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

Jill Wood^{1,2}, Stuart Siedman³, Jennifer Siedman³, Paul Levy⁴, Kyle Brown⁵, Kim McBride⁶, Kevin Flanigan⁶, Raquel Marques¹, Arleta Feldman⁷ and Robert Pleticha⁸.

¹Jonah's Just Begun, P.O. Box 150057, Brooklyn, NY 11215, USA, ²Phoenix Nest, P.O. BOX 150057, Brooklyn NY 11215, USA, ³Ben's Dream, Sanfilippo Research Foundation, P.O. Box 81268, Wellesley, MA 02481-0002, ⁴The Children's Hospital at Montefiore, MMC CHAM, 3415 Bainbridge Avenue, Bronx, NY 10467, ⁵Patient Crossroads, 4 West 4th Avenue, Penthouse C, San Mateo, CA 94402, ⁶Nationwide Childrens Hospital, 700 Children's Drive Columbus, Ohio 43205, ⁷Mały Maciek i Wielcy Czarodzieje OS. Mozarta 1/32, 31-232 Krakow, Poland, ⁸RareConnect.org, A Partnership of Eurordis and NORD, Spain

Abstract

In the past 5 years, two clinical trials, for Sanfilippo type A, have been conducted, namely Shire's enzyme replacement therapy and Lysogene's gene therapy. Nationwide Children's Hospital is aiming to start gene-therapy clinical trials for types A & B in 2014. For other Sanfilippo types C and D the research is at preclinical stages including gene-therapy (Type C) and developing and characterizing a knock-out mouse model (Type D). These recent scientific advancements towards treatments for Sanfilippo Syndrome indicate that it is time for us to collect and analyze information on Sanfilippo patients in a single centralized registry as part of the PatientCrossroadsCONNECT 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 RareConnect 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 Childrens 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 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 is estimated at 1: 70 000 births. It is an **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 several countries and have combined resources to form HANDS. We work with Scientists and clinicians and fund their research.

Research Funded by HANDS Consortium*

Initiated and created the type C mouse model

Principal Investigator: Alexey Pshezhetsky, Montreal University

Chaperone Therapy

Principal Investigator: Alexey Pshezhetsky, Montreal University

Correction of "splicing" and "non-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; Portuguese PhD student Carla Martins is participating on the project in Canada

Assessment of the Efficacy of Long-Term Intracerebral AAV-hHGSNAT Delivery in MPSIIIC Mice – Gene therapy
Principal Investigator: Brian Bigger, Manchester University

Initiated and created the type D mouse model
Principal Investigator: Matt Ellinwood, Iowa State University ***With Taconic**

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

CONNECT is a shared, open-access patient registry able to collect data on any disease, from the most rare to more common diseases. In the **CONNECT** Registry platform, patients own their data, opting in and consenting to share their de-identified information. The registry helps us to build a relationship with NIH and EU health entities.

Benefits of 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 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 and NORD 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

Collaboration = Cure

Jonah's Just Begun
www.jonahsjustbegun.org