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Instability of Hemoglobin Molecule — A Review. Part I.

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ABSTRACT. The stability and solubility of hemoglobin (Hb) molecule depends upon an ordered tertiary structure and requires that each globin chain undergoes a minimum conformational changes. There are several processes by which the stability of hemoglobin molecule can be affected. Of many, the most common involves the replacement of those amino acids which are either in direct contact with heme group or in the viscinity of heme pocket. Substitution at the $\alpha_1\beta_1$ contact can result in weakening of the linkages. Deletion of certain amino acids residues from a polypeptide chain of hemoglobin is known to disrupt the secondary structure of the molecule itself. The subunit structure can also be affected due to replacement of helical residue by a proline residue. In many cases the stability of the molecule is also associated with oxidative changes in the molecule producing methemoglobin. There are also examples in which the instability of Hb molecule is self-causing due to the change in size of the substituted amino acid residue. The present review deals with molecular basis of instability of 109 unstable hemoglobins reported to date and comprehensive hematological data has been presented on these variants in various tables for ready reference. Also an attempt has been made to classify these unstable hemoglobins according to their clinical manifestations. It will be noticed that many of the mutant exhibits a mild instability of the hemoglobin molecule but, there are examples in which the hemolytic process is severe and this can be directly correlated to a given substitution to its particular site or kind of amino acid substitution in the Hb molecule.

Key words : Hemoglobin molecule — unstable hemoglobin — hemolytic anemia

INTRODUCTION

The human hemoglobin (Hb) is a tetramer of four polypeptide chains (2 α ; 2 nonα) which are held together by weak noncovalent bonds. Each globin chain has globular structure, composed of two layers of amino acids, internal and externals. The internal layer consist of non polar, non charged and hydrophobic amino acids while the external layer is made of polar, charged and hydrophobic amino acid residues. The arrangement of these amino acids is such that each globin chain should have a relatively rigid tertiary structure and undergoes little conformational changes. For example, any exposure of hydrophobic amino acid residues surrounding the heme pocket to water can decrease the stability of hemoglobin molecules and its ultimate precipitation

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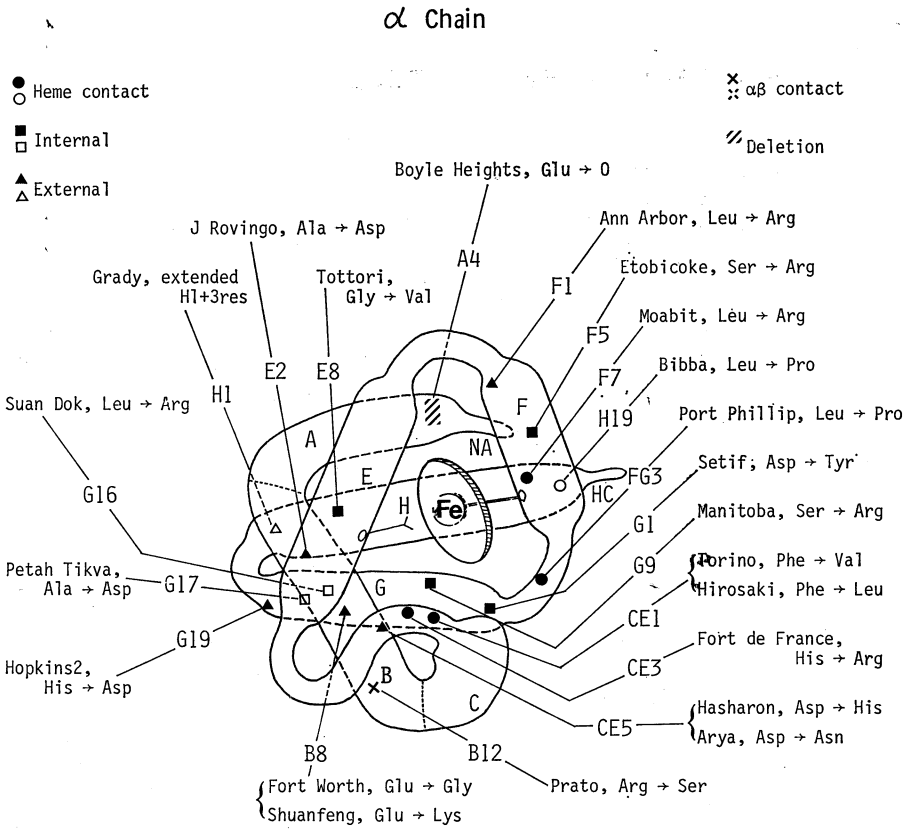

Fig. 1. Representing the position of α-chain unstable hemoglobin variants in their respective helices.

within the red cells. An abnormal hemoglobin known as mutant or variant results when one or more amino acids are replaced or deleted from a normal polypeptide chain. But there are several other mechanisms by which a variant can be formed. These mutants which result from a triplet base change in the DNA molecule may or may not have the altered stability and functional properties. There are several types of mutants and they all belong to two well recognized groups of hemoglobinopathies. The first group includes the stable hemoglobin variants of which many have no clinical significance. However, among these stable variants are those which considerably affect the functional properties of hemoglobin molecule and produce the disease like erythrocytosis. These variants have already been reviewed by Niazi and Huisman.[1)]

The unstable hemoglobin mutants belong to the second group of abnormal hemoglobins and the instability of these variants depend upon the kind and site of amino acid substitution or deletion in the hemoglobin molecule. In many cases the heme dissociates from the hemoglobin molecule and globin precipitates intracellularly and aggregates to form Heinz bodies which become attached to surface of the red cell membrane through hydrophobic contacts. This causes the ultimate premature destruction of the red cells as the red cells containing

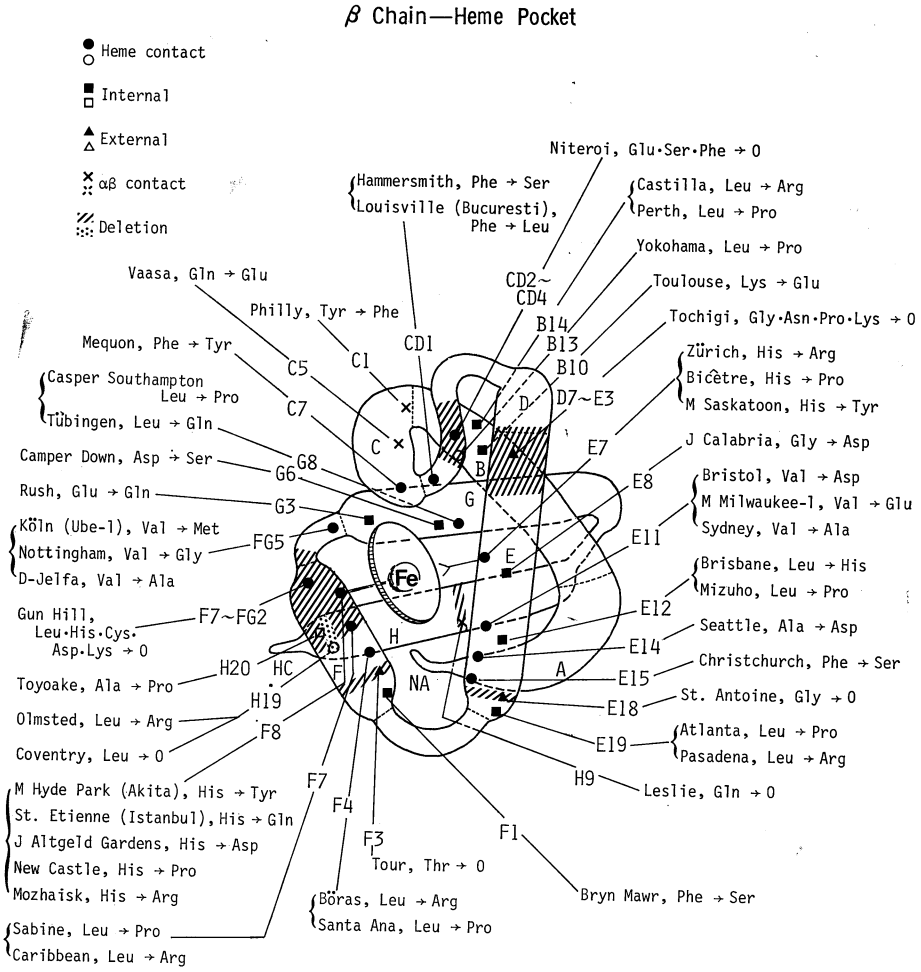

Fig. 2. Denotes the positions of β-chain unstable mutants in their respective helices. Those with substitution or deletion of amino acid residues in heme pocket are collected.

Heinz bodies have decreased pliability and filterability. This impaired viability of hemoglobin molecule is responsible for hemolytic disorder known as unstable hemoglobin hemolytic anemia (UHHA). The UHHA has been known as clinical syndrome since 1952 when Cathie[2] described the first case of congenital Heinz body hemolytic anemia due to an unstable hemoglobin, later identified as Hb Bristol and since then many unstable variants have been reported from all over the world. Figs. 1, 2 and 3 show the altered positions of various unstable hemoglobins in their appropriate helices. There is a total of 109 unstable hemoglobins reported to date of which 22 are the α chain variants, 86 β chain variants and one γ chain variant, Hb F-Poole, [γ130(H8] Trp→Gly).[3] Hb Ube-1 (Hb Köln) was the first example of unstable hemoglobin reported from Japan and since then 23 other unstable variants have been described and they form an important group of hemoglobinopathies in Japan.[4–6] Nine out of these 24 unstable mutants have been present exclusively in Japanese and rest

are shared by the people around the world. (To be continued)

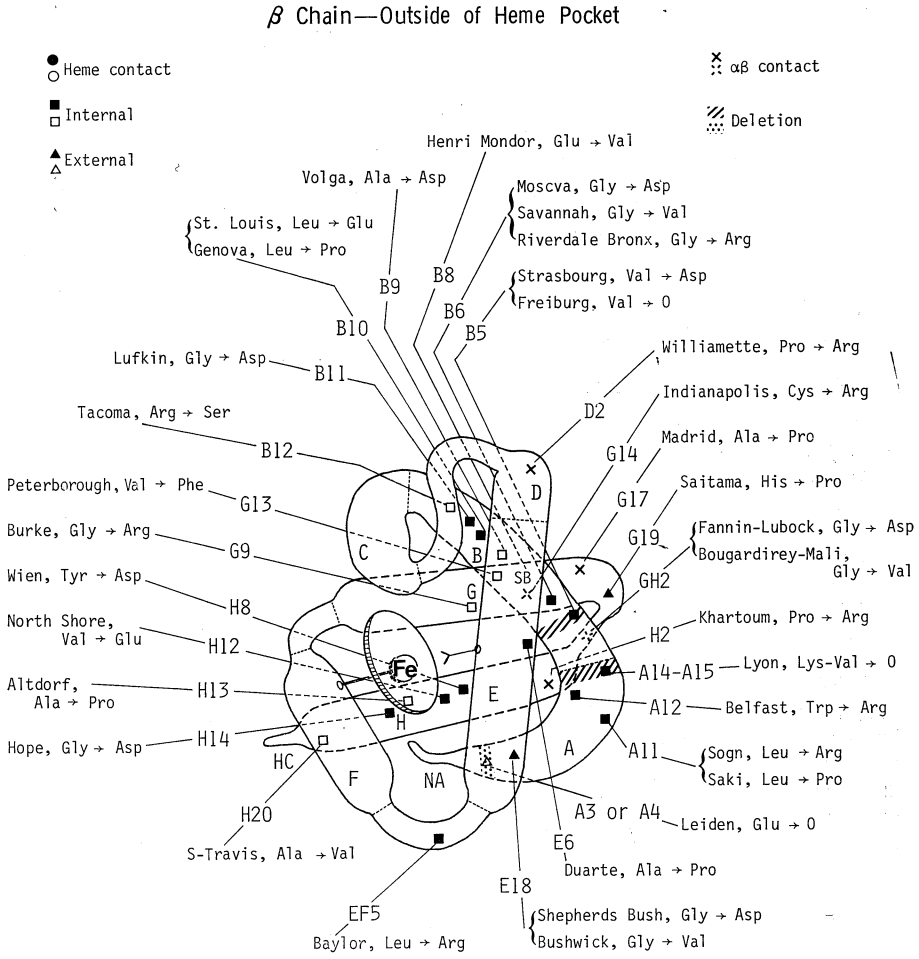

Fig. 3. Denotes the position of β-chain unstable mutants in their respective helices. Those with substitution or deletion in the positions outside of heme pocket are collected.

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