No pain, no gain: a case of exercise-induced rhabdomyolysis

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Case presentation

- A 26 year old male presented to neuromuscular clinic for further evaluation of hyperCKemia and possible myopathy.

- During childhood, he had 2 episodes of muscle stiffness:
  - Generalized stiffness during a hospitalization for a respiratory infection at age 2.
  - Brief, mild stiffness of his upper extremities following water rafting at age 10.

- He reported having had an extensive neurogenetic workup, including muscle and skin biopsies with no conclusive diagnosis.

- Otherwise, he was asymptomatic in childhood and had remained very active throughout his life.
- During routine checks, he would have elevated CK and transaminases.
- He denied episodes of myalgia or dark urine.

- Past medical history: as above
- Past surgical history: right shoulder arthroscopy 2012
- Medications: none
- Allergies: NKA
- Family history: Dementia, stroke; no h/o NM disease
- Social history: works as a landman- oil and gas; social alcohol consumption, no tobacco or illicit drug use
- ROS: fatigue, anxiety
- Neurologic exam: unremarkable

Initial diagnostic testing

- Lab studies: Pyruvate, lactic acid, acylcarnitine, free fatty acids, urine organic acids, plasma amino acids, and transaminases (GGT, AST, ALT) all unremarkable
  - CK persistently elevated: **3580** at initial visit; **448** when checked 1 month later
- EMG/NCV
- Unable to obtain previous biopsy slides from childhood

Motor Nerve Conduction:

Nerve and Site	Lat ms	Amp mV	Segment	Dist mm	Lat Diff ms	CV m/s
Median.R to Abductor pollicis brevis (C8-T1).R						
Wrist	3.2	13.4	Abductor pollicis brevis (C8-T1)-Wrist	70	3.2	
Elbow	7.3	11.8	Wrist-Elbow	245	4.1	60
Tibial.R to Abductor hallucis (S1-S2).R						
Ankle	4.3	20.0	Abductor hallucis (S1-S2)-Ankle	90	4.3	

Nerve	M-Lat ms	F-Lat ms	F-Lat Nl ≤ ms
Tibial.R	4.3	46.3	56.0

Sensory and Mixed Nerve Conduction:

Nerve and Site	Onset Lat ms	Peak Lat ms	Amp µV	Segment	Dist mm	CV m/s
Median.R to Digit II (index finger).R						
Wrist	2.4	3.1	44	Wrist-Digit II (index finger)	130	54
				Wrist-Digit II (index finger)	130	54
Sural.R to Ankle.R						
Lower leg	2.8	3.5	19	Ankle-Lower leg	140	50

Needle EMG Examination:

Muscle	Insertion Activity	Spontaneous Activity				Volutional MUAPs					
		Fibs	PSW	Fasc	Other	Poly	Amp	Dur	Rate	Pattern	Effort
Tibialis anterior (L4-L5).R	Normal	0	0	0		None	Normal	Normal	Normal	Normal	Normal
Vastus lateralis (L2-L4).R	Normal	0	0	0		None	Normal	Normal	Normal	Normal	Normal
Iliopsoas (L3-L4).R	Normal	0	0	0		None	Normal	Normal	Normal	Normal	Normal
Biceps brachii (C5-C6).R	Normal	0	0	0		Few	Normal	Normal	Normal	Normal	Normal

Follow-up

- 6 months later, he experienced severe low back pain after an intense cross-fit exercise workout.
  - PCP prescribed pain and steroid medications.
  - That evening he developed dark urine, for which he presented to the ED, and was admitted and treated for rhabdomyolysis.

- CK trend:

Day 1	Day 2	Day 3	Day 4	Day 5
48,303	55,196	**68,762**	29,279	6,439

What would you do next?

- Repeat muscle biopsy?
- Genetic testing?
- Liver US?
- Non-ischemic forearm exercise test?

Genetic testing

Myopathy/Rhabdomyolysis

Myopathy/Rhabdomyolysis Panel by Massively Parallel Sequencing (BCM-MitomeNGS℠)

Overall Results Summary

74533-2247746

A heterozygous deletion involving the entire exon 18 of the LPIN1 gene and a heterozygous novel variant of uncertain significance, c.1535+4_1535+7delAGTA, in the LPIN1 gene, were detected.

Pathogenic Variant(s)/ Mutation(s)

Gene	Inheritance	OMIM	Change	Location	Zygosity	Reference(s) / Comment(s)
LPIN1	AR	605518	c.2295-865_2410-30del (p.E766_S838del)	exon 18	heterozygous	PMID: 20583302

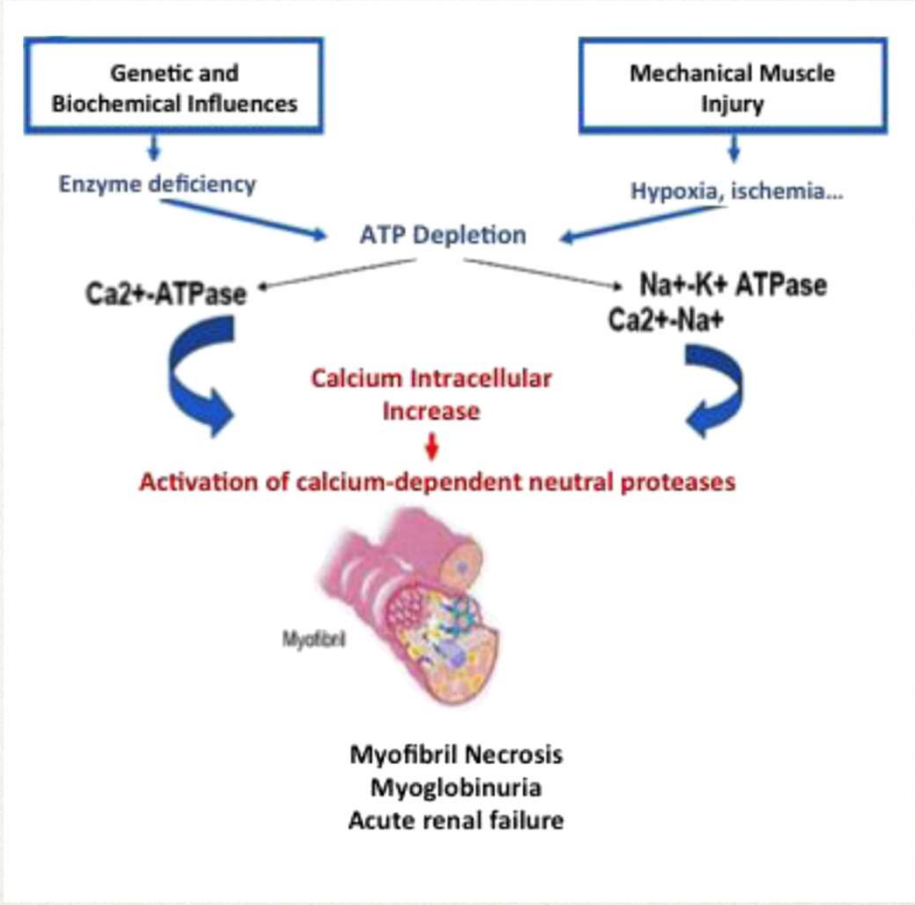
Variant(s) of Uncertain Significance

Gene	Inheritance	OMIM	Change	Location	Zygosity	Reference(s) / Comment(s)
LPIN1	AR	605518	c.1535+4_1535+7delAGTA	intron 10	heterozygous	uncertain significance

LPIN1 mutation

Recurrent rhabdomyolysis

- Acquired vs. hereditary
  - Metabolic with failure of energy production (**mitochondrial FAO defects**, inborn errors of glycogenolysis and glycolysis)
  - Structural (muscular dystrophies, myopathies)
  - Problems with calcium pump (*RYR1* mutation)
  - Inflammatory (myositis)
- Approximately half of patients <u>will not show</u> a defect in these pathways

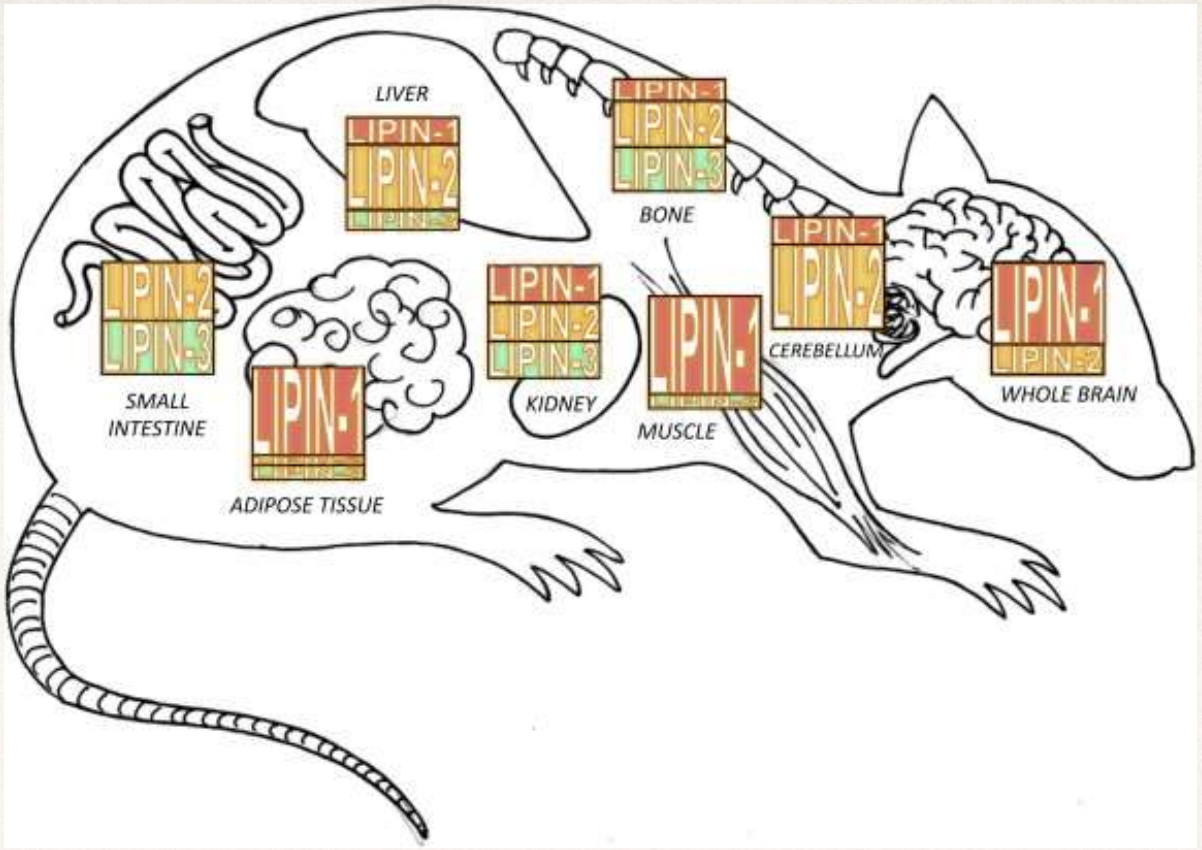


Hamel et al., J Inherit Metab Dis (2015)
Zeharia et al., Am J Hum Genet (2008)

LPIN1 mutations in mice

- >20 years ago: *LPIN1* mutations described in mice
  - Fatty liver dystrophy, peripheral neuropathy (lipin-1 expression in epineurium, endoneurium, perineurium)
  - Insulin resistance, severe hypertriglyceridemia
  - Overexpression of lipin-1 in transgenic mice caused obesity

Reue et al., FEBS Letters (2008)



- Mammalian lipin family: Lipin-1, Lipin-2, Lipin-3
  - *LPIN2*: Majeed syndrome- chronic recurrent multifocal osteomyelitis and congenital dyserythropoeitic anemia
  - *LPIN3*: Not known to cause human disease

Csaki et al., Prog in Lip Res (2013)

Michot et al., J Inherit Metab Dis (2012)

LPIN1 mutations in humans

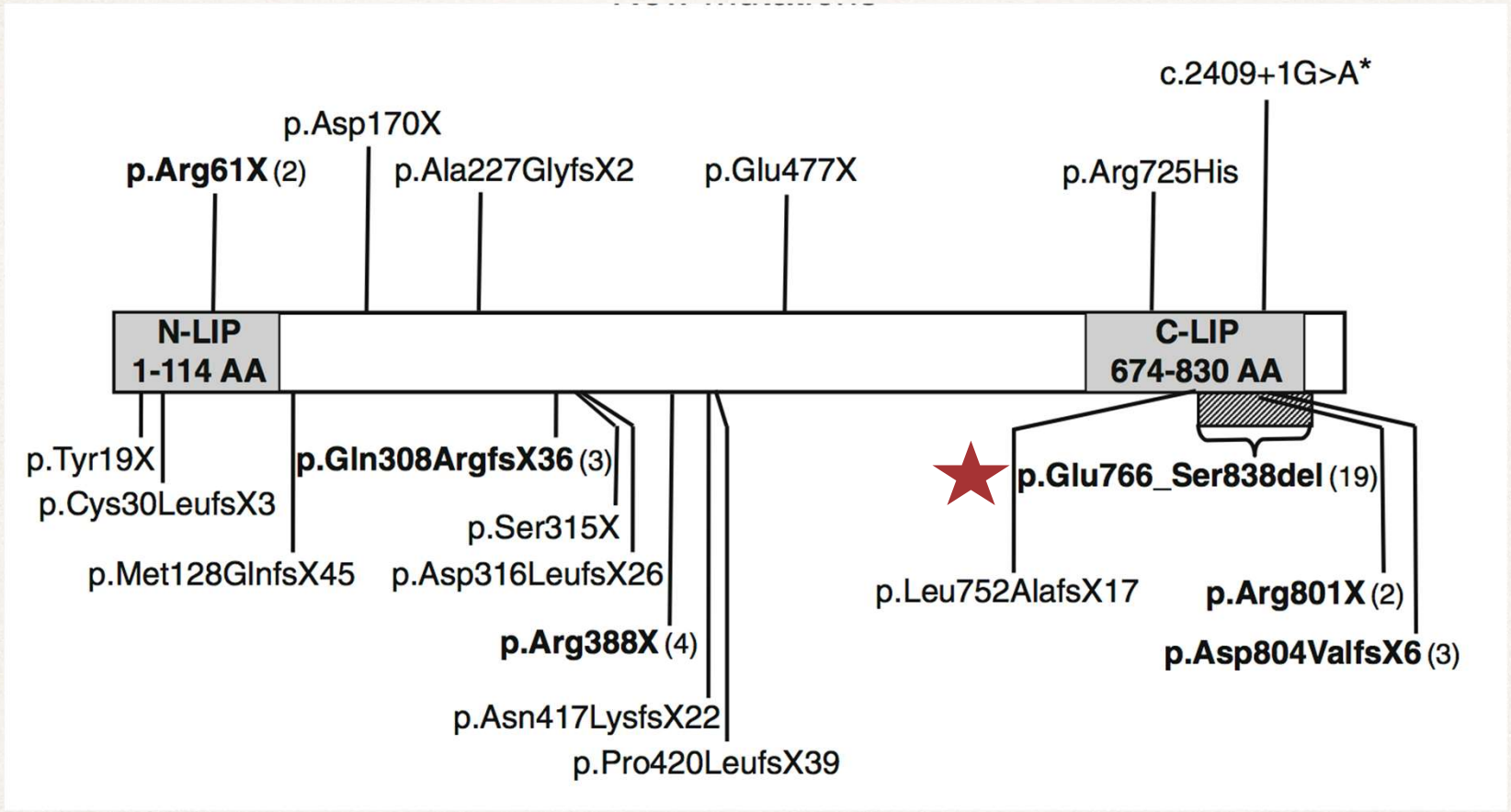
- Zeharia et al. (2008)
  - Pediatric patients (n= 3) w/ life-threatening episodes of rhabdomyolysis; mutations in *LPIN1* gene (early stop codon)
  - Additional 22 pediatric patients w/ recurrent rhabdomyolysis; identified 5 additional *LPIN1* mutations
  - Healthy in between episodes; normal fat distribution, lipid profile, glucose (including during episodes)
- Michot et al. (2010, 2012)
  - 29 pediatric patients w/ severe episodes of rhabdomyolysis in infancy
    - 59% cohort lipin-1 deficient (recessive nonsense or frameshift mutations, large-scale deletion)
  - No defects of *LPIN2*, *LIPN3* genes a/w muscular manifestations

Lipin-1 deficiency

- Autosomal recessive
- *LPIN1* mutations 2nd MCC of early-onset recurrent rhabdomyolysis (after FAO defects)
- Rhabdomyolysis episodes usually began before age 6
- MC triggers: febrile illness > prolonged exercise, fasting, anesthesia
- Lipin-1 expressed most in adipocytes and skeletal muscle

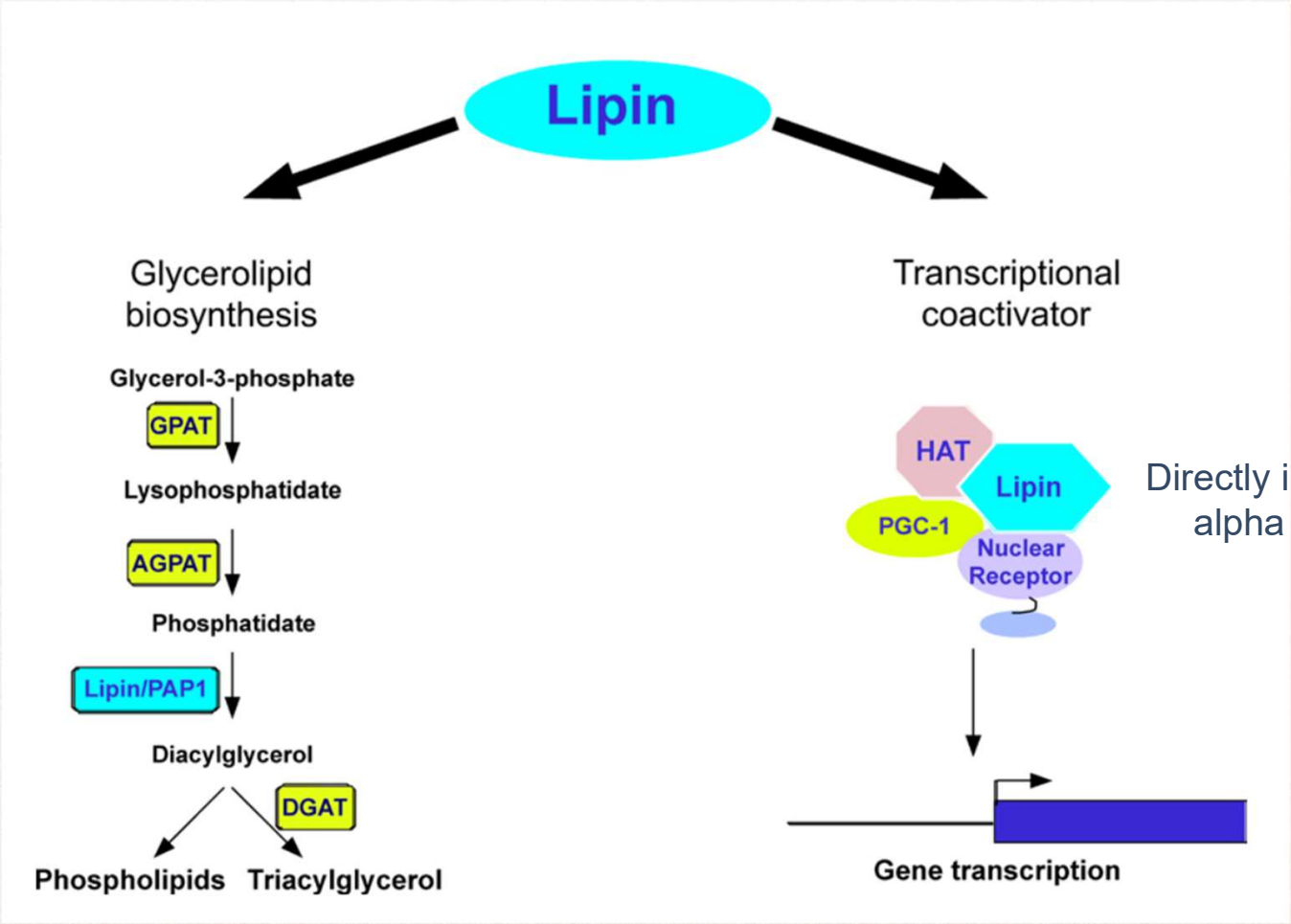
Pathogenic mechanism of *LPIN1* mutation causing rhabdomyolysis uncertain

Michot et al., J Inherit Metab Dis (2012)



Michot et al., J Inherit Metab Dis (2012)

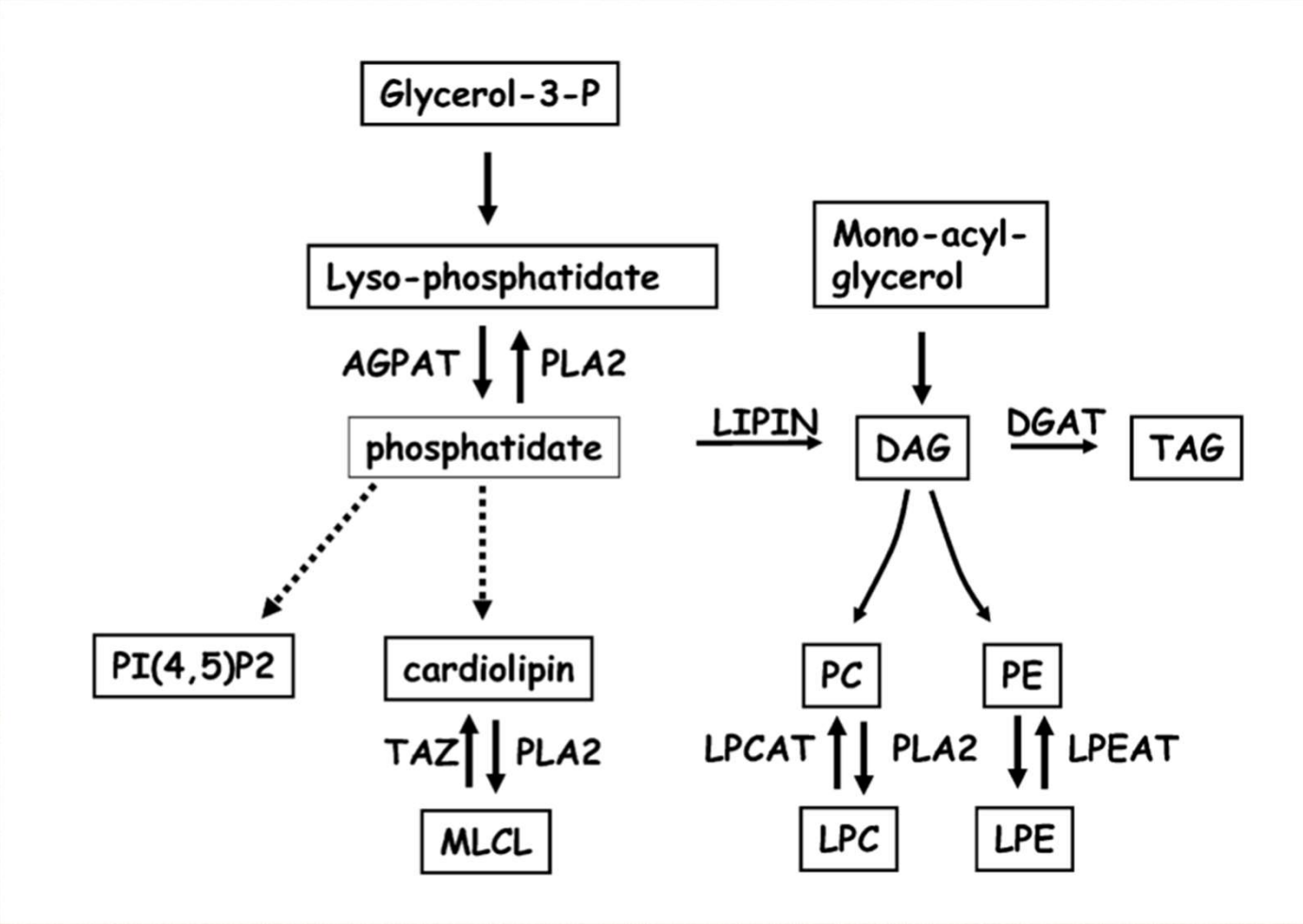
Dual role of lipin-1



Directly interacts w/PPAR-alpha & PGC-1alpha

Reue et al., FEBS Letters (2008)

Triglyceride and phospholipid pathway



Zeharia et al., Am J Hum Genet (2008)

Potential treatment strategies

Symptomatic management

- Early detection
- Hyperhydration
- High energy intake from carbohydrates
- Monitoring for complications: hyperkalemia (cardiac monitoring), hypocalcemia, hepatic inflammation; acute renal failure due to myoglobinuria (late)

Meijer et al., Mol Genet Metab Rep (2015)

Establishing anabolism

- Pichler et al. (2015), proposed treatment with high-concentration glucose solution for prevention and early treatment of catabolism to improve prognosis in lipin-1 deficient patients
- Hyperhydration using 3 L/m2/day of 10% glucose (+NaCl, KCl)
- Reduced duration of rhabdomyolysis from 7-10 days (reported in literature) to 5 days (CK <10,000)

Decreasing inflammation

- Catabolic stress (febrile illness, exercise) creates pro-inflammatory state
- High levels of circulating pro-inflammatory mediators chemokines, cytokines (TNF1-alpha, IL-1beta)—> exacerbate lipin-1 deficiency
- Dexamethasone (PGC-1alpha inducer) stimulates lipin-1 expression in adipose and liver, decreases inflammation
- Meijer et al. (2015) used dexamethasone, in addition to standard protocol
  - 4 y/o with *LPIN1* mutation and severe clinical course
  - For 2 episodes: dexamethasone 0.6 mg/kg q24 hours (with 1 & 4 repeated doses, respectively)
  - Lower peak CK levels, well-tolerated

Summary

- Lipin-1 deficiency is an autosomal recessive disorder, common cause for recurrent rhabdomyolysis with onset in childhood
- Lipin-1 most commonly expressed in skeletal muscle, adipocytes; role in TAG and phospholipid metabolism, mitochondrial energy pathway
- Potential treatment strategies to reduce severity and duration of rhabdomyolysis episodes include
  - High concentration glucose solution (anabolism)
  - Dexamethasone (stimulates lipin-1 expression, anti-inflammatory)

Resources

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Pichler K, Scholl-Buergi S, Birnbacher R, et al. A novel therapeutic approach for *LPIN1* mutation-associated rhabdomyolysis- The Austrian experience. Muscle Nerve. 2015;52:437-439.

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