Letters with Connections: GGC, ISMRD, ML II and III
By Sara Cathey, MD

Did you know the Greenwood Genetic Center (GGC) has been connected with mucolipidosis (ML) II and III since these disorders were first described?

-Dr. Jules Leroy described the first ML II patient in 1970. Dr. Leroy is a regular presence at GGC as one of our most frequent Visiting Senior Genetics Scholars. In his role at GGC he continues to study all aspects of ML II and III while educating doctors and scientists about these and related rare disorders.

-In the early 1970's Dr. Hal Taylor not only cofounded the Greenwood Genetic Center, but also produced the first reports on the biochemical characteristics of ML II and III.

-Around the same time another Senior Genetics Scholar at GGC, Dr. Jurgen Spranger, a renowned expert in skeletal diseases, further described and classified ML.

Thirty-five years after Dr. Leroy met his first ML II patient, I had the privilege of meeting my first ML II patient with Dr. Leroy in Greenwood, South Carolina. The family had traveled to GGC to meet Dr. Leroy and have their child evaluated by him. That visit profoundly impacted the course of my professional career.

The family was eager to help us learn more about ML, and they were already connected to other ML families through the ISMRD. Just a few weeks before the visit, reports of the genetic cause of ML were published. Right away GGC was analyzing the GNPTAB gene in more than a dozen ML patients we came to know through ISMRD. It was not long before ISMRD said "Dr. Cathey, would you like to meet some of the patients?" The ML Project was off to an amazing start!

The first ML Clinic at GGC was held in 2006. Twelve ML families travelled from far and farther to Greenwood, South Carolina. And three years later, they came again, along with new families. In 2009 the ML Project expanded to become what we now call the Longitudinal Studies of the Glycoproteinoses. This is a natural history study of patients with any of the rare disorders included under ISMRD's umbrella. In 2009, ISMRD took the project Down Under allowing us to meet and evaluate patients in New Zealand and Australia.

The Longitudinal Studies received 5 years of support from the National Institutes of Health through the Rare Disease Consortium called the Lysosomal Disease Network. Discoveries in GGC's biochemical and molecular laboratories helped define the Webb type Intermediate ML, distinct clinically and biochemically, associated with a specific gene mutation. Additional support from the National MPS Society and the Yash Gandhi Foundation in 2012 funded research on ML cells. Currently the biochemical laboratory at GGC is leading the field in tandem mass spectrometry analysis of the glycoproteinoses.

GGC has collaborated with ML researchers around the world. Along the way we've presented at professional meetings, published papers, and worked hard to push toward treatment. Talks and posters have been presented at numerous professional meetings including annual meetings of the

American College of Genetics and Genomics, The American Society of Human Genetics, the WORLD meeting, the Southeastern Regional Genetics Group, and the Association of Genetic Technologists. Longitudinal Studies are still open to new patients but lack the funding to bring patients to South Carolina for evaluations. We appreciate the records you gather and send. We want to keep track of you so when treatment comes, we know where to find you!

GGC publications related to ML

- Prenatal mucolipidosis type II (I-cell disease) can present as Pacman dysplasia. Saul RA, Proud V, Taylor HA, Leroy JG, Spranger J. Am J Med Genet A. 2005 Jun 15;135(3):328-32.
- Mucolipidosis II. Leroy JG, Cathey S, Friez MJ. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. 2008 Aug 26 [updated 2012].
- Mucolipidosis II. Leroy JG, Cathey S, Friez MJ. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. 2008 Aug 26 [updated 2012].
- Mucolipidosis III Alpha/Beta. Leroy JG, Cathey SS, Friez MJ. In: Pagon RA, Bird TD, Dolan CR, Stephens K, editors. GeneReviews [Internet]. Seattle (WA): University of Washington, Seattle; 1993-. 2008 Aug 26 [updated 2012].
- Phenotype and genotype in mucolipidoses II and III alpha/beta: a study of 61 probands. Cathey SS, Leroy JG, Wood T, Eaves K, Simensen RJ, Kudo M, Stevenson RE, Friez MJ. J Med Genet. 2010 Jan;47(1):38-48. Epub 2009 Jul 16.
- Towards a selected reaction monitoring mass spectrometry fingerprint approach for the screening of oligosaccharidoses. Sowell J, Wood T. Anal Chim Acta. 2011 Feb 7;686(1-2):102-6.
- Mucolipidosis type III α/β: the first characterization of this rare disease by autopsy. Kerr DA, Memoli VA, Cathey SS, Harris BT. Arch Pathol Lab Med. 2011 Apr;135(4):503-10.
- A novel intermediate mucolipidosis II/III alpha/beta caused by GNPTAB mutations in the cytosolic N-terminal domain. Leroy JG, Sillence D, Wood T, Barnes J, Lebel RR, Friez MJ, Stevenson RE, Steet R, Cathey SS. Eur J Hum Genet. 2014 May;22(5):594-601. Epub 18 Sept 2013.
- Eight years experience from a skeletal dysplasia referral center in a tertiary hospital in Southern India: a model for the diagnosis and treatment of rare diseases in a developing country. Nampoothiri S, Yesodharan D, Sainulabdin G, Narayanan D, Padmanabhan L, Girisha KM, Cathey SS, De Paepe A, Malfait F, Syx D, Hennekam RC, Bonafe L, Unger S, Superti-Furga A. Am J Med Genet A. 2014 Sep;164A(9):2317-23. Epub 2014 Jul 14.
- Outcomes after hematopoietic stem cell transplantation for children with I-cell disease. Lund TC, Cathey SS, Miller WP, Eapen M, Andreansky M, Dvorak CC, Davis JH, Dalal JD, Devine SM, Eames GM, Ferguson WS, Giller RH, He W, Kurtzberg J, Krance R, Katsanis E, Lewis VA, Sahdev I, Orchard PJ. Biol Blood Marrow Transplant. 2014 Nov;20(11):1847-51. Epub 2014 Jul 10.
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- Measurement of Elevated Concentrations of Urine Keratan Sulfate by UPLC-MSMS in Lysosomal Storage Disorders (LSDs): Comparison of Urine Keratan Sulfate Levels in MPS IVA Versus Other LSDs. Ellsworth KA, Pollard LM, Cathey S, Wood T. JIMD Rep. 2016 Jul 28. [Epub ahead of print].
- Measurement of Elevated Concentrations of Urine Keratan Sulfate by UPLC-MSMS in Lysosomal Storage Disorders (LSDs): Comparison of Urine Keratan Sulfate Levels in MPS IVA Versus Other LSDs. Ellsworth KA, Pollard LM, Cathey S, Wood T. JIMD Rep. 2017;34:11-18. doi: 10.1007/8904_2016_1. Epub 2016 Jul 28.