LGMD-1D DNAJB6 Foundation

and International Autosomal Dominant Muscular Dystrophy Registry

and

MYOSYND™

A 501 (C)(3)

The Newsletter 4/2/2021

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Preface

This newsletter is divided into two parts, one for people who have a genetic diagnosis of an autosomal dominant muscular dystrophy (page 3) and the second part (pages 4-9) for people who are searching for the exact genetic diagnosis. The second group likely has or will have a gene panel that shows a "VUS" or Variant of Uncertain Significance. The next steps toward VUS resolution is an important aspect of this edition of the newsletter. You will find the respective links and videos scientifically challenging as I did but try to step back and absorb the general message that advances are occurring quickly.

I try to stay on top of evolving trends in genetic diagnosis and therapy and give them to you in a timely fashion. These leads and links are not an exhaustive analysis of the industry but a good start for you and your medical team.

My disclaimer is that I am not on any industry or other payroll and I do this solely to help everyone who struggles for answers.

William Lowery MD

Annual MDA Virtual Conference:

Breakthroughs in Treatment for

AD Muscular Dystrophy

March 15-18, 2021

Evolving therapy in autosomal dominant neuromuscular disorders:

(very explosive, very technical videos but highly recommended)

Autosomal dominant ALS

COL6A Myopathy

FSHD

LGMDD1

Myotonic Dystrophy Type 1

How Can I Make a Genetic Diagnosis?

A lot of people are stuck with a genetic test which says "VUS" which is a "variant of uncertain significance." This VUS can be a high probability or low probability of causing your symptoms. As time goes by these will be resolved but who has time?

I have collected a list of helpful resources from free to proprietary sources for taking the next steps and their rationale. These have to be discussed with your care team.

First, a genetic muscle weakness can be a disorder (myopathy, muscular dystrophy) with elevated creatinine kinase (CK) and a typical muscle biopsy or a genetic degenerative nerve process called a neuropathic disorder like Charcot Marie Tooth or ALS. These and a host of acquired conditions can look similar and occur spontaneously with or without a genetic cause. This is the challenge.
Finally and to make things more complicated there are genetic mitochondrial disorders, the "powerhouses of the muscle cell" that do not produce power for the muscles.

The Next Step Toward a Genetic Diagnosis

I refer you to Khan Academy for prep courses in genetics if needed. A deeper dive into the depths of gene therapy are found HERE.

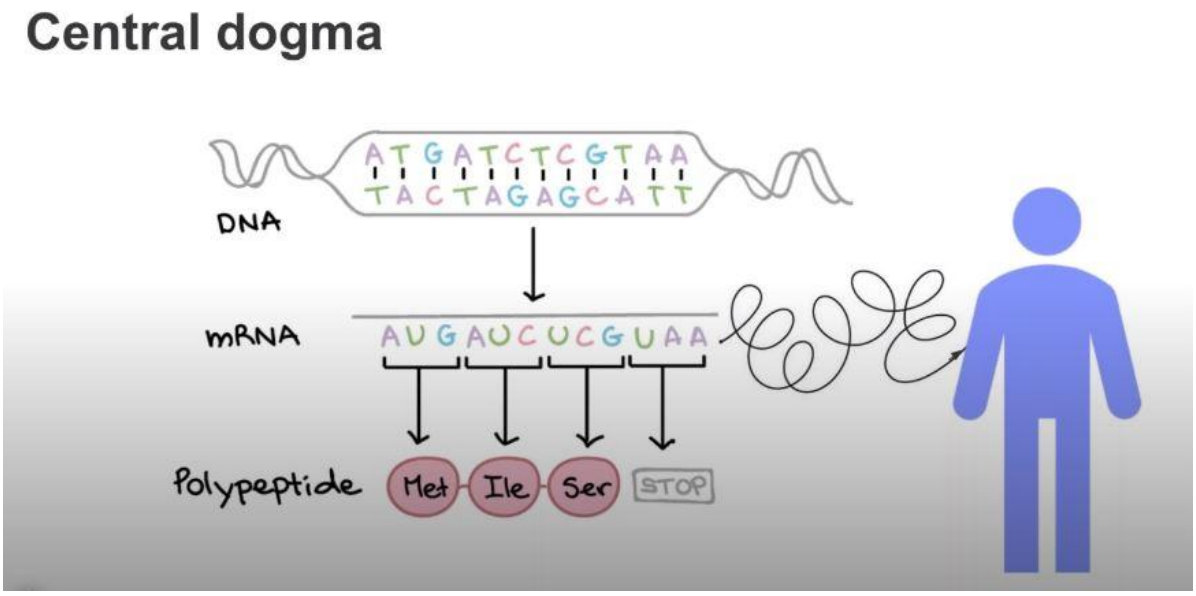
A. Whole Exome Sequencing (WES), your gene panel did not show a definitive diagnosis, the whole exome should be analyzed (the working part of your DNA)

1. WES/ Whole Genome, NIH free program

2. WES DIY, (probably $250)

3. Invitae Whole Exome Analysis , The Video

B. RNA Sequencing:



A "VUS" result in your DNA at a "SPLICE SITE" can ultimately be responsible for a bad mRNA resulting in a bad protein causing your symptoms. Please look at your variant analysis for this detail and share this with your medical team.

Invitae Working on RNA Sequencing

Supplemental RNA Analysis Further Deepens Variant Classification:

While most gene changes associated with a hereditary disease have their effect by directly altering the function of the protein that is specified by that gene, a small fraction of gene changes are known to alter the way messenger RNAs (mRNAs), the blueprints for proteins, are made in the body. A growing area of research has focused on using RNA analysis to help resolve variants of uncertain significance (VUS), particularly those VUS that are predicted to affect mRNA creation, also known as RNA splicing. In order to contribute to this research and further reduce the uncertainty inherent in genetic testing results, Invitae has added supplemental RNA testing for VUS that are predicted to affect RNA splicing and have been identified in a gene from any of our hereditary cancer panels.

Invitae's approach to supplemental RNA analysis, RNA-seq, includes both qualitative (evaluation of abnormal mRNAs) and quantitative (the amount of mRNAs) results, which ultimately provides deeper insight into the variant-disease relationship compared to the use of qualitative results alone.

1. **Invitae RNA Sequencing, The Video**

C. Muscle Biopsy:

This is generally done after genetic panels are not diagnostic. Any VUS gene variant however can give a neuromuscular pathologist a heads up as to which protein in the muscle specimen could be abnormal. It also helps to refer to a neuromuscular pathology center of excellence after a regional hospital has analyzed. I have found this center is such a resource:

Univ of Iowa, special muscle stains:

Director of Neuropathology
Office: 5239B Roy Carver Pavilion
Phone: 319-384-9084

D. Do I Have Mitochondrial Myopathy?

Mitochondria live within all cells and supply power to the cells, their DNA for the most part is separate from the DNA that resides in the nucleus of each cell. Typical gene panels do not look for mitochondrial DNA. WES will pick up nuclear DNA that codes for certain aspects of mitochondria but will not pick up bad intrinsic mitochondrial genes. This is a separate process.

1. **Mitochondrial disorders**

2. **Mitochondrial diagnosis , The Video**

3. **Mitochondrial genetic testing which is separate from conventional gene panels and WES.**

4. **Muscle biopsy can use special stains for diagnosing some mitochondrial disorders.**

MYOSYND™

MYOSYND™ (our "myopathy syndicate") was formed in 2020 as a subsidiary of the foundation to register all persons with autosomal dominant muscular dystrophies, their support persons and associated foundations with similar goals. To date we have 80 individuals and added a new group, the Myofibrillar Myopathy organization. We encourage not only affected individuals but their families and friends to join as one voice since our conditions are not experienced in isolation. Patients may register HERE and support persons HERE .

Sponsored Genetic Testing

As mentioned above we have access to sponsored genetic testing for muscular dystrophy which has been a big hit. To apply please follow this link: FREE MUSCULAR DYSTROPHY GENETIC TESTING HERE

Many doctors are not comfortable ordering genetic tests however we have been able to do this with widespread patient and primary care doctor acceptance. The sponsored testing encompasses many other areas and diseases not specifically in our expertise but we would be willing to assist patients, families and primary care doctors in search for a genetic diagnosis. (Please see this list) Again, this would be a selective process with full consent of a patient and their primary care doctor. Contact us for follow up: wslowery.57@lgmd1d.org

Gene Matchmakers?

Yes, you knew it would only be a matter of time before a "Match.com" site would be available for people and their specific gene variants. Now this isn't a site to post your gene for "blue eyes" and see who else has blue eyes, this is a serious site to post a known gene variant or an uncertain gene variant causing or suspected to cause a certain disease, however rare in hopes of connecting. This has tremendous social and research possibilities but first a genetic test must be done. The research we have done suggests 3 sites for public use:

MyGene2: ready now.

GenomeConnect: ready now.

Rare-X: ready now.

All are very protective of your data and you do not have to reveal any identification. This could be helpful for those persons with one or several "variants of uncertain significance." I have registered on all three.

Giving

1. **OUR WEBSITE** **(a secure site with all the listings below)**
2. **AMAZON SMILE** **(list the LGMD-1D DNAJB6 Foundation for donation with each purchase at no cost to you.)**
3. **PAYPAL** **(Our foundation secure site)**
4. **CREDIT CARD** **(GuideStar charity secure portal)**
5. **VENMO** **(@William-Lowery-24) Foundation Acct (This Venmo account is the Foundation account and not personal)**
6. **Accepting Bitcoin through COINBASE**
7. **If you are over 72 consider a Qualified Charitable Distribution (QCD) from a traditional IRA and lower that dreadful RMD and avoid that higher tax bracket. Also available to Roth IRA participants.**

   RMD calculator HERE, medicare income bracket HERE.
   tax bracket for SS HERE.

Thank you for your support, William Lowery MD