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Thesis Abstract

Molecular characterization of globin chain mutants (Caracterização molecular de mutantes de cadeias globínicas)

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Over 800 hemoglobin variants have already been described, most of them resulting from changes in the sequence of nucleotides, generating replacements of amino acids in the polypeptide chain and leading to the formation of hemoglobin molecules with physical-chemical characteristics different from normal hemoglobins. In Brazil, the several ethnic origins and different degrees of miscegenation have resulted in the dispersion of genes previously characteristic of Negroid and Caucasian peoples. Many hemoglobin mutants are still partially characterized, whereas others remain without an accurate identification of the molecular defect. We analyzed 220 blood samples from different regions of the country. The methodologies included electrophoretic procedures, such as electrophoresis in cellulose acetate with alkaline pH and on agar gel at acid pH, isoelectric focusing and electrophoresis of the globin chains in cellulose acetate at alkaline pH; high-pressure liquid chromatography and cytological tests were also used. The molecular characterization was performed after the extraction of the genomic DNA, by amplification, enzymatic digestion, hybridization with specific allele oligonucleotide probes, and sequencing. The mutants were classified according to the altered globin chain. There were 43 mutants of the alpha chain, 73 mutants of the beta chain, 11 probable mutants of the delta chain and 2 of the gamma chain, in addition to 7 individuals with fusion of chains, originating Hb Lepore. Nineteen samples with globin chains that migrated similar to the normal standard were also found. It was not possible to perform electrophoresis of the globin chains in 18 individuals, and an association of variant hemoglobins was observed in 10 samples. Thirty-eight samples were found with electrophoretic standards similar to Hb S or C and with an altered chromatographic profile. Fifty samples, including carriers and their relatives, were characterized by molecular biology, with Hb D - Los Angeles in heterozygosis and in association with other abnormal hemoglobins, an Hb E carrier and 10 Hb Hasharon carriers. The use of electrophoretic and chromatographic methodologies together has provided means for the accurate diagnosis of the

variants and has directed the molecular evaluations, particularly for determining the altered globin chain. The information obtained and the confirmations of the mutants have been essential for the genetic counseling of the carriers and their relatives. It has favored the implementation of therapeutic measures applied to each case by the physicians in charge, and has contributed to our knowledge of abnormal hemoglobins in the Brazilian population.

Key words: Hemoglobinopathies, Hemoglobin variants, Laboratory diagnosis