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Clinical Trial Readiness for Childhood Onset HSP
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Their clinical research has one main goal: which is to create clinical trial readiness for childhood onset HSP. They are building a foundation for clinical trials. They plan to have many different kinds of therapies available. They will test them and make sure they are working.

The main program they have is a natural history study. Many people in the audience had already met with their team, and understand that a natural history study is a longitudinal study where they meet at regular intervals to take all sorts of skill level tests.

They collect information that serves multiple purposes: 1. They are building a community which is very important. 2. They are learning about the symptoms. Hereditary spastic paraplegia is a rare disease in many forms are ultra rare diseases.

Many neurologists, even in highly specialized hospitals do not have enough experience with all types of HSP. The benefit is that they are able to guide families better and to offer anticipatory guidance. From a research perspective, this really builds a foundation to design clinical trials. They started this a few year's ago, and they opened up to all forms of HSP in January 2021.

At this time, they have met with over 450 families with HSP. The goal is to meet with families, longitudinally, and to learn and discover. Well, they have seen over 450 children with HSP, they have only seen about 100 for a second visit. This is a number that they are building right now. Everyone's contribution to this research is very valuable and appreciated.

So, what have we learned? They have learned some very important key things that are important for families with Hereditary Spastic Paraplegia. He is starting with what are called the autosomal dominant kinds of HSP's. The main ones are SPG4 (SPAST), SPG3A (ATL1), and what he termed, as "others".

With the help of these families and some international collaborators, they are approaching the knowledge of de novo variants in a whole new way. A de novo variant is a variant that occurs in an individual for the very first time and are not inherited. They have done a very heavy analysis of cases of denovo variants.

Most of their work has been on autosomal forms of HSP. These include SPG11, SPG15 (ZFYVE 26), AP4 HSP (AP4 subunits), SPG 49 (TECPR2). They have discovered unusual forms of inheritance.

They have developed tools to interpret miss-sense variants. These can be difficult to interpret sometimes, so they have developed laboratory tools. They have worked to describe the phenotype. A phenotype is the array of symptoms that are possible. This is important because it leads to a faster, diagnosis, and it builds the foundation for natural history studies.

One particular challenge, they face because they see children from around the world with second or third opinions is that in about 20 to 30% of the cases where they think this is a clinical diagnosis of HSP, they don't find a causative mutation with whole exome sequencing. So, to address this and provide families with extra tools, they have launched a second study that they call the HSP sequencing initiative. Here, they provide families with more advanced testing on a research basis. This is particularly for families where the diagnosis of HSP's has been made but no gene has been identified.

Why is this important? Why do they care about it? They care about it because as we are discovering these diseases on a molecular level, and they are understanding what the molecular mechanism is, there are exciting new avenues for treatment.

Lastly, it is always important to identify those conditions that mimic hereditary spastic paraplegia, but actually have different causes that require very different treatments. On the screen were listed: Dopa Responsive dystonia (GCH1), Arginase deficiency (ARG1) and Aicardi-Goutieres syndrome (ADAR) which are treatable inborn errors of metabolism.

Why is all of this important for you? Why do we care about this? We care about it, because as we are understanding these disorders on a molecular level, we are understanding what the molecular mechanism is, and there are exciting new avenues for treatment. Building an avenue for clinical trial readiness program serves the purpose of being ready when these treatments become available.

We will be able to use these new treatments in an efficient way and we can test them in an efficient way and be able to weigh the risks and benefits of all of these different treatments. He did not want to go to in-depth detail, but he suggested to the audience that they had all heard the terms gene therapy and gene editing and other approaches that use so-called anti sense autologous nucleotides. All of these are coming to a stage where they will be used clinically.

Many of you are familiar with the applications for spinal muscular atrophy. Many of you are familiar with the treatment that was approved just yesterday for Duchenne's muscular dystrophy. These things are coming and he thinks we need to be prepared to embrace these new technologies and use them for both children and adults with HSP. Listed on the screen were 4 different groups of HSP. Those 4 different groups are Bi-allelic loss of

function variants (which include small molecules, Gene replacement, ASO (exon skipping), Gene editing), haplo-insufficiency (which include Small molecules, Gene replacement, ASO (block of non-productive splicing events and Gene editing), dominant-negative effect (gain of function) (which include Small molecules, ASP (i.e. allele-specific), RNAi and Gene editing and Other ASO amenable variants (which include Poison exons (exclusion), Abnormal splice site (splice modulation) and Pathological repeat expansions (RNase H mediated degeneration).

If anyone is inter-ested in participating in one of their two studies, please reach out to Amy Tam BS at either 617-355-2698 or Amy.tam@childrens.harvard.edu. Set up an appointment to visit them in Boston or they can do remote visits if necessary.