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REFINING THE MOLECULAR CHARACTERIZATION OF CALPAINOPATHY (LGMD2A) PATIENTS

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Introduction: Mutations in the gene *CAPN3* are responsible for calpainopathy or limb-girdle muscular dystrophy type 2A (LGMD2A), one of the most frequent forms of LGMD. The gene *CAPN3* codes for calpain-3 (or CAPN3), a muscle-specific calcium-dependent protease functionally regulated via its autolytic activity. Most of the patients show differences in CAPN3 abundance in muscle samples as compared to control muscles, by immunoblot analysis. Interestingly, a smaller group of patients with normal protein abundance presents abnormal CAPN3 autolytic function.

We intend to complement the molecular studies already carried out on small group of Portuguese LGMD2A patients in order to establish genotype/phenotype correlations.

Materials and methods: Muscle biopsy samples of 9 LGMD2A patients diagnosed in our laboratory were subjected to protein analysis and functional tests by western blotting and densitometry analyses. Additionally, gene expression studies were performed using real-time quantitative PCR.

Results and discussion: The autolytic CAPN3 biochemical test was used in the patients that presented "normal" CAPN3 abundance in muscle biopsies (3 out of 9). The data obtained suggested that two of these patients had lost CAPN3 autolytic activity. Although, only one mutated allele had been found in one of these 2 patients after molecular genetic testing, this biochemical test was important in providing a differential diagnosis of LGMD2A in these patients.

Real-time quantitative PCR was done in order to quantify differences in the expression level of the *CAPN3* gene between patients' samples and controls. Interestingly, no reduction of *CAPN3* expression was observed in the samples tested (= 5). Additionally, two of them presented an overexpression of *CAPN3* gene as compared to controls. Once again, in these 2 patients only one mutated allele had been detected. In these cases, the data suggests that the diagnosis of calpainopathy may be excluded in these 2 patients.