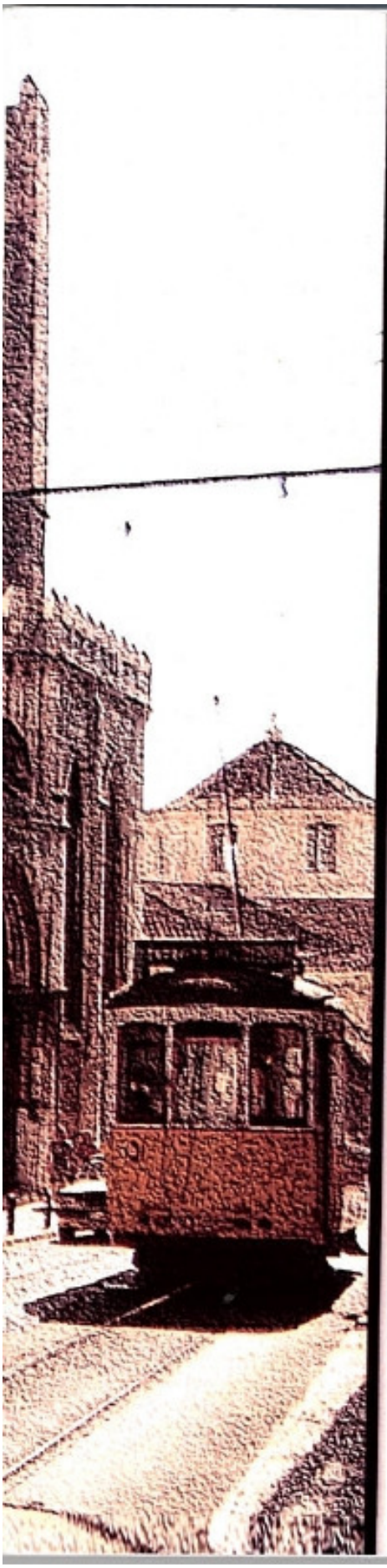

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ANOCTAMIN 5: A NEW CANDIDATE GENE FOR PORTUGUESE PATIENTS WITH ADULT ONSET LIMB-GIRDLE MUSCULAR DYSTROPHY

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Introduction: The limb-girdle muscular dystrophies (LGMDs) show wide genetic and clinical heterogeneity. Recessive mutations in the *ANO5* gene, which encodes a putative calcium-activated chloride channel of the anoctamin family, have been recently identified in families with LGMD type 2L and non-dysferlin distal muscular dystrophy (MMD3). The LGMD2L phenotype is characterized by proximal weakness, with prominent asymmetrical quadriceps femoris and biceps brachii atrophy, whereas MMD3 is associated with distal weakness, particularly of calf muscles.

Methods: In a group of 125 patients with clinical LGMD, but no mutations in other candidate genes involved in LGMD, we screened the "common" mutation c.191dupA. Subsequently, in 10 selected patients the entire coding region of *ANO5* was fully sequenced.

Results: Mutations were identified in 4 patients (3 families), all presenting hyperCKemia and adult onset proximal lower limb weakness. The common mutation c.191dupA was found in one family (2 patients), in a homozygous state. This mutation results in a frameshift with a consequent premature stop codon (p.Asn64LysfsX15), triggering nonsense-mediated mRNA decay. A novel substitution identified in exon 18 (c.2012A>G), predictably a missense mutation, was shown to in fact create a new donor splice site. mRNA studies confirmed aberrant splicing in exon 18, promoting an in-frame deletion of 18 nucleotides (r.2012_2029del) that results in a truncated protein (p.Tyr671_Val677delinsPhe). The third patient had a heterozygous nucleotide substitution in exon 8, c.692G>T, predicted to result in a missense mutation (p.Gly231Val). The Gly231 residue, localized in the N-terminal domain, is evolutionarily conserved. In this patient the second mutation has not yet been identified.

Conclusion: Although c.191dupA was detected in only 1/125 patients, systematic sequencing of *ANO5* in 10 patients revealed a further two positive cases, indicating that the anoctaminopathies may account for a reasonable number of our LGMD patients.