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Thesis Abstract

Contribution to the study of molecular defects of hemoglobin in the Brazilian population

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The hemoglobinopathies belong to a diverse group of inherited disorders characterized by the reduced synthesis of one or more globin chains (thalassemia) or the synthesis of a structurally abnormal hemoglobin (Hb). Approximately 900 different hemoglobin variants characterized by mutations involving alpha, beta, gamma, and delta globin chains have been described worldwide. In Brazil, the high degree of ethnic admixture among native Americans and African and European descendants has produced elevated frequencies of Hb alterations. The aim of the present study was to characterize globin chain mutants based on classical laboratory tests and molecular analyses to supply detailed information about the Hb diseases to health professionals and to contribute to the knowledge of abnormal hemoglobins in Brazil. A total of 242 samples were submitted to classical tests selected for hemoglobinopathies, and molecular screening was carried out by PCR-based techniques that included allele-specific PCR, multiplex PCR, restriction enzyme analysis PCR, and direct sequencing. After conducting the classical tests, the samples were divided into five groups in accordance with the mutant chain. The groups with alpha and beta globin chain mutants were the most frequent, with 81 samples each. Another group with a large number of samples was that of unidentified mutants, with 56 samples. The delta and fusing delta/beta globin chain groups had fewer numbers of samples, respectively, 13 and 11. The most frequent electrophoretic profile was the Hb S-like, followed by fast variants. Some sample of the beta globin chain group could only be identified after sequencing, such as the samples Hb D-Los Angeles, Hb Korle-Bu, Hb K-Woolwich, Hb E, Hb Deer Lodge, Hb Osu-Christiansborg, and Hb Ohio. It was possible to detect a previously undescribed variant in four individuals of this sampling, who were not related and from different locations. For the alpha globin chain mutants, sequencing of the samples was not possible; therefore, the results presented were obtained by only classical laboratory techniques with the exception of Hb Hasharon, which was diagnosed by PCR-RFLP technique. Hb Hasharon was the most frequent variant among the alpha globin chain mutants, followed by Hb J-Oxford. Other variants had lower frequencies, such as Hb Q-India, Hb Queens and Hb Montgomery. For delta chain mutants, a new PCR-RFLP strategy was designed to identify Hb B2, but it was not possible to deduce a suspect phenotype for the

other mutants. After the classical laboratory techniques, the hybrid delta/beta mutants were confirmed by multiplex PCR, such as the Hb Lepore-Baltimore. In the group where the mutant chain could not be identified, because the variant fraction did not separate from the normal fraction by electrophoresis, only 3 samples could be assigned to a suspect phenotype, two Hb Köln and one Hb Okayama. For the other samples, it was not possible to obtain a suspect diagnosis. The results confirmed the several influences in Brazil, which reflect the diversity of ethnic origins in the country. The correct characterization of these variants using molecular biology supplies health professionals with accurate information about the mutants, assisting them in genetic counseling and providing a better understanding of the population.

