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Molecular analysis of *LPIN1* in Jordanian patients with rhabdomyolysis

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ABSTRACT

Recessive mutations in *LPIN1*, which encodes a phosphatidate phosphatase enzyme, are a frequent cause of severe rhabdomyolysis in childhood. Hence, we sequenced the 19 coding exons of the gene in eight patients with recurrent hereditary myoglobinuria from four unrelated families in Jordan. The long-term goal is to facilitate molecular genetic diagnosis without the need for invasive procedures such as muscle biopsies. Three different mutations were detected, including the novel missense mutation c.2395G>C (Gly799Arg), which was found in two families. The two other mutations, c.2174G>A (Arg725His) and c.1162C>T (Arg388X), have been previously identified, and were found to cosegregate with the disease phenotype in the other two families. Intriguingly, patients homozygous for Arg725His were also homozygous for the c.1828C>T (Pro610Ser) polymorphism, and were exercise-intolerant between myoglobinuria episodes. Notably, patients homozygous for Arg388X were also homozygous for the c.2250G>C silent variant (Gly750Gly). Taken together, the data provide family-based evidence linking hereditary myoglobinuria to pathogenic variations in the C-terminal lipin domain of the enzyme. This finding highlights the functional significance of this domain in the absence of structural information. This is the first analysis of *LPIN1* in myoglobinuria patients of Jordanian origin, and the fourth such analysis worldwide.

1. Introduction

Rhabdomyolysis results from acute breakdown of skeletal muscle sarcolemma due to acquired factors, which constitute over 75% of the cases, or due to familial factors (Zutt et al., 2014; Hamel et al., 2015). In these patients, sustained activation of several Ca^{+2}-dependent signaling cascades causes the leakage of electrolytes, myoglobin, and the sarcoplasmic enzymes creatine kinase, aspartate aminotransferase, and alanine transaminase into the blood stream (Zutt et al., 2014). Notably, Ca^{+2} in skeletal muscle fibers is increased 11 times in patients with acute rhabdomyolysis (López et al., 1995). Acute renal failure and cardiac arrhythmia are the most critical clinical complications, and are usually associated with high mortality rate (Melli et al., 2005; Michot et al., 2010).

In lipid metabolic diseases of which rhabdomyolysis is a component, defects in mitochondrial fatty acid oxidation are a frequent cause. However, where such defects have been excluded by biochemical analysis, mutations in *LPIN1* were identified in a significant percentage of the cases. In 2008, homozygosity mapping and DNA sequencing identified a Glu215X mutation in *LPIN1*, along with five other mutations, in seven patients with severe rhabdomyolysis and myoglobinuria (Zeharia et al., 2008). Subsequently, Michot and colleagues found other mutations in a larger cohort of patients (Michot et al., 2010; Bergounioux et al., 2012; Michot et al., 2012). Notably, loss-of-function mutants of *Lpin1* were originally associated with fatty liver dystrophy in mice, which also exhibit lipodystrophy and insulin resistance (Péterfy et al., 2001). In contrast, children with *LPIN1* mutations do not present lipodystrophy, nor are *LPIN1* mutations present in lipodystrophy patients (Cao and Hegele, 2002; Zeharia et al., 2008; Michot et al., 2010). Nevertheless, single nucleotide polymorphisms in *LPIN1*, or specific haplotypes composed of several such polymorphisms, are significantly associated with body mass index, insulin sensitivity, obesity, and other metabolic traits in several ethnic groups (Suviolahti et al., 2006; Loos et al., 2007; Fawcett et al., 2008; Wiedmann et al., 2008; Chang et al., 2010; Zhang et al., 2013). Moreover, a correlation between metabolic phenotypes and *LPIN1* mRNA abundance in adipose tissue has been consistently observed (Suviolahti et al., 2006; Chang et al., 2010).

The mechanism that drives rhabdomyolysis in *LPIN1*-deficient mice was recently established to be impaired autophagy of damaged mitochondria (Zhang et al., 2014). On the other hand, pro-inflammatory cytokines have been found to notably increase the volume of lipid droplets and upregulate *ACACB* in *LPIN1*-deficient myoblasts (Michot et al., 2013).

LPIN1 encodes lipin-1, an enzyme that dephosphorylates phosphatidic acid to generate diacylglycerol, a precursor to triglycerides (Takeuchi and

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Reue, 2009). Multiple isoforms are expressed by alternative splicing of the *LPIN1* transcript. Three isoforms, lipin-1α, β, and γ, have been characterized in humans and mice (Péterfy et al., 2005; Han and Carman, 2010). The isoforms are enzymatically active, but have different substrate affinities. The human *LPIN* homologs *LPIN1*, *LPIN2*, and *LPIN3*, share the same structural organization, in which all introns are located at homologous positions. These homologs are also differentially expressed in tissues (Péterfy et al., 2001). Lipin-1 is predominantly expressed in skeletal muscle and adipose tissue (Péterfy et al., 2001; Donkor et al., 2007; Donkor et al., 2009), and accounts for most, if not all, of phosphatidate phosphatase activity in skeletal muscle (Donkor et al., 2007).

The N-terminal lipin (N-LIP) and C-terminal lipin (C-LIP) domains are highly conserved among lipin proteins and across species (Péterfy et al., 2001). The C-LIP domain contains the Mg^{2+}-dependent catalytic Asp-X-Asp-X-Thr motif, which is shared among haloacid dehalogenase-like enzymes, along with three other signature motifs (Burroughs et al., 2006; Han et al., 2006; Seifried et al., 2013). These four motifs have been mapped to corresponding regions in human lipin-1 (Donkor et al., 2009). An additional motif, Leu-X-X-Ile-Leu, facilitates complex formation with transcriptional coactivators and nuclear factors to induce expression of several enzymes in mitochondrial fatty acid β-oxidation and in the tricarboxylic acid cycle in hepatocytes (Finck et al., 2006). Similar transcriptional coactivation activity has been described for lipin-2 (Donkor et al., 2009).

In this study, we sequenced *LPIN1* in eight Jordanian patients with severe recurrent myoglobinuria, a condition associated with high mortality and significant morbidity. The goal was to facilitate molecular genetic diagnosis without the need for invasive procedures such as muscle biopsies.

2. Materials and Methods

2.1. Families

Eight patients (5 males and 3 females) from four different consanguineous families (A, B, C, and D) that reside in different locations in Jordan were referred to the Metabolic Genetics Clinic at King Hussein Medical Centre, Amman, Jordan with rhabdomyolysis and severe myoglobinuria. In family A, four children were affected (A-1, A-2, A-3, and A-4), and two were healthy. Two of three children in family B were affected (B-1 and B-2), as was one individual in family C (C-1). A child in family D was affected (D-1), although a sibling died at the age of 1 year with severe weakness and dark urine. This patient was not characterized at time of death. Each patient experienced 1–4 episodes of myoglobinuria, the first of which occurred between the ages of 3 months and 6 years (Table 1). Patients underwent extensive examinations including full blood count, kidney and liver function tests, and assays for creatine kinase, alanine transaminase, aspartate amino transferase, lactate and lactate dehydrogenase, acylcarnitine, urine organic acids, and plasma amino acids. Patient B-1 underwent a muscle biopsy. DNA samples were collected from 50 control individuals, and DNA samples are available from all patients, parents, and unaffected siblings of families A and B for screening of mutations in *LPIN1*. Blood samples were provided to the Princess Haya Biotechnology Center Laboratory with informed consent from parents. This study was approved by the institutional review board committees at Jordan University of Science and Technology and King Abdullah University Hospital.

2.2. Sequence analysis

The 19 coding exons of *LPIN1* were amplified from genomic DNA by polymerase chain reaction (PCR). Forward and reverse primers were designed in Primer3 (http://frodo.wi.mit.edu/primer3) to encompass exon-intron junctions in the NCBI reference sequences for the *LPIN1* gene (NG_012843.2) and cDNA (NM_145693.2). Primer sequences and PCR parameters are available upon request.

PCR products were purified, and sequenced in both directions using Big-Dye Terminator v3.1 Cycle Sequencing Kit on a 3130xl Genetic Analyzer (Applied Biosystems). Sequencing data were compared to reference sequences using ChromasPro 1.34 (Technelysium Pty. Ltd., Australia). Mutations and variants were designated according to guidelines of the Human Genome Variation Society (http://www.hgvs.org/mutnomen).

2.3. Phylogenetic and pathogenicity analyses

Multiple sequence alignments of lipin proteins were generated using Clustal Omega (http://www.ebi.ac.uk/Tools/msa/clustalo/). The potential pathogenicity of mutations in Arg725 and Gly799 was analyzed using PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/).

3. Results

3.1. Clinical and biochemical features

All patients voided dark urine and experienced muscle weakness in at least one episode in early life (Table 1). In all patients except A-3, the first of these episodes presented along with acute febrile illnesses. At age 3 months, patient A-3 was not breast-fed for a week, during which the first episode manifested. During episodes, patients had significant weakness and decreased deep-tendon reflexes, especially in the lower limbs. Muscles presented mild to moderate tenderness, but not significant swelling. Patients did not present symptoms of complications in the central nervous system, and had normal echocardiograms. Patients were healthy between episodes, except A-1, A-2, and A-4, who were exercise-intolerant. In addition, these three children have impaired renal function during episodes, but recover without sequelae.

Patient B-1, who had mild, residual weakness of the limb girdle, underwent muscle biopsy immediately after the third episode at the age of 4 years. Results indicated myositis and atrophy of type II fibers, but normal histochemistry staining for all enzymes including cytochrome

Table 1
Clinical, laboratory, and genetic features.

Patient	Sex	Age	Age at onset	Number of episodes	Creatine kinase UI/L*	Mutation	Amino Acid Change
A-1	F	16 years	6 years	2	37,787	c.2174G>A	Arg725His
A-2	M	15 years	3 years	2	15,000	c.2174G>A	Arg725His
A-3	M	9 years	3 months	1	296,000	c.2174G>A	Arg725His
A-4	M	19 years	3 years	3	36,000	c.2174G>A	Arg725His
B-1§	F	5 years§	18 months	4	142,000	c.2395G>C	Gly799Arg
B-2	M	2 years	16 months	1	32,668	c.2395G>C	Gly799Arg
C-1	F	8 years	2 years	3	70,000	c.2395G>C	Gly799Arg
D-1†	M	6 years	8 months	3	200,000	c.1162C>T	Arg388X

* Normal range: 45–195 UI/L.
§ Died at this age.
† Had a sibling who died of myoglobinuria.

oxidase, Gomori trichrome, and NADH. She died at the age of 5 years in a regional hospital after a very short bout of febrile illness and diarrhea secondary to cardiac complications. Her parents presented myalgia, whereas all other parents were unaffected.

Creatine kinase (normal range: 45–195 UI/L) was elevated in all patients (Table 1), while acylcarnitine, urine organic acids, and plasma amino acids were normal. In patients A-1, A-2, A-3, B-1, B-2, and D-1, aspartate aminotransferase (normal range: 0–37 UI/L) and alanine transaminase (normal range: 0–41 UI/L) ranged from 217 to 2390 UI/L and from 203 to 2141 UI/L during episodes.

3.2. LPIN1 mutations and polymorphisms

All four affected children in family A were homozygous for the transition point mutation c.2174G>A (Fig. 1A), which is in exon 17 and results in the substitution of Arg725 with His. The parents were carriers, but the unaffected children were not. This mutation was not found in 100 control chromosomes. Haplotypes for this mutation were phased using four variants identified in family A (Fig. 1B). The disease-causing mutation, c.2174G>A (Arg725His), appears to be carried on a chromosome with a haplotype that includes alleles C, T, T, and T at the four polymorphic loci: c.192+17C>T (rs10209969, intron 2); c.193-47C>T (rs45509591, intron 2); c.552C>T, p.Ile184Ile (rs11538448, exon 4); and c.1828C>T, p.Pro610Ser (rs4669781, exon 14).

In families B and C, a novel c.2395G>C transversion (Fig. 1C) was identified in exon 18. This mutation replaces Gly799 with Arg. Patients B-1, B-2, and C-1 were homozygous, while parents were heterozygous, and the unaffected child in family B was homozygous wild type. The mutated allele was not detected in control individuals. Notably, all three patients were also homozygous for the 'T' allele, a c.1698+41G>T (rs7561070) polymorphism in intron 12.

The c.1162C>T transition (Fig. 1D) in exon 8, which converts Arg388 to a stop codon and truncates the enzyme by 502 residues, was found in both alleles in patient D-1. Both parents were carriers. The patient was also homozygous for the 'C' allele, a c.2250G>C silent variant (Gly750Gly, rs61732581), for which one of the 50 control individuals was heterozygous.

3.3. Pathogenicity potential of lipin-1 missense mutations

Arg725 and Gly799 are conserved among orthologous lipin-1 proteins (Fig. 2). Additionally, mutations of both residues were predicted by PolyPhen2 to be probably damaging, with score 1.000. In PolyPhen2, scores represent the probability that missense substitutions are damaging, and values approaching 1.000 suggest deleterious consequences (Adzhubei et al., 2010).

4. Discussion

In this study, we identified a novel *LPIN1* missense mutation in Jordanian patients with autosomal recessive rhabdomyolysis syndrome. We also detected missense and nonsense mutations that have been

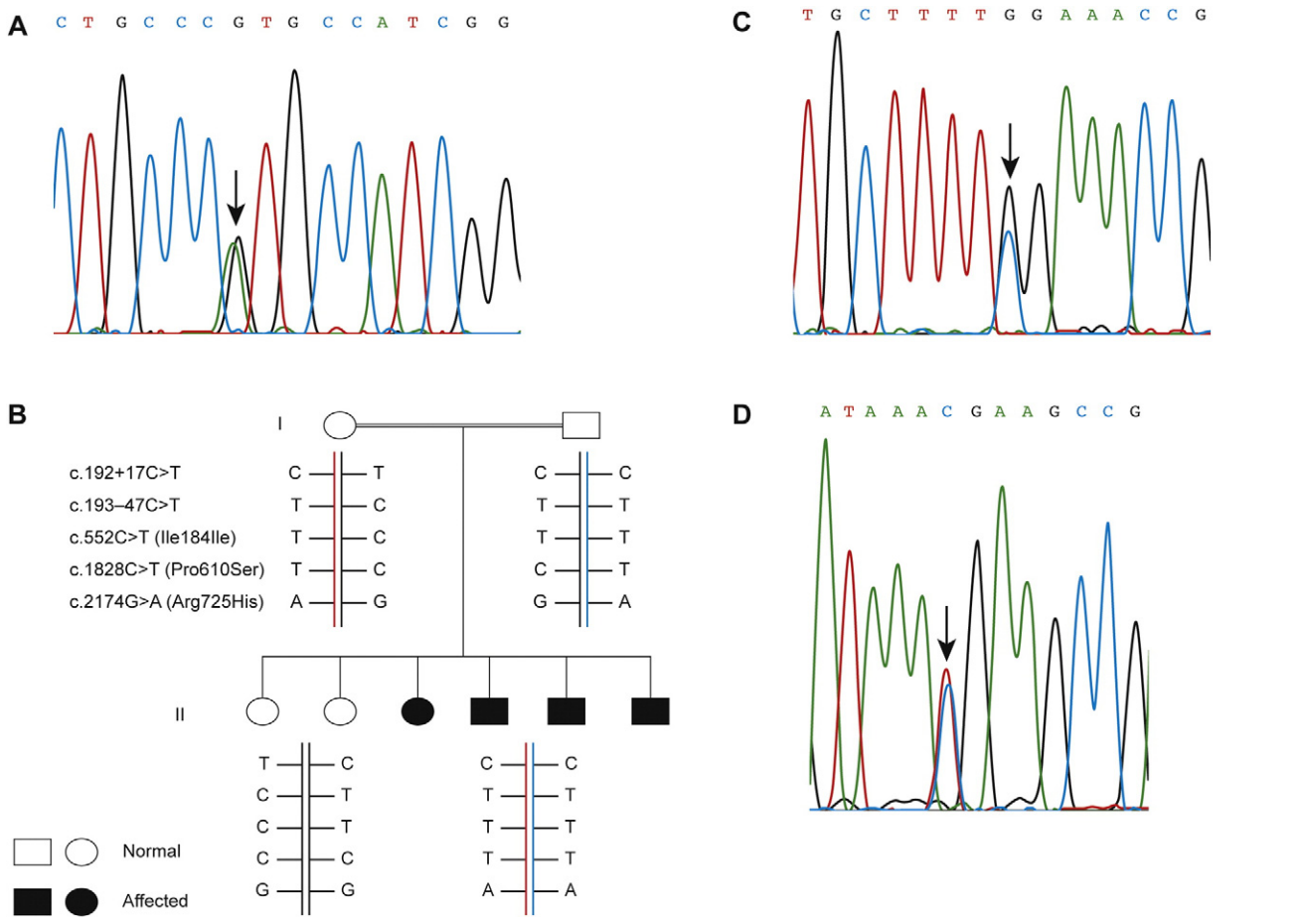

Fig. 1. Sequencing chromatograms encompassing *LPIN1* mutations, and phasing haplotypes. (A) c.2174G>A (Arg725His) in exon 17, heterozygous. The mutation cosegregated with the disease in family A, along with c.1828T (Pro610Ser). Unaffected siblings were wild type at both positions. (B) Phasing haplotypes constructed using the variants c.192+17C>T, c.193-47C>T, c.552C>T (p.Ile184Ile), and c.1828C>T (p.Pro610Ser), which were found in family A. (C) c.2395G>C (Gly799Arg) in exon 18, heterozygous. (D) c.1162C>T (Arg388X) in exon 8, heterozygous. Arrows mark nucleotide substitutions.

Fig. 2. Multiple sequence alignment of lipin proteins from various species. Arg725 and Gly799 in the C-LIP domain, which were found mutated in different families, are highlighted in green. Asp678, Asp680, Ser723, and Asp804, which are strictly conserved in haloacid dehalogenase-like proteins including lipins, were used to anchor alignments, and are highlighted in red. Alignments were generated in CLUSTAL Omega.

previously associated with the disorder. All patients were homozygous for the underlying mutation in *LPIN1*, and Mendelian inheritance was confirmed in all four families.

In one family, cosegregation of Arg725His with the disease phenotype confirms the pathogenicity of this mutation, which was originally described as a compound heterozygous genotype in a Caucasian baby who presented myoglobinuria at 18 months (Michot et al., 2012). In contrast, this mutation was found homozygous in all four affected children in the family. In addition, the patients were homozygous for the Pro610Ser variant, while unaffected siblings were wild type at both positions. Pro610Ser was originally characterized in an adult Ashkenazi patient who was treated with statins for hypercholesterolemia, and then developed myopathy and high levels of plasma creatine kinase (Zeharia et al., 2008). Notably, this variant reverses the mutant phenotype in yeast from which the *LPIN1* homolog has been deleted, indicating that the enzyme is functional. However, the homozygosity of all patients in one family for both Arg725His and Pro610Ser is intriguing. Whether this haplotype reflects linkage disequilibrium or not is a possibility, and could be resolved by additional genotyping and analysis of allele and haplotype frequency in Jordan. Notably, these patients experience renal impairment during episodes, and are exercise-intolerant between episodes. There are extreme variability in mortality, cardiac arrhythmia, and acute kidney injury in patients with severe rhabdomyolysis. For instance, acute kidney injury occurs in 13 to 46% of patients. Mortality from rhabdomyolysis with acute kidney injury is similarly variable, and ranges from 3.4% to 32% (Bosch et al., 2009). Finally, only 15% are exercise-intolerant between episodes (Michot et al., 2012).

Out of 20 different mutations identified in *LPIN1* so far, Arg725His is the only pathogenic missense mutation (Michot et al., 2012). We have identified a new pathogenic missense mutation, Gly799Arg, in the C-LIP domain in two families in Jordan. Notably, both parents in one of these families present mild myalgia that cannot be attributed to age or to statin-induced myopathy, to which *LPIN1* carriers are susceptible. Exercise-induced myalgia is indicated in at least 40% of carriers (Michot et al., 2012).

Both Arg725 and Gly799 are strictly conserved in orthologous lipin proteins from plants to humans. Arg725 is next to a conserved motif that positions the lipin-1 substrate for nucleophilic attack by Asp678 (Burroughs et al., 2006; Donkor et al., 2009; Seifried et al., 2013). On the other hand, Gly799 is in the vicinity of Asp804, a residue that coordinates Mg^{2+} along with two other Asp amino acids (Burroughs et al., 2006; Seifried et al., 2013). Interestingly, the splicing mutation *LPIN1*^{1Hubr}, which disrupts Asp804 in rats, completely inactivates the enzyme (Mul et al., 2011).

The variants Gly750Gly in exon 17 and Arg388X in exon 8 were inherited *in cis* on the same chromosome by patient D-1. Whether this suggests linkage disequilibrium or not remains to be elucidated. The Gly750Gly variant is predicted to abolish binding of the SC35 splicing factor, and was previously characterized in an Arabic patient who presented statin-induced myopathy (Zeharia et al., 2008). However, this variant was also found in unaffected individuals, and co-segregated with Arg388X, implying that it is a synonymous polymorphism rather than a causative mutation. On the other hand, Arg388X truncates lipin-1 into a fragment that, if stable, would lack catalytic and transcriptional activities (Péterfy et al., 2001; Péterfy et al., 2005; Finck et al., 2006). This severe loss of function is consistent with early onset and frequent episodes in this patient, and with death of a sibling at the age of 1 year. This mutation is the most prevalent identified to date in Arabic patients, while the putative founder mutation, c.2295-866_2410-30del, is the most common in Europeans (Zeharia et al., 2008; Michot et al., 2010; Michot et al., 2012).

In conclusion, we have detected three *LPIN1* mutations in four Jordanian families. Two of these mutations have been previously identified, and were confirmed in two different families to segregate with the disease. The third mutation is reported for the first time. These results will facilitate molecular genetic diagnosis of severe rhabdomyolysis with myoglobinuria, and potentially eliminate the need for painful and invasive muscle biopsies.

Conflict of interest

The authors declare no conflict of interest.

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References

Adzhubei, I.A., Schmidt, S., Peshkin, L., Ramensky, V.E., Gerasimova, A., Bork, P., et al., 2010. A method and server for predicting damaging missense mutations. Nat. Methods 7, 248–249.

Bergounioux, J., Brassier, A., Rambaud, C., Bustarret, O., Michot, C., Hubert, L., et al., 2012. Fatal rhabdomyolysis in 2 children with LPIN1 mutations. J. Pediatr. 60, 1052–1054.

Bosch, X., Poch, E., Grau, J.M., 2009. Rhabdomyolysis and acute kidney injury. N. Engl. J. Med. 361, 62–72.

Burroughs, A.M., Allen, K.N., Dunaway-Mariano, D., Aravind, L., 2006. Evolutionary genomics of the HAD superfamily: understanding the structural adaptations and catalytic diversity in a superfamily of phosphoesterases and allied enzymes. J. Mol. Biol. 361, 1003–1034.

Cao, H., Hegele, R.A., 2002. Identification of single-nucleotide polymorphisms in the human LPIN1 gene. J. Hum. Genet. 47, 370–372.

Chang, Y.C., Chang, L.Y., Chang, T.J., Jiang, Y.D., Lee, K.C., Kuo, S.S., Lee, W.J., Chuang, L.M., 2010. The associations of LPIN1 gene expression in adipose tissue with metabolic phenotypes in the Chinese population. Obesity 18, 7–12.

Donkor, J., Sariahmetoglu, M., Dewald, J., Brindley, D.N., Reue, K., 2007. Three mammalian lipins act as phosphatidate phosphatases with distinct tissue expression patterns. J. Biol. Chem. 282, 3450–3457.

Donkor, J., Zhang, P., Wong, S., O'Loughlin, L., Dewald, J., Kok, B.P., et al., 2009. A conserved serine residue is required for the phosphatidate phosphatase activity but not the transcriptional coactivator functions of lipin-1 and lipin-2. J. Biol. Chem. 284, 29968–29978.

Fawcett, K.A., Grimsey, N., Loos, R.J., Wheeler, E., Daly, A., Soos, M., et al., 2008. Evaluating the role of LPIN1 variation in insulin resistance, body weight, and human lipodystrophy in U.K. Populations. Diabetes 57, 2527–2533.

Finck, B.N., Gropler, M.C., Chen, Z., Leone, T.C., Croce, M.A., Harris, T.E., et al., 2006. Lipin 1 is an inducible amplifier of the hepatic PGC-1alpha/PPARalpha regulatory pathway. Cell Metab. 4, 199–210.

Hamel, Y., Mamoune, A., Mauvais, F.X., Habarou, F., Lallement, L., Romero, N.B., et al., 2015. Acute rhabdomyolysis and inflammation. J. Inherit. Metab. Dis. 38, 621–628.

Han, G.S., Carman, G.M., 2010. Characterization of the human LPIN1-encoded phosphatidate phosphatase isoforms. J. Biol. Chem. 285, 14628–14638.

Han, G.S., Wu, W.I., Carman, G.M., 2006. The *Saccharomyces cerevisiae* lipin homolog is a Mg2 + −dependent phosphatidate phosphatase enzyme. J. Biol. Chem. 281, 9210–9218.

Loos, R.J., Rankinen, T., Pérusse, L., Tremblay, A., Després, J.P., Bouchard, C., 2007. Association of lipin 1 gene polymorphisms with measures of energy and glucose metabolism. Obesity 15, 2723–2732.

López, J.R., Rojas, B., Gonzalez, M.A., Terzic, A., 1995. Myoplasmic Ca2 + concentration during exertional rhabdomyolysis. Lancet 345, 424–425.

Melli, G., Chaudhry, V., Cornblath, D.R., 2005. Rhabdomyolysis: an evaluation of 475 hospitalized patients. Medicine (Baltimore) 84, 377–385.

Michot, C., Hubert, L., Brivet, M., De Meirleir, L., Valayannopoulos, V., Müller-Felber, W., et al., 2010. LPIN1 gene mutations: a major cause of severe rhabdomyolysis in early childhood. Hum. Mutat. 31, E1564–E1573.

Michot, C., Hubert, L., Romero, N.B., Gouda, A., Mamoune, A., Mathew, S., et al., 2012. Study of LPIN1, LPIN2 and LPIN3 in rhabdomyolysis and exercise-induced myalgia. J. Inherit. Metab. Dis. 35, 1119–1128.

Michot, C., Mamoune, A., Vamecq, J., Viou, M.T., Hsieh, L.S., Testet, E., et al., 2013. Combination of lipid metabolism alterations and their sensitivity to inflammatory cytokines in human lipin-1-deficient myoblasts. Biochim. Biophys. Acta 1832, 2103–2114.

Mul, J.D., Nadra, K., Jagalur, N.B., Nijman, I.J., Toonen, P.W., Médard, J.J., et al., 2011. A hypomorphic mutation in Lpin1 induces progressively improving neuropathy and lipodystrophy in the rat. J. Biol. Chem. 286, 26781–26793.

Péterfy, M., Phan, J., Xu, P., Reue, K., 2001. Lipodystrophy in the fld mouse results from mutation of a new gene encoding a nuclear protein, lipin. Nat. Genet. 27, 121–124.

Péterfy, M., Phan, J., Reue, K., 2005. Alternatively spliced lipin isoforms exhibit distinct expression pattern, subcellular localization, and role in adipogenesis. J. Biol. Chem. 280, 32883–32889.

Seifried, A., Schultz, J., Gohla, A., 2013. Human HAD phosphatases: structure, mechanism, and roles in health and disease. FEBS J. 280, 549–571.

Suviolahti, E., Reue, K., Cantor, R.M., Phan, J., Gentile, M., Naukkarinen, J., Soro-Paavonen, A., Oksanen, L., Kaprio, J., Rissanen, A., Salomaa, V., Kontula, K., Taskinen, M.R., Pajukanta, P., Peltonen, L., 2006. Cross-species analyses implicate lipin 1 involvement in human glucose metabolism. Hum. Mol. Genet. 15, 377–386.

Takeuchi, K., Reue, K., 2009. Biochemistry, physiology, and genetics of GPAT, AGPAT, and lipin enzymes in triglyceride synthesis. Am. J. Physiol. Endocrinol. Metab. 296 (E1195-209).

Wiedmann, S., Fischer, M., Koehler, M., Neureuther, K., Riegger, G., Doering, A., Schunkert, H., Hengstenberg, C., Baessler, A., 2008. Genetic variants within the LPIN1 gene, encoding lipin, are influencing phenotypes of the metabolic syndrome in humans. Diabetes 57, 209–217.

Zeharia, A., Shaag, A., Houtkooper, R.H., Hindi, T., de Lonlay, P., Erez, G., et al., 2008. Mutations in LPIN1 cause recurrent acute myoglobinuria in childhood. Am. J. Hum. Genet. 83, 489–494.

Zhang, R., Jiang, F., Hu, C., Yu, W., Wang, J., Wang, C., Ma, X., Tang, S., Bao, Y., Xiang, K., Jia, W., 2013. Genetic variants of LPIN1 indicate an association with type 2 diabetes mellitus in a Chinese population. Diabet. Med. 30, 118–122.

Zhang, P., Verity, M.A., Reue, K., 2014. Lipin-1 regulates autophagy clearance and intersects with statin drug effects in skeletal muscle. Cell Metab. 20, 267–279.

Zutt, R., van der Kooi, A.J., Linthorst, G.E., Wanders, R.J., de Visser, M., 2014. Rhabdomyolysis: review of the literature. Neuromuscul. Disord. 24, 651–659.