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LPIN1 deficiency: A novel mutation associated with different phenotypes in the same family

Rhabdomyolysis (RM) is characterized by acute and often severe skeletal muscle damage resulting in myoglobinuria and, in severe cases, acute renal failure [1]. In adults is typically due to trauma, intoxication or infection, whereas in children is frequently associated with inherited muscle disorders [2]. *LPIN1* mutations were identified as a cause of severe recurrent RM, which usually begin in childhood, and infections are the most frequent trigger [3,4]. *LPIN1* spans 19 exons and encodes lipin-1, an 890 amino acid protein predominantly expressed in skeletal muscle and adipose tissue, which accounts for phosphatidic acid phosphatase activity [2,5]. To date, 36 *LPIN1* mutations have been described related with RM (Fig. 1a).

We report a 35-year-old female patient presenting myalgia, muscle weakness, general fatigue and sleep apnea. Her first child born from an apparently non-consanguineous marriage (father already dead), presented normal growth and psychomotor development until the age of 2 years, when developed recurrent RM events precipitated by infections, without symptoms and normal plasma creatine kinase between episodes. The child died at 4-year-old due to a crisis of RM during gastroenteritis. A novel *LPIN1* splicing mutation (c.2142-2 A > G) was identified in heterozygous state, in the index case, however, her child was homozygous (Fig. 1b). This novel mutation is probably pathogenic, predicted by bioinformatics tools, due to the break of acceptor site which affect the splicing mechanisms [6,7].

LPIN1 mutations appear as the second most common cause of early-onset RM, after primary fatty acid oxidation defects as a whole [8]. Heterozygous *LPIN1* mutations may also produce symptoms of cramps and exercise-induced myalgia or mild muscular symptoms [2], as occurred in our family.

This study allowed the identification of the first *LPIN1* mutation in Portuguese patients and corroborates the importance of a molecular testing to confirm *LPIN1* patients (children and adults) with recurrent RM.

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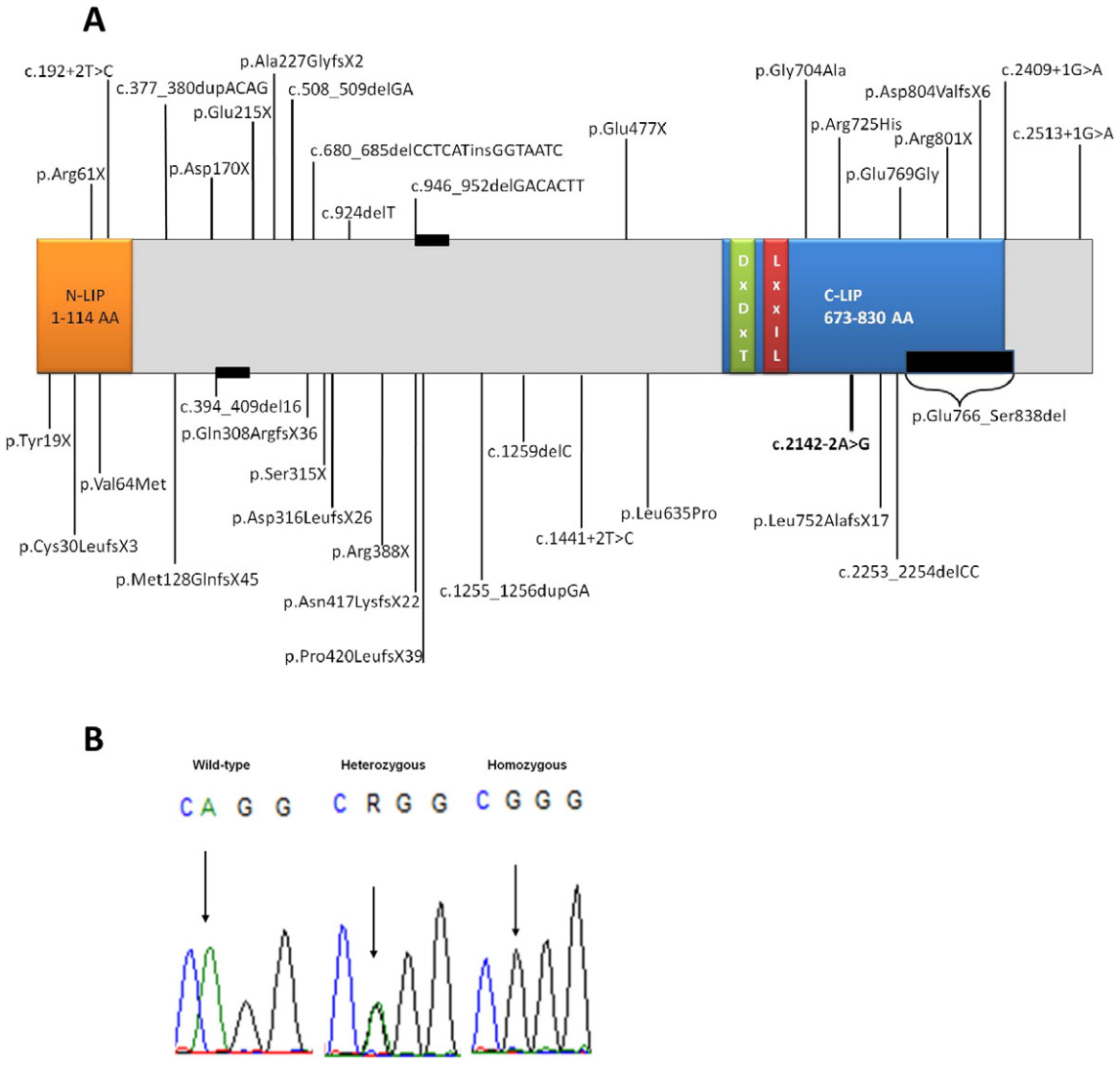

Fig. 1. — A) Schematic representation of described mutations in *LPIN1* gene. The new splicing mutation found in this study is shown in bold. B) *LPIN1* splicing mutation (c.2142-2A>G) in heterozygous and homozygous state, compared to the wild-type sequence.