LGMD-1D DNAJB6 Foundation

and International Autosomal Dominant Muscular Dystrophy Registry

and

MYOSYND™

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The Newsletter 7/20/2021

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Preface: The VUS edition

Variants of Uncertain Significance

Muscle weakness at any age can be genetic or acquired. Acquired causes can include diabetes, thyroid disease, autoimmune, a full list is HERE. Genetic causes are likely if common acquired things have been excluded and a family history or genetic testing is suggestive of this disorder. Genetic causes of muscle weakness can be divided into gene variants affecting the nerves or NEUROPATHIES, those gene variants affecting muscle or MYOPATHIES (AKA muscular dystrophy) or MITOCHONDRIAL disorders (see page 8). Your genetic panels may have revealed several variants that show a "VUS" or Variant of Uncertain Significance. The next steps toward VUS resolution is an important aspect of this edition. 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. My disclaimer: I do not receive income from any company. Any clinical decision for your particular case must be between your care team and yourself not based on information listed here.

The Next Steps Toward VUS Resolution

Whole Exome Sequencing (WES):

Two percent of our 23 pairs of chromosomes are responsible for most of the life sustaining proteins and are called exomes. WES looks at these to detect variants causing genetic disorders. Whole genome sequencing looks at every part of your 23 chromosomes whether relevant or not.

Most of you have had gene panels looking at variants specific to muscle and nerve disorders which could result in classic limb girdle muscular dystrophy (LGMD). Those panels are not static; every six months to year the number of new disorders expand. In addition, current VUSs are reclassified and included in new diagnoses of LGMD. Time may solve these issues however a next step for VUS resolution is WES or WGS to expand the search with references listed below. If you have not started with a sponsored gene panel see page 10.

1. Free Genome testing:

NIH: Rare Genomes Project

Harvard: Personal Genome Project

2. Video:

Invitae Whole Exome Analysis

3. Proprietary testing:

WES by Invitae

After watching the video and if you are interested in Invitae WES then there are several ways to finance this. First, insurance can cover in some cases with little or no copay. They have a list of in network plans listed HERE. Invitae has an assistance application HERE. The out of pocket cost is 1,250 dollars; as the video illustrates they stay on top of the science to arrive at an answer. An alternative is to repeat a sponsored panel at least once a year.

The Next Steps Toward VUS Resolution

Muscle Biopsy:

This can be done if genetic panels are not diagnostic. Any VUS gene can give a neuromuscular pathologist a road map to which protein in the muscle specimen they should look for. It also helps to refer to a neuromuscular pathology center of excellence after a regional hospital has analyzed the muscle specimen.

The following is very important if you are considering a muscle biopsy but is very technical.

First, your hospital should be a research or research affiliated hospital with a neuropathologist. The best muscle biopsy is a thigh specimen but deltoid is easier but not as much tissue.

Muscle Biopsy:

Second, ideally 3 specimens of muscle should be obtained for your future diagnosis and therapy. One specimen for your local neuropathologist, one for a national center of excellence in neuropathology (see page 7) if you chose a second opinion, and one for a tissue bank which research centers will likely need to enroll you in a therapeutic trial. I know this sounds complex but it is the best information to date from the experts in the field.

After the biopsy, muscle tissue must be handled properly for all of the above purposes and I have provided instructive links for the doctors overseeing this process. For second opinion and tissue banking muscle tissue needs to be oriented correctly longways, then frozen in -180 degree isopentane to avoid ice crystals in muscle. Then wrap in foil and keep at -80 degrees indefinitely. Place a small piece of muscle in glutaraldehyde if electron microscopy is needed.

Muscle Biopsy:

Neuropathology center of excellence:

Univ of Iowa, Neuropathology Dept.

Iowa muscle specimen handling

Iowa muscle biopsy requisition

Iowa Wellstone Tissue Bank

Practical Guide to Muscle Biopsy

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. Most mitochondrial disorders usually affect several organs including muscle and is an uncommon cause of LGMD.

1. **Mitochondrial disorders**

2. **Video: Mitochondrial diagnosis**

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.**

Mitochondrial Myopathy:

Patients with experience in mitochondrial disorders have forwarded me to these sites specializing in this. UMDF may be offering free testing.

1. **MitoAction**

2. **United Mitochondrial Disease Foundation**

Sponsored Gene Panel Testing

We have access to sponsored genetic testing for muscular dystrophy. To apply please follow this link: FREE MUSCULAR DYSTROPHY GENETIC TESTING HERE We find new genes added every six months and encourage repeat testing on a yearly basis.

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:

GenomeConnect:

Rare-X:

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