Detection of compound heterozygous variants in LPIN1 does not necessarily imply pathogenicity in a patient with rhabdomyolysis [version 1; peer review: 4 approved]

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Abstract
In a recent article by Yim et al., a 15-month-old male is described who experienced severe rhabdomyolysis with a creatine-kinase value (CKV) of 127494 U/l one day after intramuscular injection of an unidentified drug by the general practitioner. Rhabdomyolysis was not attributed to this injected drug but to compound heterozygous variants in LPIN1. The study has a number of shortcomings. Triggers of rhabdomyolysis should be unequivocally identified, a more extensive family history should be taken, and previous CKVs should be provided. Functional and biochemical tests should be carried out to confirm or exclude pathogenicity of the LPIN1 variants.

Keywords
LPIN1, rhabdomyolysis, myoglobinurea, renal insufficiency, genetics

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| version 1 | ✓ | ✓ | ✓ | ✓ |
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Any reports and responses or comments on the article can be found at the end of the article.
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In a recent article, Yim et al. reported a 15-month-old male who experienced severe rhabdomyolysis with a creatine-kinase value (CKV) of 127494 U/l one day after intramuscular injection of an unidentified drug by the general practitioner (GP)1. Rhabdomyolysis was not attributed to this injection but to compound heterozygous variants in LPIN11. Each of the parents carried one of these variants but was clinically unaffected1. This correspondence article provides reasonings as to why the detection of heterozygous variants in LPIN1 does not necessarily imply pathogenicity in this case.

Rhabdomyolysis may not only occur in mitochondrial disorders (beta-oxidation defects are mitochondrial disorders) and glycogenoses, but more frequently in response to drugs or toxins2. Thus, it is crucial to find out which drug the GP injected one day prior to admission, not only to identify the compound, but also to ensure that other patients were not exposed to any hazardous risks due to a possibly toxic drug.

Since the variant c.1949_1967dupGTGTCACCACGCAGTACCA was classified as likely pathogenic, the variant c.2410G>C as a variant of unknown significance, and since one parent each carried one of either variants, it is conceivable that the parent who carried the variant c.1949_1967dupGTGTCACCACGCAGTACCA also had experienced muscle manifestations previously. However, the family history is described as negative for rhabdomyolysis, malignant hyperthermia, or neuromuscular disorders making the pathogenicity of this variant quite unlikely. However, an extended family history should also be taken from the grandparents from the mother’s and father’s side to assess if they ever experienced any muscle symptoms.

Since LPIN1 variants have been previously reported in association with recurrent rhabdomyolysis3,4, it is quite likely that the index patient or one of the parents had elevated CKVs. Thus, the records of the index patient or the parent who carried the likely pathogenic LPIN1 variant should be checked to see if these individuals ever showed elevated CKVs. Of particular interest are CKVs after birth, exercise, infection, anaesthesia, or application of drugs. This is because CKV may particularly increase with these conditions. Since the younger sister of the index patient also carried the compound heterozygous LPIN1 variants, we should be informed about the course of the mother’s pregnancy with this younger child, about the sister’s CKVs at birth and later, and further follow-up, including genetic counselling.

In the case report1, the patient has a second episode of rhabdomyolysis at the age of six years. Current medication the index patient was taking at the time of this second episode should be examined, and also if the cause could have been triggered by exercise5. A male of 6 years of age most likely is lively and usually highly physically active.

Overall, this interesting case report has some limitations, which should be addressed before attributing rhabdomyolysis to the LPIN1 variants. Triggers of rhabdomyolysis should be unequivocally identified, a more extensive family history taken, and previous CKVs provided. Functional and biochemical tests should be carried out to confirm or exclude pathogenicity attributed to LPIN1 variants.

Data availability

No data is associated with this article.

References

1. Yim SW, Chan TVC, Belaramani KM, et al.: Case Report: The first probable Hong Kong Chinese case of LPIN1-related acute recurrent rhabdomyolysis in a boy with two novel variants [version 1; peer review: 2 approved]. F1000Res. 2019; 8: 1566. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

2. Cervellin G, Comelli I, Benatti M, et al.: Non-traumatic rhabdomyolysis: Background, laboratory features, and acute clinical management. Clin Biochem. 2017; 50(12): 666–662. [PubMed Abstract] [Publisher Full Text]

3. Meijer IA, Sasarman F, Mathei C, et al.: LPIN1 deficiency with severe recurrent rhabdomyolysis and persistent elevation of creatine kinase levels due to chromosome 2 maternal isodisomy. Mol Genet Metab Rep. 2015; 5: 85–88. [PubMed Abstract] [Publisher Full Text] [Free Full Text]

4. Bergounioux J, Brassier A, Rambaud C, et al.: Fatal rhabdomyolysis in 2 children with LPIN1 mutations. J Pediatr. 2012; 160(6): 1052–4. [PubMed Abstract] [Publisher Full Text]

5. Rausa J, Shetty I, Loomba RS: Troponin elevation in the setting of exercise-induced rhabdomyolysis in an athletic teenager. Cardiol Young. 2019; 3: 1–4. [PubMed Abstract] [Publisher Full Text]
I have read with interest the correspondence from Josef Finsterer and Rahim Aliyev entitled “Detection of compound heterozygous variants in LPIN1 does not necessarily imply pathogenicity in a patient with rhabdomyolysis”.

I agree that in the article by Yim et al. the triggers of rhabdomyolysis have not been clearly determined and discussed. More importantly, the drug that was injected before the first episode of rhabdomyolysis was not specified so it is not possible to exclude that it triggered the episode. The identification of the trigger is crucial as it can guide the process of the differential diagnosis (Quinlivan R and Jungbluth H, 2012).

Yim et al. do not clearly state what type of genetic testing was performed in the patient, i.e. rhabdomyolysis panel, exome, or genome sequencing. This is important to understand what other genetic causes of recurrent rhabdomyolysis have been excluded in the patient, especially given the fact that a muscle biopsy was not performed.

In heterozygous carriers, LPIN1 mutation can cause cramps, myalgia and can trigger statin-induced myotoxicity, although it is not uncommon for parents to be asymptomatic. However, in the text, it is not specified if parents were taking statin.

Despite the points discussed by Finsterer and Aliyev that should be addressed in the original article, the recurrent rhabdomyolysis, the fever in both episodes, the age of onset, the normal CK and examination between episodes, are in line with descriptions of LPIN1 associated rhabdomyolysis.

References
1. Quinlivan R, Jungbluth H: Myopathic causes of exercise intolerance with rhabdomyolysis. Dev Med Child Neurol. 2012; 54 (10): 886-91 PubMed Abstract | Publisher Full Text
Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Inherited muscular disorders, mitochondrial diseases, rhabdomyolysis.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

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**Reviewer Report 17 August 2020**

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**Pushpa Raj Joshi**
Department of Neurology, Martin-Luther-University Halle-Wittenberg, Halle, Germany

The correspondence ‘Detection of compound heterozygous variants in LPIN1 does not necessarily imply pathogenicity in a patient with rhabdomyolysis’ by Josef Finsterer and Rahim Aliyev well argue against the conclusion of original submission ‘Case Report: The first probable Hong Kong Chinese case of LPIN1-related acute recurrent rhabdomyolysis in a boy with two novel variants’ by SW Yim and colleagues. In this submission, the authors are not sure which drug was administered to the patient prior to admission and Dr. Finisterer and Dr. Aliyev rightly point out that rhabdomyolysis should not have necessarily be triggered by the LPIN1 mutations but might have been due to the effect of the compounds in the injection. SW Yim and colleagues should find out the composition of the injection and prove that rhabdomyolysis was not triggered by any of the compounds in the injection.

On the other hand, it is very likely that the conclusion of SW Yim might be correct. Although the pathogenicity of the reported mutations is not clear, the compound heterozygosity might be the cause of rhabdomyolysis and the mutations are, in fact, pathogenic. This is strongly supported by the fact that the child suffered from the second attack of rhabdomyolysis. However, the report on detailed family history, as pointed out by Dr. Finisterer and Dr. Aliyev, will be helpful in arguments
about the pathogenicity of the mutations. Despite autosomal recessive inheritance of LPIN1 mutations, the parent(s) with only one mutation might also suffer from attack(s) of rhabdomyolysis with very mild to severe intensity. Symptomatic heterozygous cases are sporadically reported in other autosomal recessive disorders such as CPT II deficiency, also contributing to rhabdomyolysis. Overall, the original submission is interesting but needs to address the points raised by Dr. Finisterer and Dr. Aliyev to draw the conclusion that rhabdomyolysis is triggered by novel LPIN1 mutations.

Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

**Competing Interests:** No competing interests were disclosed.

**Reviewer Expertise:** Neuromuscular disorders, mitochondrial myopathy, Rhabdomyolysis

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 13 August 2020

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Karolina M. Stepien
Mark Holland Metabolic Unit, Adult Inherited Metabolic Diseases Department, Salford Royal NHS Foundation Trust, Salford, UK

I note the comments from Finsterer and Aliyev. I agree that it would be worth learning more about the first episode of rhabdomyolysis in this child who was confirmed to be compound heterozygous for two mutations causing LIPIN1. A causal relationship between this episode and the administered injection needs to be considered, and detail is given on what the injection was including dose, route, number of doses, indication,
etc. This is a fundamental point that has not been addressed in the case report. Drug-induced rhabdomyolysis is relatively common. Although 40% of heterozygous carriers for LPIN1 missense mutations may be symptomatic, myopathy has been reported in these individuals in response to statin drug treatment (Zhang et al. 2014). The authors listed several factors that may trigger rhabdomyolysis in LIPIN1. The fact that in humans episodes of myoglobinuria in LIPIN1 are mostly precipitated by febrile illnesses (Michot et al. 2014) emphasizes a critical role of the inflammatory stress response as a potential triggering factor of rhabdomyolysis.

I agree with the authors that there are some limitations of the case report by Yim et al. 2019. Firstly, a CK of 127,000 U/L may have detrimental consequences in a toddler. Dexamethasone was shown to decrease the number of lipid droplets in lipin-1 deficient patients' myoblasts with a decrease in peak CK concentration during acute rhabdomyolysis. This therapy may prove to be beneficial for severe decompensation (Majer et al. 2015). Was it considered during the acute illness? What about renal function and fluid management?

References
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3. Meijer IA, Sasarman F, Maftei C, Rossignol E, et al.: LPIN1 deficiency with severe recurrent rhabdomyolysis and persistent elevation of creatine kinase levels due to chromosome 2 maternal isodisomy. Mol Genet Metab Rep. 2015; 5: 85-88 PubMed Abstract | Publisher Full Text

Is the rationale for commenting on the previous publication clearly described?
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Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Inherited Metabolic Diseases
Panupong Hansrivijit
Department of Internal Medicine, University of Pittsburgh Medical Center Pinnacle, Harrisburg, PA, USA

Thank you for pointing out other etiologies that the original authors might have missed. However, I agree with the original authors' conclusion that rhabdomyolysis in this infant is related to spontaneous rhabdomyolysis from compound heterozygous variants of LPIN1 but the fact that we do not know what medication was given has raised some concerns for the accuracy of the diagnosis. Please add another reference that covers the genetic perspectives of rhabdomyolysis as attached. I believe this additional article will be helpful to the readers who are interested in reading up further.

References
1. Scalco RS, Gardiner AR, Pitceathly RD, Zanoteli E, et al.: Rhabdomyolysis: a genetic perspective. Orphanet J Rare Dis. 2015; 10: 51 PubMed Abstract | Publisher Full Text

Is the rationale for commenting on the previous publication clearly described?
Yes

Are any opinions stated well-argued, clear and cogent?
Yes

Are arguments sufficiently supported by evidence from the published literature or by new data and results?
Yes

Is the conclusion balanced and justified on the basis of the presented arguments?
Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Minor revision is advised without the need to return the article to me.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.
expertise to confirm that it is of an acceptable scientific standard.

Comments on this article

Reader Comment 15 Jan 2020
Felix Chi Kin Wong, Department of Chemical Pathology, Prince of Wales Hospital, Shatin, Hong Kong

As one of the co-authors of the article by Yim et al (https://f1000research.com/articles/8-1566/v1), I would like to reply on behalf of my co-authors to the points raised by Drs Finisterer and Aliyev:

1. "It is conceivable that the parent who carried the variant c.1949_1967dupGTGTCACCACGCAGTACCA also had experienced muscle manifestations previously." Our reply: LPIN1-related rhabdomyolysis is an autosomal recessive disorder (MIM #268200, Myoglobinuria, acute recurrent, autosomal recessive). Finsterer and Aliyev stated that the parents of our proband should have symptoms and cited two references (Ref 3 and 4). However, in both cited references the probands carry either homozygous or compound heterozygous variants. In ref 3, the mother of the proband was heterozygous and the plasma CK was normal despite her history of nonspecific unexplained mild chronic myalgia. In ref 4, there is no description on the parents’ status. Although some literature revealed that around 40% heterozygous carriers of LPIN1 may be symptomatic, majority of the carriers can still be asymptomatic.

2. "Since the younger sister of the index patient also carried the compound heterozygous LPIN1 variants, we should be informed about the course of the mother's pregnancy with this younger child, about the sister's CKVs at birth and later, and further follow-up, including genetic counselling." Our reply: As mentioned in the paper, the younger sister had genetic testing done soon after birth. The antenatal history was unremarkable. She was all along followed up by paediatricians and had no episodes of rhabdomyolysis as at the time of reporting. The highest CK level in the younger sister was 202 U/L (reference interval: 37-173 U/L).

3. Thus, it is crucial to find out which drug the GP injected one day prior to admission, not only to identify the compound, but also to ensure that other patients were not exposed to any hazardous risks due to a possibly toxic drug."and"Current medication the index patient was taking at the time of this second episode should be examined, and also if the cause could have been triggered by exercise." Our reply: We agree that it is useful to review the drug history. The index patient was given IM injection prior to the first episode of rhabdomyolysis (years ago) by a GP outside Hong Kong so we have difficulty in contacting the GP. At the time of the second episode of rhabdomyolysis, the index patient was not on any medication, and there was no evidence that the second rhabdomyolysis was triggered by exercise.
4. "Functional and biochemical tests should be carried out to confirm or exclude pathogenicity attributed to LPIN1 variants." **Our reply:** We followed the ACMG consensus 2015 (Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. Genet Med. 2015;17(5):405-24.) for the classification of pathogenicity of the two variants. Functional and biochemical tests are good things to have but are often not available in routine laboratories and are not a must as required by the ACMG.

In summary, we think that while the statement "detection of compound heterozygous variants in LPIN1 not necessarily implies pathogenicity" by Finsterer and Aliyev could be true, our approach followed the standard practice in variant interpretation and classification of pathogenicity. As one of the variants detected was classified as a variant of uncertain significance (VUS), we have been careful in the title and conclusion of the article, stating that it is a *probable* (not definite) case of LPIN1-related acute recurrent rhabdomyolysis.

**Competing Interests:** Nil