Mutational characterization of the P3H1/CRTAP/CypB complex in recessive osteogenesis imperfecta

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ABSTRACT. Osteogenesis imperfecta (OI) is a genetic disease characterized by bone deformities and fractures. Most cases are caused by autosomal dominant mutations in the type I collagen genes COL1A1 and COL1A2; however, an increasing number of recessive mutations in other genes have been reported. The LEPRE1, CRTAP, and PPIB genes encode proteins that form the P3H1/CRTAP/CypB complex, which is responsible for posttranslational modifications of type I collagen. In general, mutations in these genes lead to severe and lethal phenotypes of recessive OI. Here, we describe sixteen genetic variations detected in LEPRE1, CRTAP, and PPIB from 25 Brazilian patients with OI. Samples were screened for mutations on single-strand conformation polymorphism gels and variants were determined by automated sequencing. Seven variants were detected
in patients but were absent in control samples. LEPRE1 contained the highest number of variants, including the previously described West African allele (c.1080+1G>T) found in one patient with severe OI as well as a previously undescribed p.Trp675Leu change that is predicted to be disease causing. In CRTAP, one patient carried the c.558A>G homozygous mutation, predicted as disease causing through alteration of a splice site. Genetic variations detected in the PPIB gene are probably not pathogenic due to their localization or because of their synonymous effect. This study enhances our knowledge about the mutational pattern of the LEPRE1, CRTAP, and PPIB genes. In addition, the results strengthen the proposition that LEPRE1 should be the first gene analyzed in mutation detection studies in patients with recessive OI.

**Key words:** Osteogenesis imperfecta; Mutations; LEPRE1; CRTAP; PPIB