11th International Symposium

sphm Sociedade Portuguesa de Doenças Metabólicas

McArdle disease: mutational spectrum of Portuguese patients

Rocha H[1], Lopes A[1], Soares G[2], Negrão L[3], Coelho T[4], Chorão R[5], Lourenço T[6] and Vilarinho L[1].

1 - Instituto Nacional de Saúde Doutor Ricardo Jorge, Departamento de Genética Humana, Unidade de Rastreio Neonatal, Metabolismo e Genética; **2**– Centro Hospitalar do Porto; **3**– Centro Hospitalar e Universitário de Coimbra; **4**– Centro Hospitalar do Porto; **5**– Centro Hospitalar de Vila Real; **6**– Centro Hospitalar de Lisboa Ocidental, Hosp. Egas Moniz

INTRODUCTION

McArdle disease or Glycogen Storage Disease type V (GSD V; myophosphorylase deficiency; MIM 232600) its an inborn error of glycogen metabolism, caused by a deficiency in muscle specific isoform of glycogen phosphorylase. This metabolic myopathy is characterised by exercise intolerance, myalgia, cramps and episodic myoglobinuria, symptoms that usually appear during the second or third decade of life.

The diagnosis was typically made in muscle biopsy by histological analysis (demonstration of subsarcolemmal glycogen deposits and negative histochemical stain for phosphorylase) and/or measurement of muscle phosphorylase activity. Although since 1984, when the gene of muscle isoform of phosphorylase (myophosphorylase) was cloned and assigned to chromosome 11 (11q13), molecular genetics analysis has been more and more used to confirm the clinical diagnosis. Until now, 146 pathogenic mutations have been described (according to HGMD™) including nonsense, missense and framshift mutations. High genetic heterogeneity is a hallmark of McArdle disease, with a very frequent common mutation among Caucasian populations – R50X (present in about 60% of the mutated alleles) – and several rare mutations, without a clear genotype/phenotype correlation (Nogales-Gadea G *et al*, 2015). The molecular studies of PYGM gene allow the diagnosis of most McArdle patients without the need of a muscle biopsy (with great benefits to patients), the detection of carriers (providing valuable information for genetic counselling) and increase the knowledge on the molecular pathology of this disorder.

The authors present molecular data from the characterisation of 51 Portuguese patients, from 40 families, with McArdle disease.

RESULTS

Our results reveal the presence of the R50X mutation in 47 of the alleles of the index cases (55%), in accordance to what has been described to other Caucasian populations. A total of 12 different mutations in *PYGM* were identified, one of them a novel mutation (p.T677I), considered damaging by *in silico* analysis (polyphen-2).

Mutations identified in Portuguese population

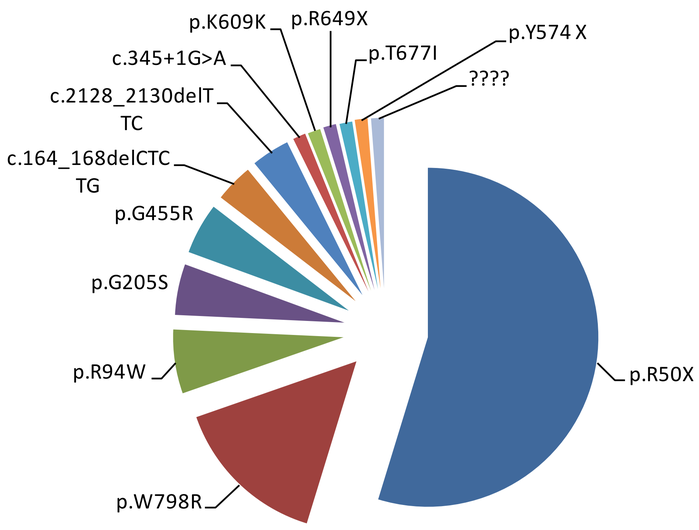
Mutation	Frequency (%)
p.R50X	55
p.W798R	15
p.R94W	6
p.G205S	5
p.G455R	5
c.164_168delCTCTG	4
c.2128_2130delTTC	4
c.345+1G>A	1
p.K609K	1
p.R649X	1
p.T677I	1
p.Y574 X	1
????	1

p.R50X allele frequency in different populations

Population	R50X allele frequency	Reference
British	81%	Bartram 1994
North-American	63%	el-Schahawi 1996
German	56%	Vorgerd 1998
French	56%	Bruno 2000
Spanish	55%	Martín 2001
Italian	43%	Bruno 2006

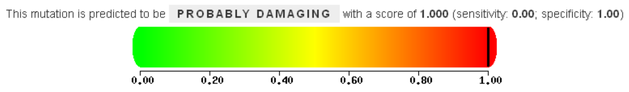
(from Andreu *et al*, 2007)

Mutation relative abundance



A novel mutation in *PYGM* – p.T677I

A new mutation "probably damaging", according to Polyphen-2



CONCLUSIONS

These results allow us the confirmation that in Portuguese population, as is described for other Caucasian populations, the R50X mutation is present in the great majority of the mutated alleles.

The realisation of molecular studies, in patients with a strong clinical suspicion of McArdle disease, avoids in the majority of the cases the need of a muscle biopsy for diagnosis confirmation, and also provide valuable information for genetic counselling and to increase the knowledge about the molecular pathology of this disorder.

ACKNOWLEDGEMENTS

The authors thanks to all clinicians that send the patients to study, as well as to the patients themselves and their families.

MATERIAL AND METHODS

We studied 51 patients with GSD V, McArdle disease, by screening mutations on *PYGM* gene.

Genomic DNA samples, from index cases, was isolated from peripheral blood and this screening was made using polymerase chain reaction (PCR) and primers designed by us.

PCR amplification and sequence analysis of all exons and intron/exon boundaries were visualized by electrophoresis on a 1% agarose, then purified and directly sequenced using the ABI Prism™ 3130XL Genetic Analyser.

References:

Andreu AL *et al* (2007). Acta Myol; 26(1):53-7.

Nogales-Gadea G *et al* (2015). J Inherit Metab Dis; 38(2):221-30.