diagnoses. Also, as more research is done on BPAN, MRI characteristics for BPAN patients are emerging, creating a more defined clinical picture of the disease.

Kids with BPAN visiting us at OHSU

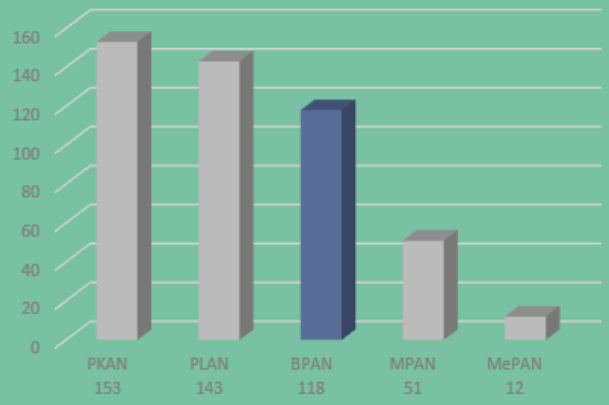
Whole Exome Sequencing

The last piece of this story is Whole Exome Sequencing (WES). WES is a type of genetic testing that is increasingly being used to diagnose patients with non-specific clinical features (like in BPAN). Unlike gene panels, WES does not focus on a few genes, but looks at all the coding genes in an individual's DNA and catches most mutations that are present.

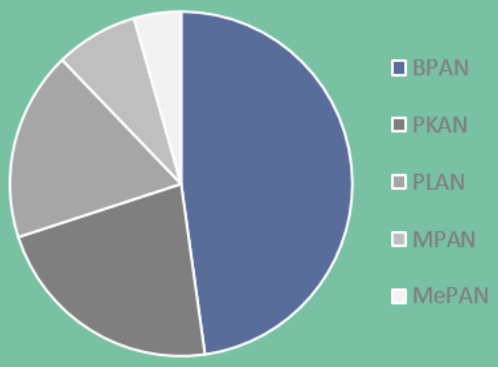
In the past 18 months, our team has seen almost as many BPAN diagnoses as all the other NBIA disorders combined. This recent increase may be a result of targeted genetic testing with seizure panels, broad genetic testing using WES, and simply "catching up" with all the people who went undiagnosed before the discovery of the *WDR45* gene. If the amount of people with BPAN continues to grow at the same rate, then BPAN may very well overtake PKAN and PLAN as the most common NBIA disorder. Time will tell whether this is true.

BPAN Today

Total NBIA Diagnoses



Diagnoses since January, 2017



These numbers were gathered through our database at OHSU, and represent people who have reached out to us, come for clinic visits, and participated in research.