Sanfilippo Syndrome Registry Project and Natural History Studies: An Example of Patients, Parents and Researchers Collaborating for a Cure

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Abstract

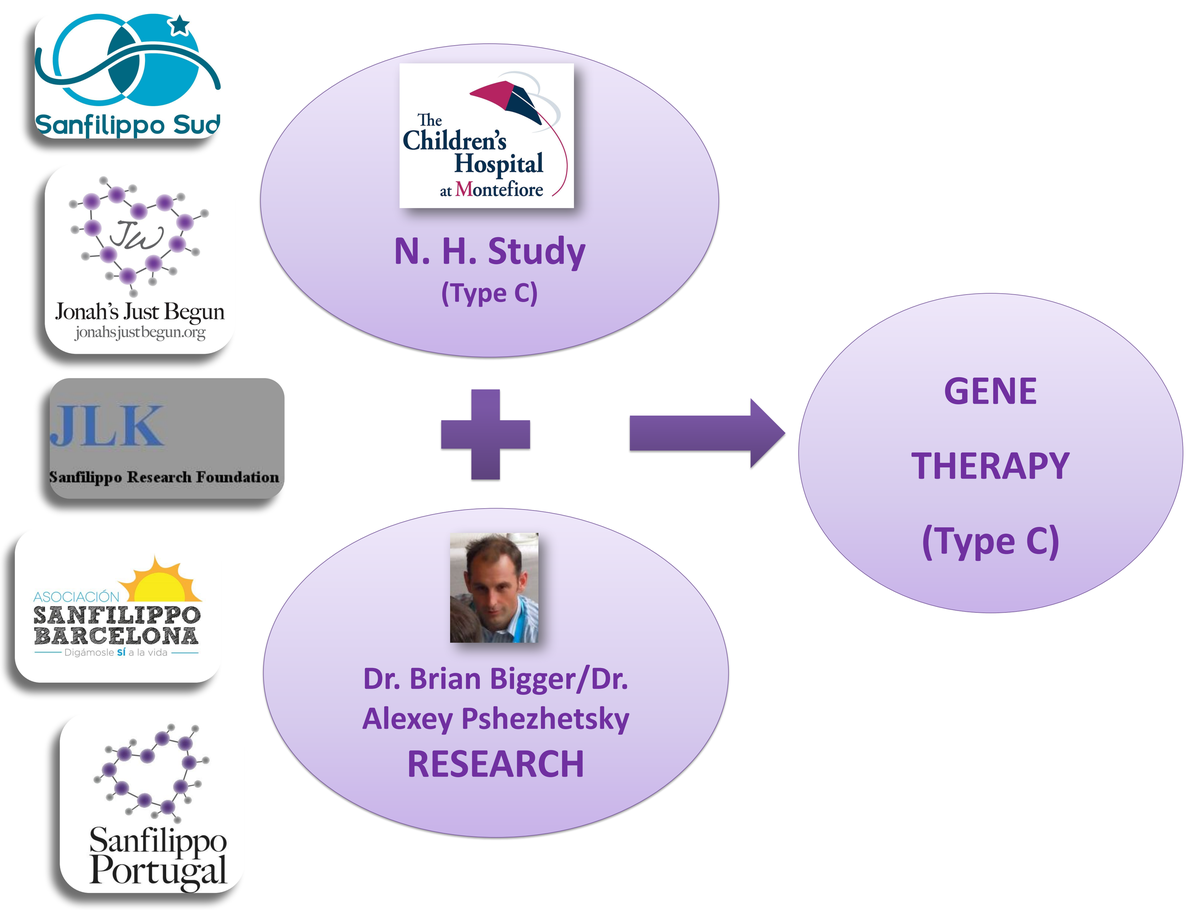
In the past few years, several clinical trials are being conducted, namely Shire's enzyme replacement therapy and Lysogene's gene therapy for Sanfilippo type A, Institute Pasteur's gene therapy and Alexion / Synageva enzyme replacement therapy for Sanfilippo type B. Nationwide Children's Hospital is aiming to start gene-therapy clinical trials for types A & B in 2016 as well as Biomarin's enzyme replacement therapy for type B, Manchester's Stem Cell Gene Therapy for types A & B and Esteve Gene Therapy for type A . For other Sanfilippo types C and D the research is at preclinical stages including gene-therapy (Type C) and developing and Enzyme replacement therapy for type D (Phoenix Nest /LABioMed). These recent scientific advancements towards treatments for Sanfilippo Syndrome indicate that it is time for us collect and analyze information on Sanfilippo patients in a single centralized registry as part of the Patient Crossroads CONNECT website (https://connect.patientcrossroads.org/?org=SanfilippoRegistry). In addition it is important we understand how the disease progresses and what differences there may be between the different types. This requires natural history studies (NHS) which can help us in determining the clinical outcome measures, identify potential surrogate endpoints via defined assessments including standardized clinical, biochemical, neurocognitive, behavioral, developmental, and imaging measures. From our experiences such data collected from NHS studies are not shared between researchers except when published as papers at a much later date. Sanfilippo Syndrome has a very small patient population and the participation in multiple NHS (which may be occurring simultaneously) places an unrealistic burden on patients and families. Sanfilippo Syndrome is ultra-rare and patients are geographically diverse. Providing patients and families with an outlet to find pertinent information pertaining to Sanfilippo, such as where Natural History Studies and clinical trials are taking place, or making themselves known by participating in a centralized registry, is essential. With the use of Rare Connect platform (https://www.rareconnect.org/en/community/sanfilippo-syndrome) we hope to bring families from around the world closer together and give them access to information that they may not have access to otherwise. We will describe how the data collected from the NHS studies for Types A and B performed at Nationwide Children's Hospital and for Type C at The Children's Hospital at Montefiore will be available to other qualified institutions to prevent repetition. Such NHS studies and registries can also help in identifying participants for clinical trials. We will illustrate how close collaborations between parent/patient led disease organizations and clinical and company researchers, is essential to ensure our limited funding and time is well spent as we try to identify treatments.

What is Sanfilippo Syndrome?

Sanfilippo Syndrome IS A PROGRESSIVE AND FATAL NEURO-DEGENERATIVE DISORDER that belongs to a group of diseases called mucopolysaccharidoses, specifically known as type III (**MPS III**). Sanfilippo children are missing a lysosomal enzyme. This enzyme is supposed to breakdown complex sugar molecules or 'substrate' – heparan sulfate. The substrate builds up in the body, stored in the lysosome of the cells, causing catastrophic health problems. The central nervous system is severely affected, causing profound brain damage. Bone deformation may occur; spleen, heart and liver damage as well.

4 subtypes designated: A, B, C, and D. There are four different enzymes responsible for breaking down Heparan Sulfate; designations A, B, C, and D refer to which enzyme is lacking. Prevalence estimated 1: 70 000 births. **AUTOSOMAL RECESSIVE GENETIC DISEASE. MEANING BOTH PARENTS MUST BE CARRIERS.**

There is no treatment but there are research efforts to find one funded primarily by multiple MPSIII disease foundations.



What we are doing about it

Parents have formed foundations in each country and have combined resources, forming groups like HANDS. We work with scientists and clinicians and fund their research on Sanfilippo A, B, C and D.

Research Funded by HANDS Consortium

Created the type C mouse model

Principal Investigator: Alexey Pshezhetsky, Montreal University

Chaperone Therapy

Principal Investigator: Alexey Pshezhetsky, Montreal University

Correction of "splicing" and "no sense" mutations

Principal Investigator : Dr. Daniel Grinberg and Dra. Lluïsa Vilageliu, Barcelona University in collaboration with INSA, Porto, Portugal

Treating Neuropathology in Lysosomal Storage Disease

Principal Investigator: Alessandro Fraldi, Telethon Institute of Genetics and Medicine (TIGEM - Italy)

Natural History Study

Principal Investigator: Paul Levy, The Children's Hospital at Montefiore NY

Defects in Communication between Brain Cells that Cause Dementia in Sanfilippo Disease

Principal Investigator: Alexey Pshezhetsky, Montreal University

Using Animal Models to Understand and Cure Sanfilippo Disease

Principal Investigator: Alexey Pshezhetsky, Montreal University

Targeting Monocyte/Macrophage Cells for Gene Therapy of MPS IIIC

Principal Investigator: Alexey Pshezhetsky, Montreal University

Assessment of the Efficacy of Long-Term Intracerebral AAV-hHGSNAT Delivery in MPSIIIC Mice – Gene therapy

Principal Investigator: Brian Bigger, Manchester University

The overall aim of this project is to expand our knowledge of the clinical features of MPS IIIC and MPS IIID disease by carrying out a prospective natural history study for a period of 5 years.

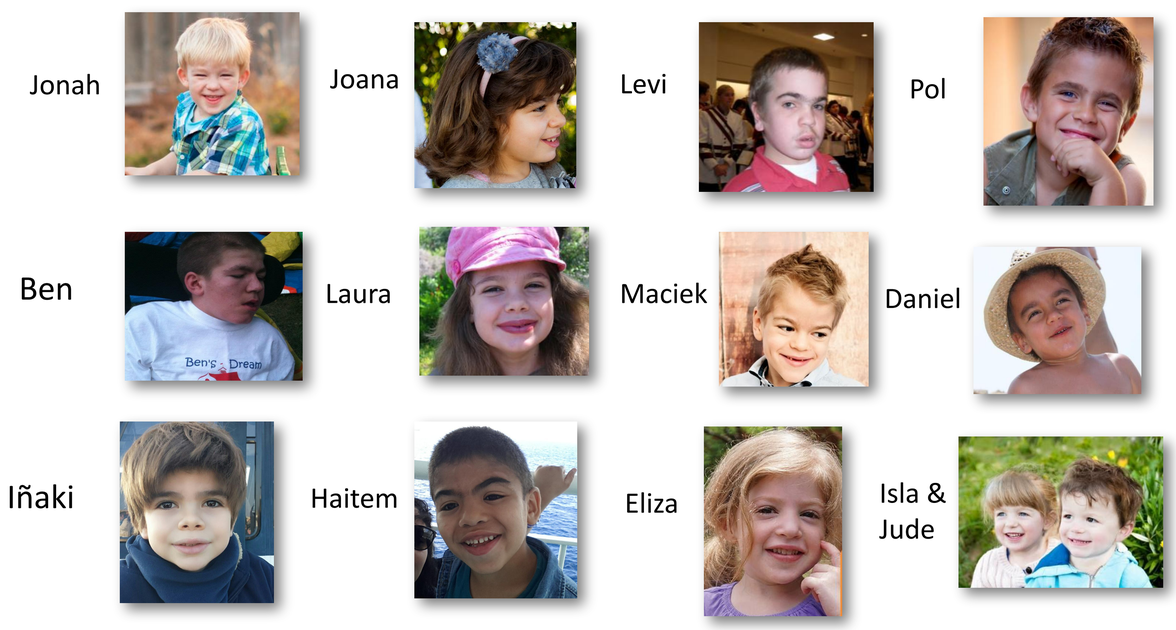
Sanfilippo Syndrome Registry

- A way in which patients, organizations and researchers work together;
- The information of the disease progression is invaluable information for scientists;
- To have an idea of how many children are affected with this disease and in which parts of the World that they are located;
- Professionals, such as researchers or healthcare providers, have access to de-identified information provided directly by participants and their families; and most importantly the chance to learn directly from those living with disease;
- Send newsletters to inform participants of new activities, developments or findings;
- Send notices to inform participants of study opportunities.

RareConnect was created by EURORDIS to provide a safe space where individuals and families affected by rare diseases can connect with each other, share vital experiences, and find helpful information and resources.

Benefits of RareConnect

- Connect with others who understand
- Learn about research and the latest treatments
- Share your own experiences
- See what advocacy organizations are doing around the world
- Find helpful resources and information from experts



Reference Wood J, Sames L, Moore A, Ekins S, The multifaceted roles of rare disease parent / patient advocates in drug discovery, Drug Disc Today, 18: 1043–1051, 2013. http://www.drugdiscoverytoday.com/download/1215