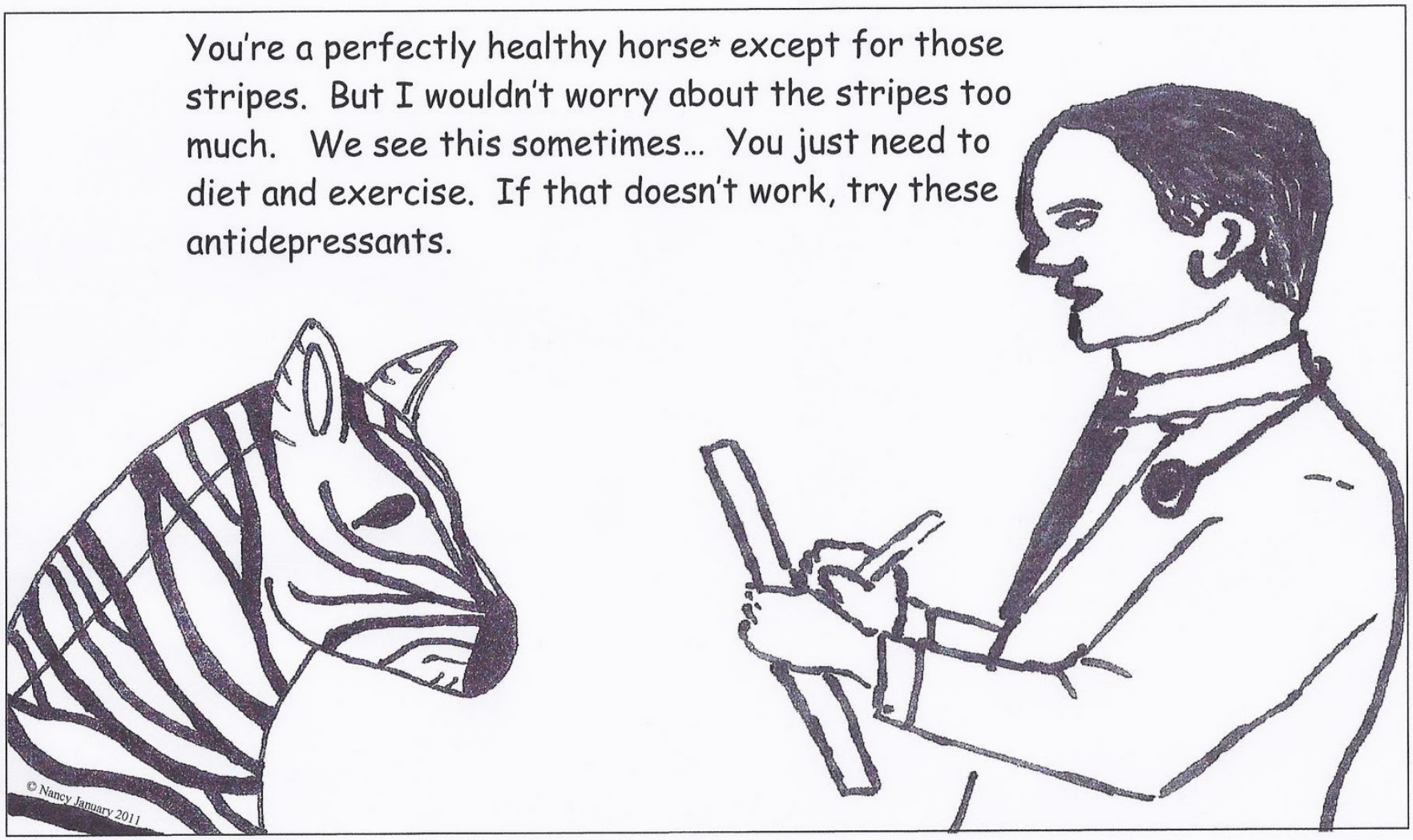
Motor Delay: When to look for zebras

Anamaria Richardson

BC Peds Society

June 23, 2021



*Medical school mantra: *"When you hear hoof beats, think horses, not zebras."* ~~ *Dr. Theodore Woodward*

Conflicts of interest

- None to declare

Who I am professionally

- Used to be a teacher
- Graduated peds UBC 2017
- Worked in Biochemical Diseases as a General Pediatrician 2017-2019
- Run a community based clinic (Granville Pediatrics and Family Medicine with a NP Partner)
- General Pediatrician for RICHER and the Jaw Clinic
- Provide community pediatrics at Lu'ma Medical Clinic
- Qualified Specialist for autism assessments at BCAAN
- Sessional work in Neuropsychiatry at BCCH
- Multiple research projects looking at improving health outcomes for children with behavioural complexity
- Sit at numerous tables and advocacy committees and groups
- Taking a year of sabbatical at UBC starting in August as a Wall Scholar

Objectives

1. Identify signs and symptoms of Pompe (metabolic myopathy) and have a differential
2. Develop an approach to weakness in infancy
3. Describe the different tests which are available to arrive at a diagnosis of patients who have weakness
4. Order a simple gene panel available to community pediatricians and understand how to interpret results

**pediatrician's perspective (not a neurologist, not a metabolisist/ geneticist)

Case 1: Marjorie

- 2 month old referred to your clinic for murmur auscultated in ED with febrile illness
- Seen in clinic, murmur II/VI SEM, pansystolic
- Echo identified large ASD, requiring surgical correction, but stable (monitor)
- Continue to follow
  - 4months: no concerns
  - 6months: not rolling, not flexing hips to lift legs
  - 8months: not rolling, not flexing hips to lift legs

Case 2: Peter

- 5 month old referred to your clinic for left metatarsus adductus
- No other major concerns
- Refer to Orthopedics and follow up in a few months
- Seen again in clinic at 7 months, decreased energy following viral URI, FTT, weak (stopped rolling)
- Seen at 9 month (could not hold head up) for US abdomen that incidentally identified hypertrophic cardiomyopathy

Definitions

Weakness:

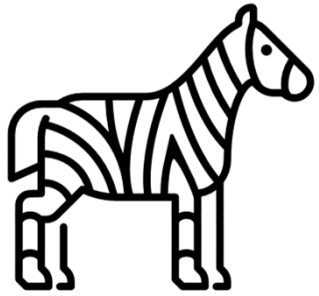
Maximum voluntary resistance to movement

- generally points to a peripheral cause
- Head lag
- DTR absent
- Reduced antigravity movements

Hypotonia:

Resistance to passive movement

- generally points to a central cause
- Limbs retain antigravity movements
- May have head lag
- DTR present



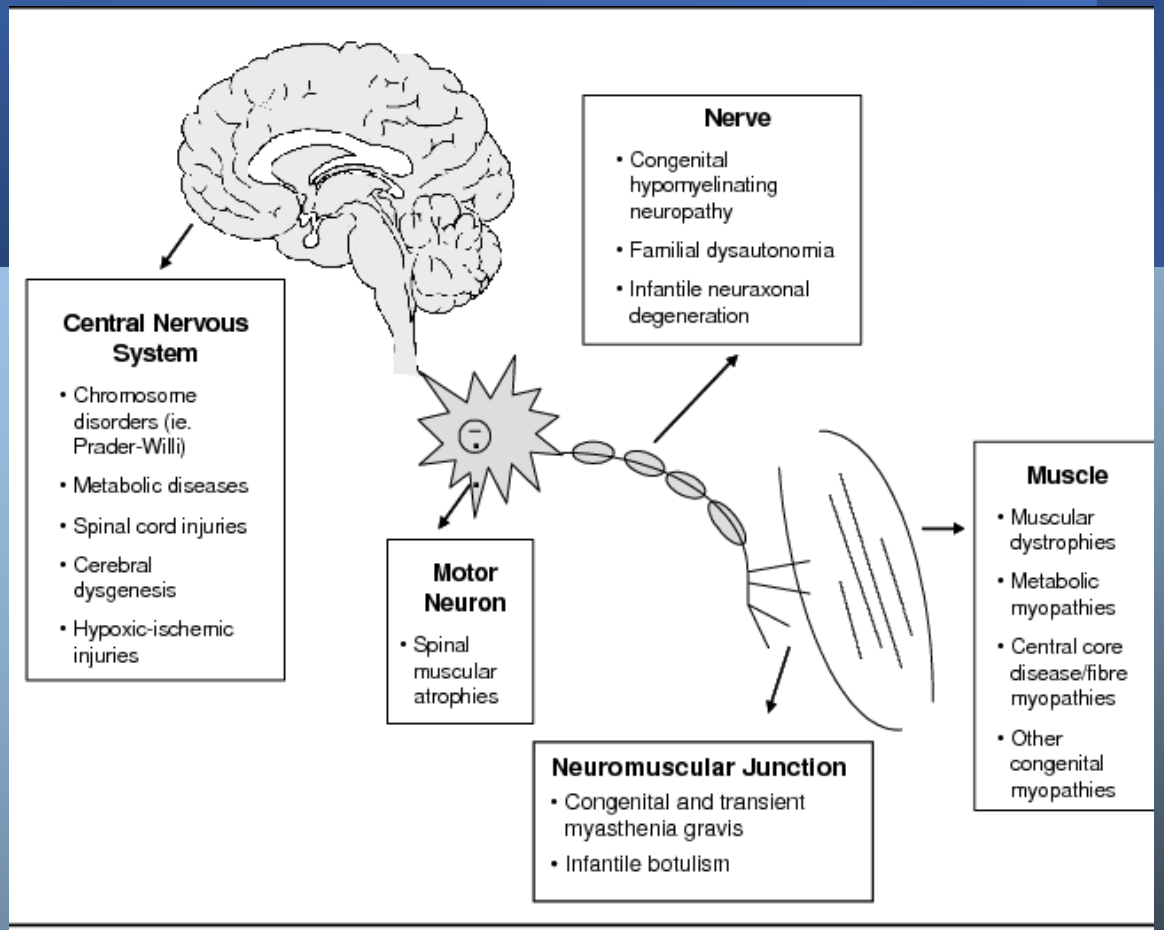


Figure 1) *Anatomical-clinical correlation illustrating differential diag*
nosis of hypotonia in infancy

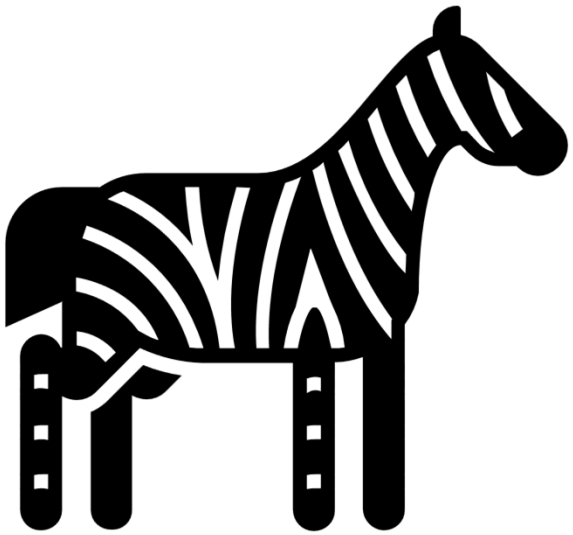
https://pubmed.ncbi.nlm.nih.gov/19668647/

Neurological Examination:

Objective – Localize the lesion.

Cranial nerves: Extraocular movements? Muscles of facial expression? Fasciculations of tongue?
Tone: Posture? Horizontal and vertical suspension? *Scissoring or spasticity?*
Strength: Proximal versus distal weakness? Symmetry?
Reflexes: *Hyperactive?* Symmetry? Readily elicited? *Clonus?*
Muscles: Atrophy? Symmetry?

	Motor Neuron	Nerve	NM Junction	Muscle
Tone*	↓	↓	normal/↓	↓
Strength	↓	↓	normal/↓	↓
Reflexes	absent	absent	normal/↓	absent/↓
Muscle Atrophy	↓	↓	normal/↓	normal/↓

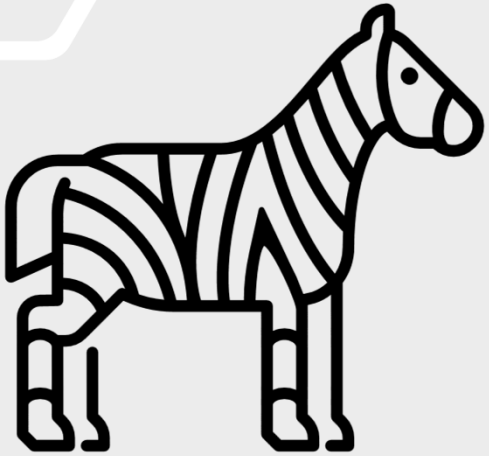


Differential (not exhaustive)

- Unwell infant: consider infection
- Genetic syndromes: T21, PWD, T18, T13, skeletal dysplasias
- IEM: CDG, carnitine pathway, GSD, OA, Peroxisomal, UCD, creatine
- Endo: thyroid
- 1o Neuromuscular
- Cerebral palsy

Considerations on exam

- Assess strength and tone
- Reflexes: hyperreflexia (UMN) versus hyporeflexia (neuropathic/ myopathic)
- Facial features: hypotonic facies (cupid's bow)
- Tongue fasciculations: SMA, plus others
- Cry/ suck/ swallow



STARTS PEDS PREP

GET AN INBORN ERROR OF METABOLISM QUESTION

The metabolic emergency

General Clinical Situations

General information

In the neonate, the early clinical features of acute metabolic decompensation are almost always non-specific; they include “unwell”, lethargy, feeding problems, vomiting, abnormal breathing, hypotonia and seizures. Disorders of glucose, protein and fat breakdown (intermediary metabolism) in the neonatal period typically have an asymptomatic interval, with clinical manifestations from the second day of life onwards (“intoxication type”), although hyperammonaemia in particular may already present on day 1. The baby's general condition will usually deteriorate rapidly despite normal or non-specific findings in routine investigations (laboratory signs of infection, lumbar puncture, chest X-ray, cranial ultrasound) and antibiotic therapy. The family history may reveal siblings who died with similar clinical manifestations (“sepsis”, “SIDS”) or unexplained disorders in other family members (progressive neurological disease, maternal PKU, multiple miscarriages, HELLP syndrome, etc.). Consanguinity increases the risk of a recessive disorder.

Metabolic disorders **after the neonatal period** may present with recurrent vomiting and lethargy progressing to coma without focal neurological signs or typical patterns of organ dysfunction. Initial management may follow similar principles as in neonates. Care must be taken to identify the conditions that triggered metabolic decompensation such as vomiting and fever or changes in the diet.

A metabolic disorder should be considered, along with other diagnoses (e.g. infection, CNS pathology) ...
… in all neonates with unexplained, overwhelming or progressive disease particularly after normal pregnancy and birth
… in all children with acute deterioration of the general condition and/or reduced consciousness, particularly when preceded by vomiting, fever or fasting
… in all children with symptoms and signs of acidosis or hypoglycaemia

Appropriate diagnostic and therapeutic measures must be initiated as soon as possible to avoid long-term damage.

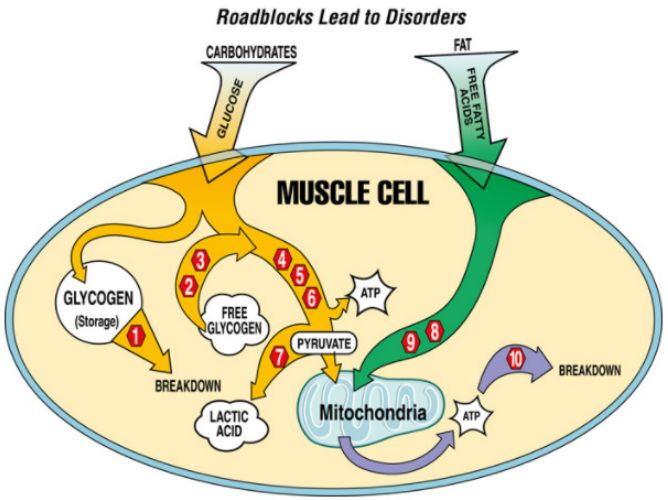
Post-mortem investigations: See link.

Phase 1: Basic metabolic emergency investigations & first line management

Stop intake of potentially toxic compounds (protein, fat, galactose, fructose)

Insert i.v. line and take blood samples for urgent analysis of:
- Electrolytes, glucose, CRP, CK, ALT, AST, creatinine, urea, uric acid, acid-base status, coagulation studies
- Ammonia, lactate
- Store plasma sample for amino acids, acylcarnitines etc.
- Store filter paper card (“Guthrie” card for newborn screening) with dried blood spots for acylcarnitines (amino acids, possibly DNA studies)
- Store the rest of the other samples for possible additional tests (inform laboratory)

Obtain urine sample:
- Check colour and odour
- Perform standard stix tests (e.g. ketone bodies, glucose, protein; pH > 5 during acidosis → DD renal tubular acidosis)
- Store urine sample from the acute phase for organic acids or additional metabolic tests



IEM = MVC

When enzymes don't work well, you have two issues:

1. Not enough product
2. Too much substrate builds up

Slide 15

RA[1 Richardson, Anamaria [CWBC], 6/22/2021

Metabolic Myopathy

Usual presentation:	Many metabolic myopathies, but only a few have treatment
• MIXED picture, hypotonia and weakness, with poor muscle mass • CARDIOMYOPATHY common presentation • Progressive	• Carnitine transporter defects • FAOD • mitochondrial • GSD2

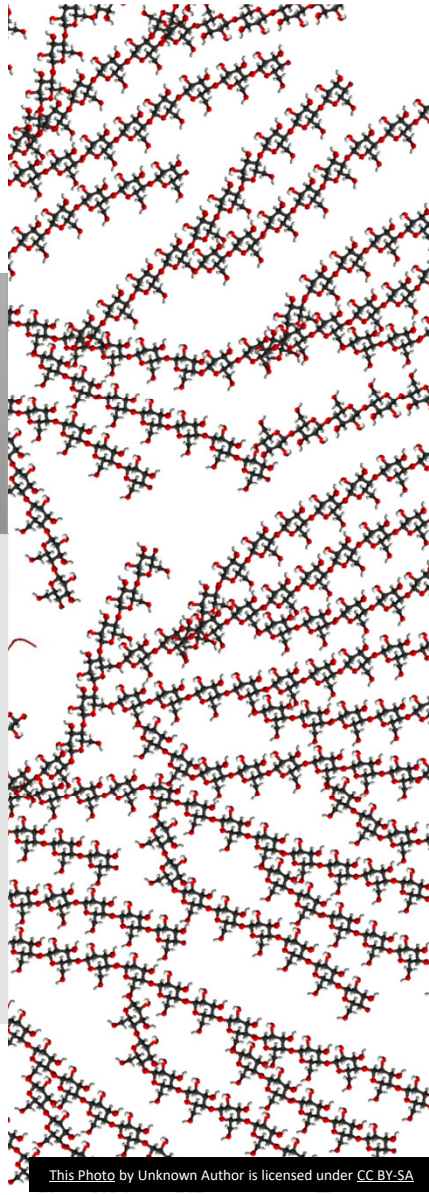
Metabolic Myopathy

Issue in converting fuel (carbs/ fats) into energy (ATP)

- Mitochondrial
- Lipid metabolism (CPT I/II, FAOD,
- Glycogen metabolism (glycolysis, glycogenolysis, glycogenesis)

Some clues

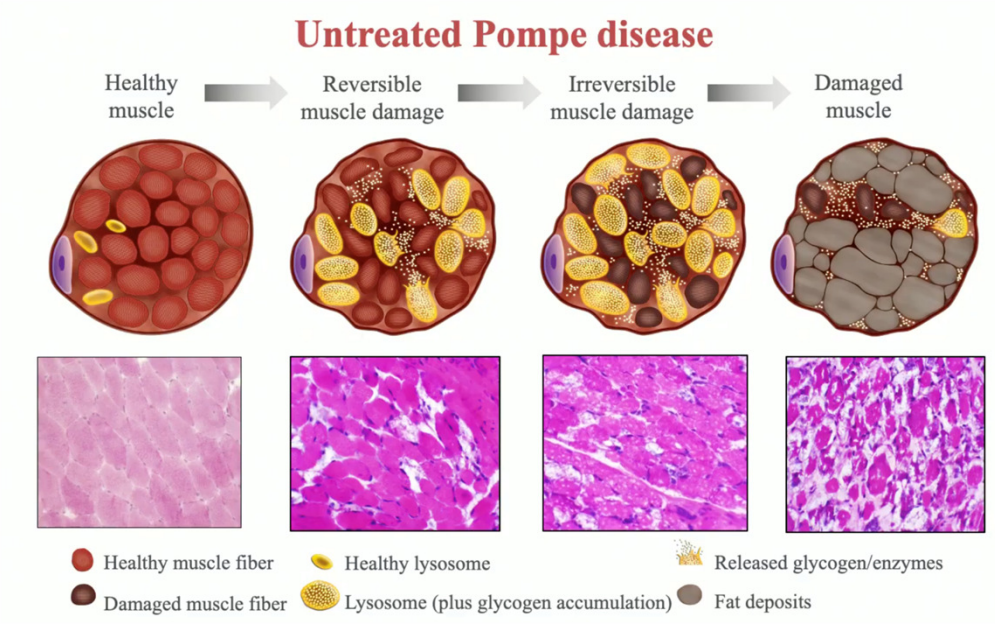
- Exercise intolerance + second wind phenomena
- Cramping
- Cardiac issues
- Rhabdomyolysis



Pompe

Acid maltase deficiency = acid alpha glucosidase deficiency
Glycogen Storage Disease II (GSDII)
Lysosomal Storage Disease (LSD)

- Infantile Onset Pompe (IOPD)
  - <1year
- Late onset (LOPD)
  - 1 year OR no cardiac involvement



Al Jasmi *et al. BMC Neurology* (2015) 15:205
DOI 10.1186/s12883-015-0412-3

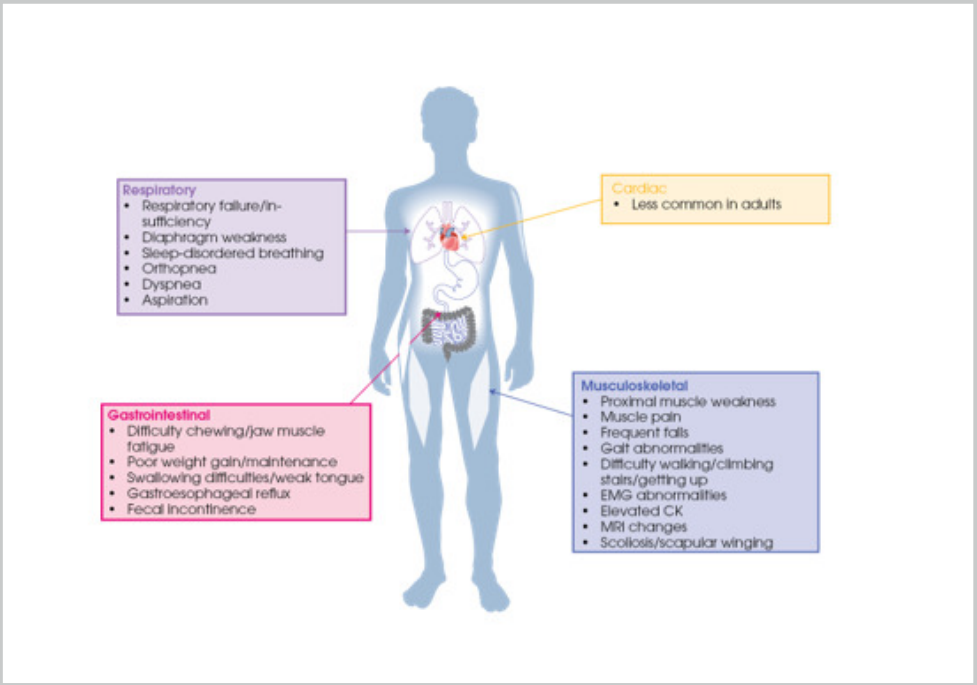
BMC Neurology

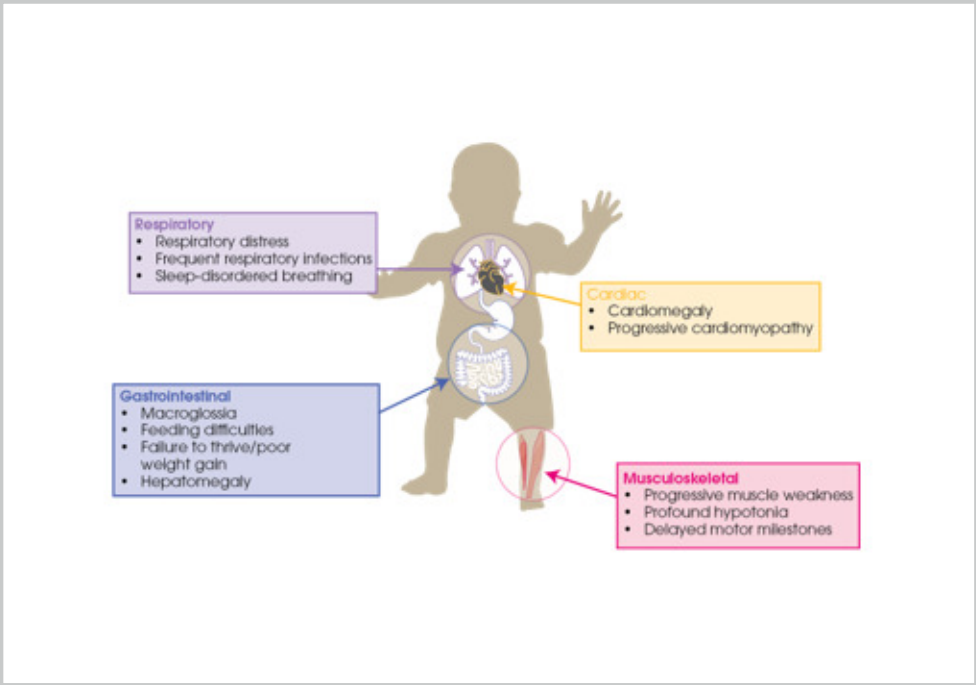
CORRESPONDENCE Open Access

Diagnosis and treatment of late-onset Pompe disease in the Middle East and North Africa region: consensus recommendations from an expert group

The MENA Pompe Working Group, Fatma Al Jasmi[1], Mohammed Al Jumah[2,3], Fatimah Alqarni[4], Nouriya Al-Sanna'a[5], Fawziah Al-Sharif[6], Saeed Bohlega[7], Edward J. Cupler[8*], Waseem Fathalla[9], Mohamed A. Hamdan[10], Nawal Makhseed[11], Shahriar Nafissi[12], Yalda Nilipour[13], Laila Selim[14], Nuri Shembesh[15], Rawda Sunbul[16] and Seyed Hassan Tonekaboni[17]

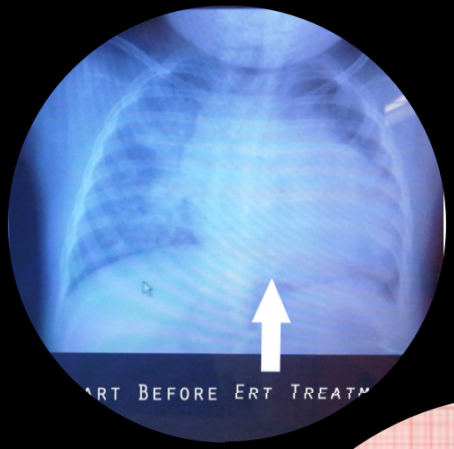
Pompe - features

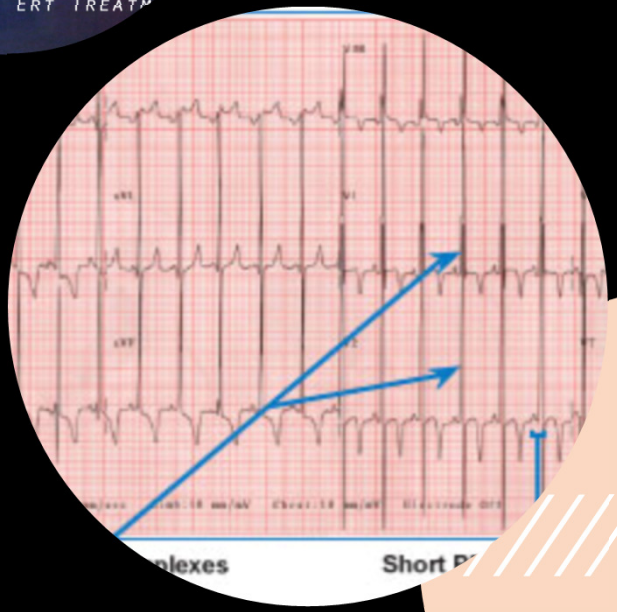




Peter…

- Rapid assessment by cardiology revealed massive cardiomyopathy
- Pathognomonic ECG
- Peter was connected with biochemical diseases, admitted, and work up diagnosed him with IOPD





Work up for weakness in clinic

- CK, LDH, AST (muscle)
- Renal
- Lactate (mitochondrial),
- Acylcarnitine profile (FAOD, carnitine defects)
- UOA
- Acid alpha glucosidase (dried blood spot/ DBS)
- Chromosome microarray (+/- PWD)
- Spinal muscular atrophy
- Consider a gene panel

Genetic sequencing

Sanger Sequencing:

- Developed in the 1970s
- Revolutionary technology
- still used to answer specific questions

Next Generation Sequencing:

"massively parallel sequencing reactions"

- Fast = not cost prohibitive

- Whole genome sequencing (WGS)
- Whole exome sequencing (WES)
- TRIO (parents and child)
- Targeted sequencing (gene panels)

Sherbrooke Genomic Medicine Muscle Disorder Panel

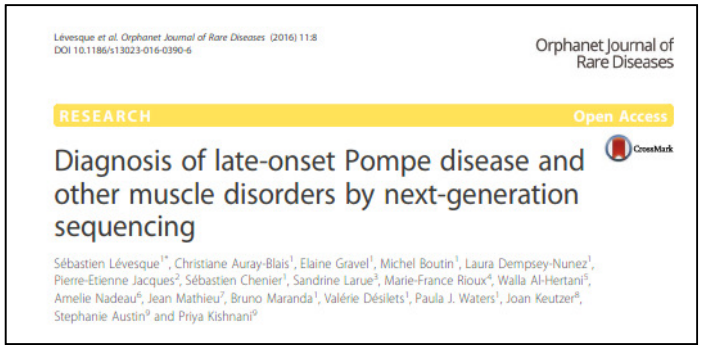
The Genomic Medicine Group at Sherbrooke University offers a platform to facilitate the differential diagnosis of a multitude of genetic neuromuscular diseases

91 gene muscle disorder panel tests for muscular dystrophies, myopathies and myasthenia syndromes showing various muscle weakness patterns. It includes the following groups of disorders:

• Congenital muscular dystrophies	• Congenital myopathies (Nemaline, myofibrillar, centronucealr, collagene 6)	• Congenital Myasthenic Syndromes
• Rigid spine syndromes	• Inclusion myopathies	Muscular dystrophies with predominant limb-girdle weakness patterns
• Scapuloperoneal Syndromes	• Metabolic myopathies	

The Sherbrooke Genomic Medicine Muscle Disorder Panel

Canadian Panel Publication in Orphanet Journal of Rare Diseases 2016



Lévesque et al. Orphanet Journal of Rare Diseases (2016) 11:8
DOI 10.1186/s13023-016-0390-6

Orphanet Journal of Rare Diseases

RESEARCH Open Access

Diagnosis of late-onset Pompe disease and other muscle disorders by next-generation sequencing

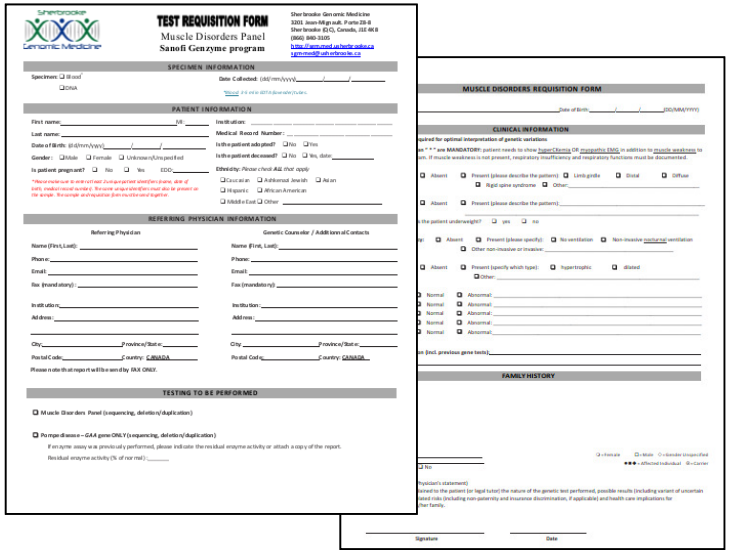
Sébastien Lévesque[1*], Christiane Auray-Blais[1], Elaine Gravel[1], Michel Boutin[1], Laura Dempsey-Nunez[1], Pierre-Etienne Jacques[2], Sébastien Chenier[1], Sandrine Larue[3], Marie-France Rioux[4], Walla Al-Hertani[5], Amelie Nadeau[6], Jean Mathieu[7], Bruno Maranda[1], Valérie Désilets[1], Paula J. Waters[1], Joan Keutzer[8], Stephanie Austin[9] and Priya Kishnani[9]

Panel is commercially available to clinicians.

Requisition and DNA sample is sent to Sherbrooke Genomics for Next Generation Sequencing analysis.

Results are provided within 6- 8 weeks

Interpretation and consultation is available to clinicians



TEST REQUISITION FORM
Muscle Disorders Panel
Sanofi Genzyme program

SPECIMEN INFORMATION

PATIENT INFORMATION

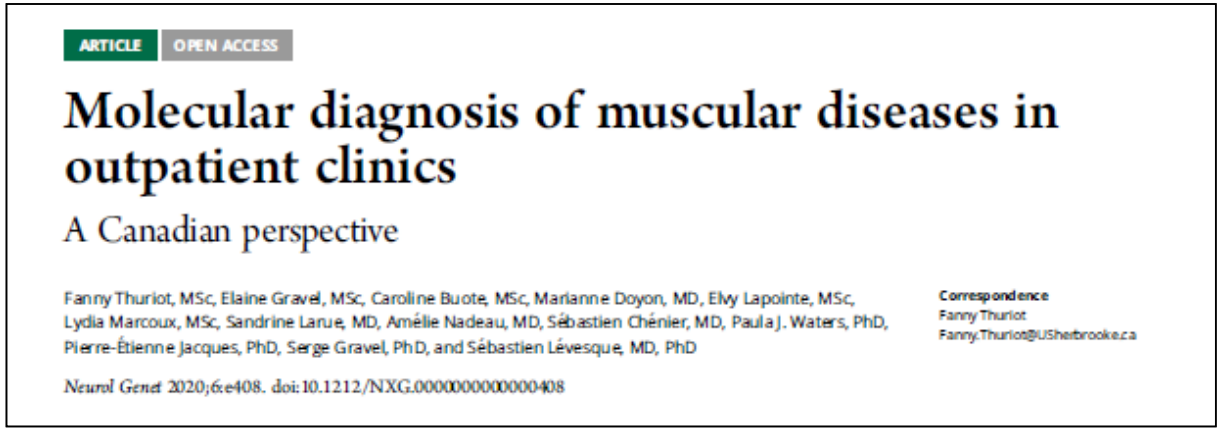
REFERRING PHYSICIAN INFORMATION

TESTING TO BE PERFORMED

MUSCLE DISORDERS REQUISITION FORM

CLINICAL INFORMATION

FAMILY HISTORY



ARTICLE OPEN ACCESS

Molecular diagnosis of muscular diseases in outpatient clinics

A Canadian perspective

Fanny Thuriot, MSc, Elaine Gravel, MSc, Caroline Buote, MSc, Marianne Doyon, MD, Elvy Lapointe, MSc, Lydia Marcoux, MSc, Sandrine Larue, MD, Amélie Nadeau, MD, Sébastien Chénier, MD, Paula J. Waters, PhD, Pierre-Étienne Jacques, PhD, Serge Gravel, PhD, and Sébastien Lévesque, MD, PhD

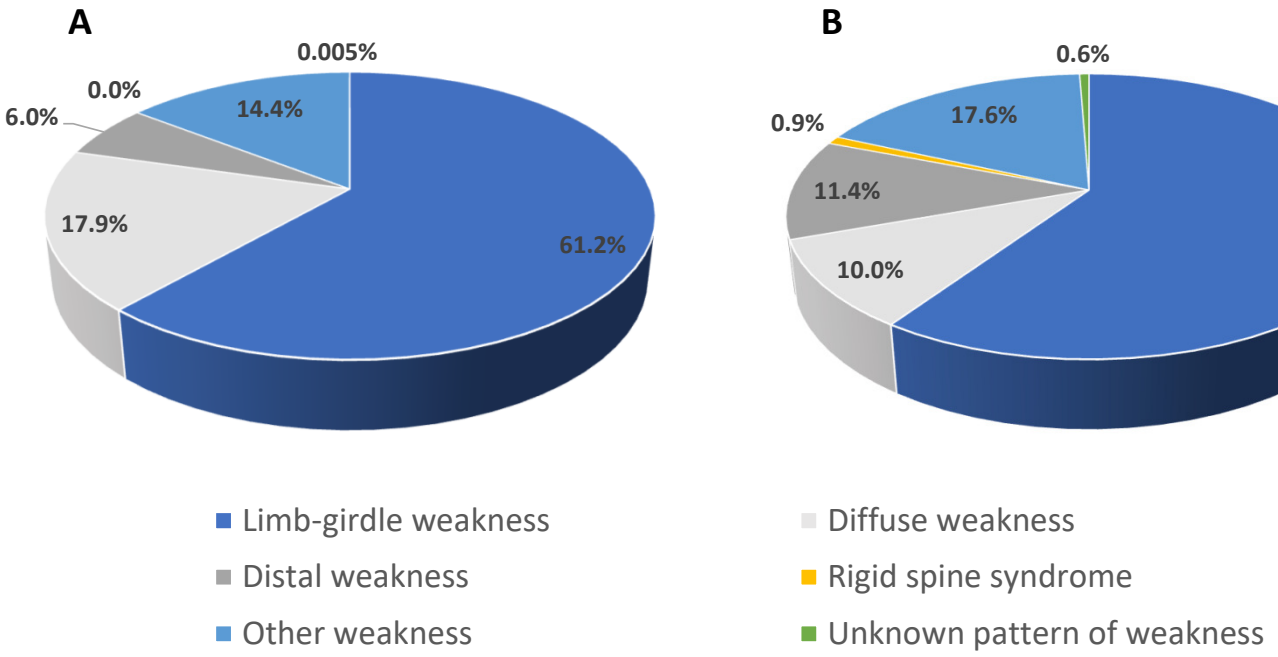
Correspondence
Fanny Thuriot
Fanny.Thuriot@USherbrooke.ca

Neurol Genet 2020;6:e408. doi:10.1212/NXG.0000000000000408

- **Objective:** To evaluate the diagnostic yield of an 89-gene panel in a large cohort of patients with suspected muscle disorders

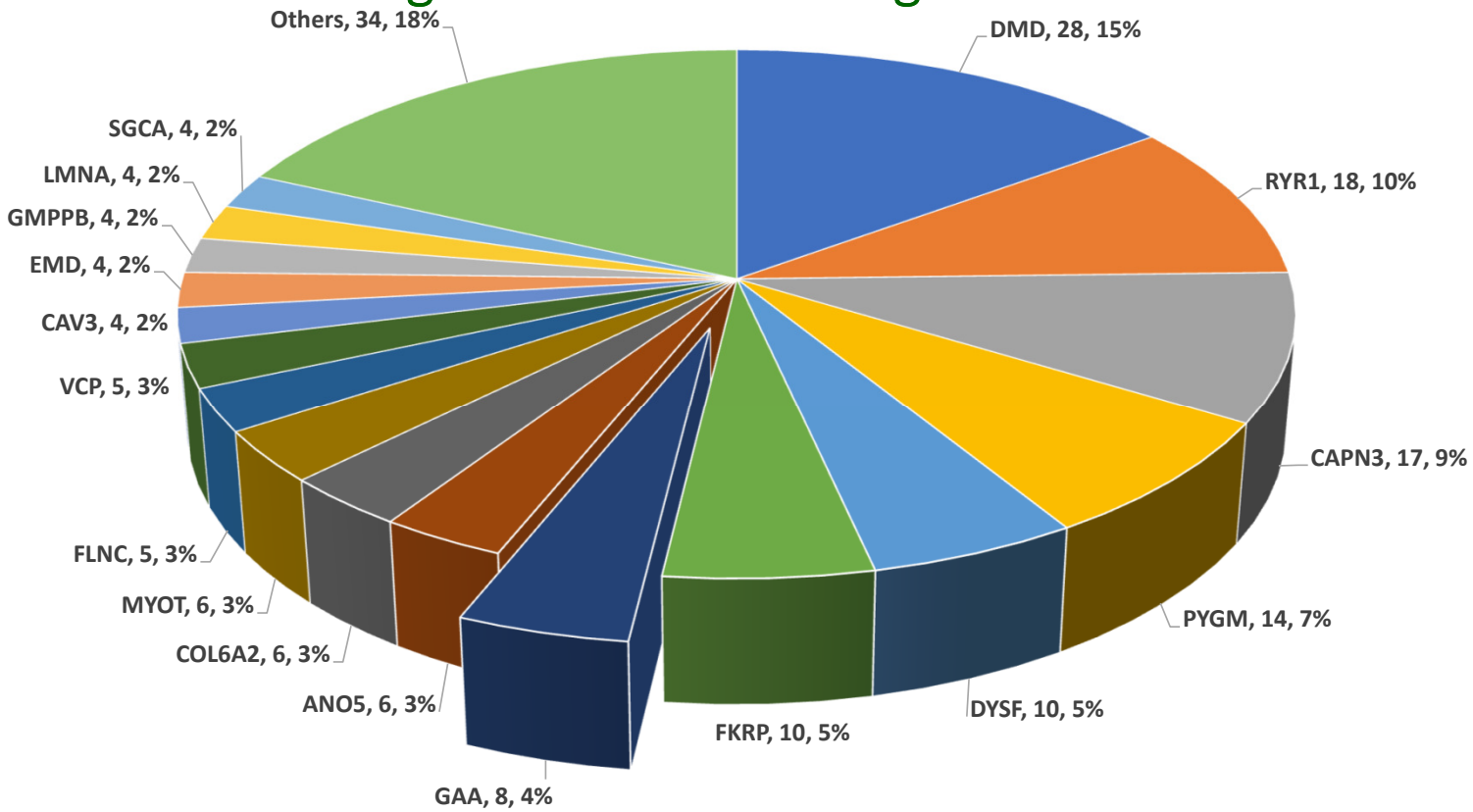
Thuriot, Fanny, et al. "Molecular diagnosis of muscular diseases in outpatient clinics: A Canadian perspective." *Neurology Genetics* 6.2 (2020).

Clinical Presentation of Pediatric (A) (n=201) and Adult (B) patients (n=1035)



Thuriot, Fanny, et al. "Molecular diagnosis of muscular diseases in outpatient clinics: A Canadian perspective." *Neurology Genetics* 6.2 (2020).

Causative Genes Among 187 Confirmed Diagnoses



35 different Genes
7 Genes account for ≈50%
15 GENS with single Cases (others)

Adapted from Thuriot, Fanny, et al. "Molecular diagnosis of muscular diseases in outpatient clinics: A Canadian perspective." *Neurology Genetics* 6.2 (2020).

ACCESSING the Sherbrooke Genomic Medicine Muscle Disorder Panel

This Muscle Disorders Panel test is available free of charge

PATIENT CRITERIA REQUIRED FOR FREE ACCESS:
1. Muscle Weakness + hyperCKemia or myopathic EMG or abnormal MRI or Muscle Biopsy
OR
2. Documented respiratory insufficiency + hyperCKemia or myopathic EMG or abnormal MRI or Muscle Biopsy
OR
3. Other Symptom(s) supporting muscle involvement (i.e. exercise intolerance, rhabdomyolysis, myalgia) + hyperCKemia or myopathic EMG or abnormal MRI or Muscle Biopsy

DBS must be ordered in parallel or documentation must be provided if already performed

Case 1. Marjorie

Sherbrooke Genomic Medicine

Molecular Analysis Report

Sherbrooke Genomic Medicine
3201 Jean-Mignault, Porte Z8-8
Sherbrooke (QC) J1E 4K8, Canada
(866) 840-3105
http://sgm.med.usherbrooke.ca/
sgm-med@USherbrooke.ca

TEST PERFORMED: Muscle disorders: Next generation sequencing of the complete coding sequences and splice site junctions of 91 genes causing muscle disorders (see appendix for complete genes list).

INDICATION FOR TESTING: confirm diagnosis - patient diagnostic assistance program

RESULT : NO established or likely molecular cause of patient phenotype was identified. Variants of uncertain clinical significance have been identified. No exon deletion or duplication was detected.

ESTABLISHED OR LIKELY PATHOGENIC VARIANTS:
None

VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

Autosomal dominant disorders
1-LMNA (NM_170707.3): heterozygous, c.1196G>A (p.Arg399His) (hg19 = chr1:156106043, dbSNP = rs267607563), uncertain significance.

Autosomal recessive disorders
2-TRIM32 (NM_012210.3): heterozygous, c.943G>A (p.Ala315Thr) (hg19 = chr9:119460964, dbSNP = rs770328940), uncertain significance.

3-MYPN (NM_032578.3): heterozygous, c.2802T>A (p.His934Gln) (hg19 = chr10:69948760, dbSNP = rs752426180), uncertain significance.

RESULT : NO established or likely molecular cause of patient phenotype was identified. Variants of uncertain clinical significance have been identified. No exon deletion or duplication was detected.

ESTABLISHED OR LIKELY PATHOGENIC VARIANTS:
None

VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE

Autosomal dominant disorders
1-LMNA (NM_170707.3): heterozygous, c.1196G>A (p.Arg399His) (hg19 = chr1:156106043, dbSNP = rs267607563), uncertain significance.

Autosomal recessive disorders
2-TRIM32 (NM_012210.3): heterozygous, c.943G>A (p.Ala315Thr) (hg19 = chr9:119460964, dbSNP = rs770328940), uncertain significance.

3-MYPN (NM_032578.3): heterozygous, c.2802T>A (p.His934Gln) (hg19 = chr10:69948760, dbSNP = rs752426180), uncertain significance.

4-ITGA7 (NM_002206.2): heterozygous, c.859C>A (p.Arg287Ser) (hg19 = chr12:56092633, dbSNP = .), uncertain significance.

X-linked disorders
None

Understanding Variants

Autosomal dominant disorders

1-LMNA (NM_170707.3): heterozygous, c.1196G>A (p.Arg399His) (hg19 = chr1:156106043, dbSNP = rs267607563), uncertain significance.

INTERPRETATION:

An established or likely molecular cause of the patient phenotype was NOT identified. Noteworthy, we identified a heterozygous variant of uncertain clinical significance in the gene LMNA known to be associated with dominant disorders. Clinical correlation is recommended. Please see recommendation below. We identified 3 heterozygous variants of uncertain clinical significance in genes (mentionned above) known to cause recessive disorders, but a second variation was not found in any of them. All exons and splice site junctions of these genes were covered at >20X and no exon deletion or duplication was detected.

Additional comments on variants of uncertain clinical significance are provided in the section below.

RECOMMENDATIONS:

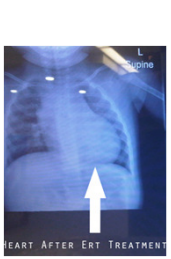
Analysis of parental DNA (if available) is needed to determine if the variant of uncertain significance in LMNA (autosomal dominant) is inherited or de novo. This may help to reclassify the variant, along with additional clinical information. Although we did not observe exon deletions or duplications, consider ruling out this possibility by an alternative method (MLPA, exon array) given the limitations of NGS technology (for additional details, please refer to the section "supplementary information on test methodology"). Genetic counselling is recommended.

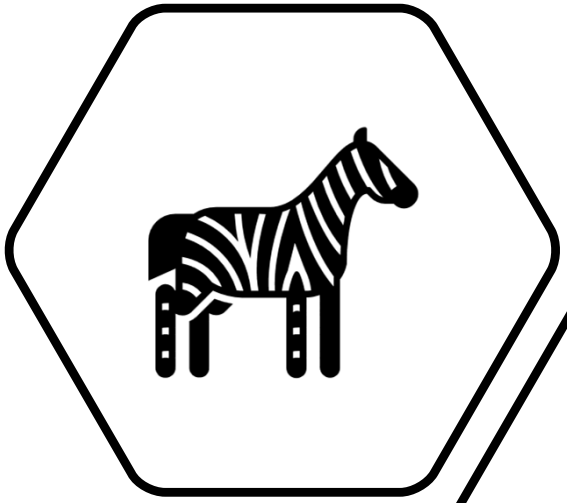
ADDITIONAL COMMENTS ON VARIANTS OF UNCERTAIN CLINICAL SIGNIFICANCE:

LMNA (NM_170707.3) : Heterozygous mutations in this gene are known to cause Autosomal dominant limb-girdle muscular dystrophy type 1B (LGMD1B; autosomal dominant). LGMD1B is a laminopathy and limb girdle muscular dystrophy that is characterized by progressive limb girdle weakness, usually affecting the pelvic girdle before humeral muscles, mild joint contractures, atrioventricular cardiac conduction disturbances and dilated cardiomyopathy. There is considerable phenotypic overlap with autosomal dominant Emery-Dreifuss (AD-EDMD) caused by LMNA mutations. In addition, mutations in LMNA are known to cause a variety of other disorders, collectively known laminopathies encompassing neuromuscular and cardiac disorders, lipodystrophy syndromes, and premature aging. The prevalence is estimated to 1-9 / 1 000 000 (Source: www.orpha.net; Orpha#264; OMIM#159001). The heterozygous variation c.1196G>A (p.Arg399His) has been reported previously in the ClinVar database (uncertain significance, rs267607563). This variant has been reported in two probands with insulin-resistant diabetes and/or lipodystrophy in the heterozygous state (Caron et al., 2007, PMID:17612587; Decaudain et al., 2007, PMID:17711925). Experimental studies have shown that this missense change disrupts interactions between lamin A and a subset of its binding partners, and that fibroblasts derived from an individual with this variant exhibit abnormal nuclear morphology (Dittmer et al., 2014, PMID:24623722; Caron et al., 2007, PMID:17612587). This variant has been reported in the Exome Aggregation Consortium (ExAC), for a population frequency of 4.118e-05. It results in an amino acid substitution. Most bioinformatic tools predict that the amino acid change is tolerated and likely does not alter protein function (MutationTaster = neutral, Sift = tolerated, Polyphen2 = possibly damaging, and LRT = neutral). The GeneDx laboratory has reported in the ClinVar database that they identified this variant in the homozygous state in a presumably healthy individual referred for genetic testing. In summary, the current evidence is insufficient to determine the role of this variant in disease. Therefore, it has been classified as of uncertain significance.

Peter…

- Peter was started on enzyme replacement therapy (ERT) – Myozyme – receiving infusions every other week
- 4 years later…
  - He's walking and getting ready for kindergarten
  - LVMI is within normal limits





Marjorie…

- Referred to neuromuscular, followed in clinic
- Diagnosis of Limb Girdle Muscular Dystrophy (LGMD) established by gene panel
- Is getting ready for pre-school!

Take home points

- Please consider Pompe when working up a child up for weakness or
  - (“DBS for Pompe” is what you write on the requisition)
  - Life expectancy (pre-Myozyme) is around 12-24months, the earlier you treat the better the outcomes
- If you would have ordered a TIDE screen, consider ordering a targeted gene panel
  - There’s a few out there
  - Now have buccal swabs, so easy to use at home (even in telehealth situation)