Opportunities in HSP's Genomics and Therapy
Center of Excellence, Research Network — HSP/PLS
Stephan Zuchner PhD
University of Miami Genomics Division

The SPF's new project called CERN or Center for Excellence Research Network will be comprised of Dr. Stephan Zuchner, Dr. Craig Blackstone, Dr. Rebecca Schuele, Dr. Darius Ebrahimi-Fakhari and Dr. John Fink. Dr. Stephan Zuchner is professor and geneticist at the University of Miami and specializes in gene identification, modifier genes, molecular disease mechanism and gene therapies. Rebecca Schuele is a professor and neurologist at the university of Heidelberg Germany. She is a leading expert about HSP in Europe. Her specialties are gene identification, clinical outcomes, natural history, studies, and gene therapies. Darius, Ebrahimi-Fakhari is an associate, professor and pediatric neurologist at Harvard university, Boston Children's Hospital. He specializes and has made a name for himself in clinical outcomes and natural history studies. Dr. Craig Blackstone is Professor and neurologist at Harvard university/ MGH and he specializes in molecular mechanisms, molecular imaging and clinical outcomes. He is an expert in the molecular mechanisms of HSP. Dr. John K. Fink is professor and neurologist at the University of Michigan. He is the scientific advisor for The Spastic Paraplegia Foundation.

Many other Rare Disease Clinical Research Networks have developed great progress through this sort of center of excellence research network. By working together, they can attract more patients to participate in these studies and find scholastic synergies to spur great advances toward therapeutic solutions. Additionally, once they start such a net work, there will be new opportunities for funding. They will have a much stronger case to acquire significant funding from such agencies as the National Institute of Health. The key goal of such an effort will be to obtain clinical and genetic data and be able to share such data. They also plan to have a registry for HSP & PLS patients available.

He wants to address the topic of the state of genetic science and cost of genetic testing. Genetics has made tremendous progress in recent decades, and much of this has been driven by technological advancements. These technological developments have led to reduced cost. Today, they can sequence a human genome for about $500 and the prices are still sinking.

Only last year, the final version of the human genome was put together and published in the journal of science. He listed three companies, Illumina, Nanopore, and PacBi, who represent the leading edge of technology in their field. While all of these technologies are remarkable, there is actually a new technology available that will allow for better whole genome, sequencing, and lead to even more great discoveries.

There are many different genes that cause HSP and they are very heterogeneous. There are over 1/3 of all patients with HSP that they cannot find the causative gene. They really want to get a much higher rate, over 90%, knowing the causative genes for

all forms of HSP. What they have learned from discovering all the many HSP genes so far is that HSP does not live in a silo. It is connected with many other disorders that affect the nerves in your spinal cord, and also diseases that affect your arms and legs. These diseases include HSAN, HSN, HMSN and ATAXIAS.

To tackle the task of discovering more HSP genes, they need to.understand the genetic mechanism of different types of HSP. By collecting genetic data sets they can learn about new and existing HSP genes. They currently have over 2,000 HSP genetic data sets available. In the past year, they have added over 1300 HSP genetic data sets.

All of this data is currently available to genetic researchers in a tool called Genesis Gene Pair. Using this tool returns a pre-filtered De-identified list of coding variants in genes of interest. In order to participate in gene pair, one must register and get approved. He showed a map of the world and countries with the most related genetic data sets (18,000 in total) were colored a darker green than other countries. There is a strong bias toward English, speaking countries.

They just recently gained the ability to share data with other scientists all over the world. The more data sharing that takes place, will allow great science advancements. Having all this data readily available helps some scientists develop new tools, such as the scientist at the University of Miami, Matt Danzi, PhD, who developed a machine learning tool called Maverick. This is now accepted for publication in a nature journal. This will give it a lot of validity and mini scientists will use this. This software can predict if a gene might be an HSP Gene, or if a certain variant in any gene could cause disease. This has had a really high success rate. With such a tool as Maverick, we can predict if variants in the spast gene are pathogenic.

He showed other tools that helped to identify different variants of HSP. He showed a gene called FIDC, which has been identified as another HSP gene through the work of both Dr. Rebecca Schuele and Dr. Stephan Zuchner. They have done many follow-up studies that have really developed interest among scientists. He showed many other examples of gene discoveries, and they are not the only samples they have. It just shows what happens when scientists can work together. This sort of synergy will continue as we establish this new HSP/PLS CERN. Since he and Rebecca have been working under an NIH grant, over the last 10 years they have published over 60 scientific papers jointly.

When you have a lot of genetic data available, and when it can be shared, and used by many scientists, the possibilities for dramatic discoveries and improvements are greatly enhanced. He showed some statistical studies done by a scientist in his lab, Dana Rid PhD who did statistical correlation studies with such diseases as HSP, and CMT, which are sometimes called axonopathies. This can sometimes generate new disease genes and risk genes or modifier genes. Despite all these efforts, they still realize there is a large diagnostic gap.

They are beginning to wonder if they may be missing things by only looking at genes. They may have to look outside of genes. The space outside of genes in the human genome is about 98% of the human genome. There are certain variations or mutations in this space there that have been identified with other diseases. They are really not up to scale yet, but this is changing with new technology. They have been interested in science in the last few years with these so-called expansion disorders. There are repetitive stretches in the genome that all of us carry. There is a catalog of over 1.7 million regions or loci in the genome.

They have been especially interested in diseases called expansion disorders.There are sections called Non-coding regions. They have recently thoroughly studied the largest lower read whole genome data set in the world, comprised of about 1,000 such data sets and they have from these 1000 people (who don't have any disease) they created over 3.5 billion alleles. This is not a minor additional place to look in the genome. It could very well be a large contributor to disease.

He showed a study done by Sarah Fazal, a PhD student in his lab who has done pioneering work on repeat expansion genome characterization, and identified which ones they should study first. Again, having a consortium and having a way to collect genetic and clinical data and share that data really helps advance scientific discoveries.

He showed an example of a discovery just a few years ago by he and others of repeat expansions in sensory neuropathies and ataxias. The gene is RFC1 and there is a non-coding, repeat expansion in this gene, it was a surprise to learn that this particular repeat expansion or mutation is the most important gene to cause sensory neuropathies and ataxias. This disorder had a large diagnostic gap and this discovery led to knowing the cause of about a third of all of those patients. There might be something like this for HSP to be discovered.

Another example was from January of 2023 where they discovered the FGF14 ataxia where a significant drug discovery would soon follow. This one repeat expansion gene is now the most common ataxia gene ever discovered. They now want to dig in to HSP data sets to discover these sort of repeat expansions.

They are already working with many different researchers all over the world. This leads to many of their scientific discovery papers have a many co-authors. These scientists will be some of who the new HSP/PLS CERN will expand to. Many of these scientists have worked together to solve problems in the ataxia field and are very similar to problems in the hSP/PLS field. He showed another example of the inherited neuropathy consortium which is also enjoying the benefit of this synergy of scientists all over the world.

His next slide was entitled "Two Sides of One Coin" and he explained that it is important to both discover and know the exact genetic diagnosis of every HSP type which leads to the exact genetic therapy to remedy those malfunctions. Those different

therapies included: Delivery modus, gene replacement, Anti-sense oligonucleotide and Gene editing (CRISPR).

The development of therapies for many diseases is at a high pace now. HSP and PLS will benefit a lot from what they learn from many of these fields. He predicts that in the next five years you will see many very promising gene therapies that companies will want to test in patients through clinical trials. We need to be prepared for this moment and it is coming. That is really good news for the SPF community.

He closed by showing a photo of his associates at the University of Miami and he wished us all a successful meeting.