



**national tay-sachs & allied diseases
association**

RESEARCH REVIEW | November 20, 2017

NTSAD Research Updates

Final Report for Research Project

The Hexosaminidase A Variants of Unknown Significance (HAVUS)

This Counsyl–JScreen research project was funded by The Cameron & Hayden Lord Foundation, The Mathew Forbes Romer Foundation, the New York Area of NTSAD, and the NTSAD Research Initiative.

Hexosaminidase A (HexA) enzyme analysis has long been considered the gold standard for Tay-Sachs disease carrier screening. Limitations of the HexA assay have led to increased utilization of DNA testing for carrier screening. DNA-based screens using sequencing technology typically have higher detection rates compared to a genotyping for common mutations, particularly in non-Ashkenazi Jewish populations. However, sequencing raises challenges in the interpretation of variants of unknown significance (VUS).

The goal of this project was to reclassify common *HEXA* VUS to likely benign/benign, thereby conferring a higher



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COMMITTEE OPINION

In March 2017, the American College of Obstetricians and Gynecologists published two Committee Opinions addressing the use of carrier screening panels to test individuals or couples for a number of disease genes at the same time.

The opinions state that expanded carrier screening is an acceptable strategy for carrier testing, and that doctors should offer screening prior to pregnancy to help ensure that at-risk couples have access to a range of reproductive options.

The opinions also emphasize that individuals with positive family histories of genetic disease should be counseled by a

carrier detection rate for sequencing. Eligible subjects were identified because they carried one of the six most common VUS. Four to five unique patient samples were sent for enzyme analysis per VUS. Results from HexA enzyme analysis revealed negative Tay-Sachs carrier states for all subjects, and all 6 variants were reclassified to likely benign/benign. These reclassifications add to the growing public repository of variant interpretations for *HEXA*. Analyses are currently underway to evaluate whether reclassification of these variants leads to an increase in detection rate for a *HEXA* DNA sequencing-based carrier screen. We will have an update for you in the spring. This research will hopefully be a meaningful milestone in the evolution for Tay-Sachs carrier screening from enzyme analysis to sequencing.

genetic counselor or other healthcare professional to ensure that appropriate carrier testing is performed on relatives of affected family members.

These Committee Opinions speak to the progress being made toward helping couples know their risks and plan ahead for the health of their future families.

HISTORY NOTE:

NTSAD played a role in ACOG issuing their position statements and committee opinions on the importance of Tay-Sachs and Canavan carrier screening along with the importance of recognizing the Ashkenazi Panel.

Read the published statements [here](#).

GM1 Patient Insight Network Launch!



Join NTSAD, the Cure GM1 Foundation and be a part of the **GM1 Patient Network [HERE](#)** to accelerate treatment for GM1 Gangliosidosis! The health information of those impacted by GM1 Gangliosidosis is essential to advancing medical research and for drug developers working to translate research to the clinic and to treat patients.

COMING SOON: GM2 Patient Insight Network for Tay-Sachs and Sandhoff

2017 Imagine & Believe: A Conversation with Our Honorees

Words of wisdom from our honorees, David Meeker, MD, and Professor Tim Cox:



- To families: Your participation, your data that you're entering into natural history data banks are the keys that will unlock this challenge. And it will make it go faster. It's hard to see the progress sometimes from the outside. And without your participation, progress can't be made.
- It's important that the community join together "to be big and approachable" to work together with researchers, companies on treatments.
- Other successes (in clinical trials for other diseases) aren't wasted – celebrate them – they will help you get closer to your goals.
- Don't be shy!
- The challenges are great, but we can get there. I believe these diseases will be beaten to a very great extent with combination of tall shoulders, precedence of work, animal models we have, and the sheer desire to do it.

Reflections on 10 years

By Sue Kahn, Executive Director



Our overall goal in research is to direct, fund and promote research to support prevention and develop treatments and cures. This fall marks my 10th anniversary with NTSAD and provides me with an opportunity to highlight some of NTSAD's key research accomplishments and how we've done towards this goal.

- Awarded \$3.4 million and 50 research grants since 2007, which has been leveraged to \$20M in larger grants and many publications moving the field forward
- Process for funding and monitoring research is in place and continually reviewed

- There have been publications and abstracts about the natural history of our diseases and more are in process. NTSAD grants are funding some of this work.
- Starting from discovery in 2007, GM2 gene therapy is now completing IND-enabling studies, i.e., in the home stretch of what needs to be done before initiating clinical trials. In general, gene therapy has been seen as a potentially effective approach for these genetic diseases affecting the central nervous system.
- Clinical trial readiness initiated to establish clinical endpoints and understanding of natural history; resulting publications and abstracts to build this body of knowledge
- Continuing to build relationships with industry, academia to attract expertise and resources to our diseases
- Established Corporate Advisory Council with industry professionals experienced in manufacturing, regulatory and commercialization processes.
- Funding research in carrier screening to support evolution of gold standard from enzyme to sequencing
- Established Annual Day of Hope in 2011 to involve families around the world in raising awareness and funds for research. Since 2011, over \$300,000 has been raised for research.
- The research grant funds have been raised in partnership with key funding partners: Cameron & Hayden Lord Foundation, Mathew Forbes Romer Foundation, Cure Tay-Sachs Foundation, Vera Pesotchinsky Research Fund, Katie & Allied Buryk Research Fund, New York Area of NTSAD.



GLOBAL
LEUKODYSTROPHY
INITIATIVE

On November 15th Sangamo Therapeutics announced that they have treated the first patient in a landmark Phase 1/2 clinical trial evaluating in vivo genome editing for mucopolysaccharidiosis II (MPS II), also known as Hunter Syndrome. The genome editing technology used in this study is zinc finger nuclease (ZFN). This technology, similar to CRISPR, takes advantage of a natural property of DNA in which a specific type of protein called a nuclease acts a sort of scissor to cut DNA. At the cut site, gene editing systems can then introduce a specifically engineered DNA construct. [See January 2016 Research Review on Gene Editing here.](#) In this study, the ZFNs are delivered by adeno-associated viral (AAV) vectors that target the liver and then insert

The 2017 Global Leukodystrophy Initiative Conference on Clinical Trial Readiness in the Leukodystrophies was held in Philadelphia November 8-10th. The attendees consisted of clinicians, researchers, FDA representatives, NIH program officers, and patient advocacy organizations. The topics included: surrogate outcomes and biomarkers, functional outcome measures and natural history studies, preclinical studies for future leukodystrophy therapies, newborn screening and genomics, and clinical trial design in leukodystrophies and other rare

a corrective copy of the iduronate-2-sulfatase (IDS) gene, the gene deficient in MPSII, into a precise location in the DNA of liver cells. The open-label clinical study is designed to assess the safety, tolerability and preliminary efficacy the investigational genome editing therapy in up to nine adult males with MPS II.

Read more [here](#).

diseases. Heather Lau, MD, from NYU and a NTSAD Scientific Advisory Committee member, presented on Canavan Disease based on her grant entitled *Defining the Natural History of Canavan Disease through Development of an International Registry* which is funded by NTSAD and the Canavan Foundation.

You can watch live stream of the 2017 GLIA conference [here](#) (confidential data has been removed).

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