

Structural analysis of the elongated part of an abnormal hemoglobin “Hemoglobin Cranston”

Research Article

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Key words: Hb Cranston, structure

Abbreviations: Haemoglobin Cranston, (HbCranston)

Received: 5 July 2005; Revised: 28 September 2005

Accepted: 22 November 2005; electronically published: February 2006

Summary

Haemoglobin variants in which a frameshift results in chain elongation are unusual. Haemoglobin Cranston (HbCranston) is an unstable haemoglobin firstly with abnormal elongation. Concerning the pathogenesis of HbCranston, the insertion of the repeated pair nucleotide pair AG into mRNA between the triplet codon of 144 Lysine (AAG) and 145 Tyrosine (UAU) is the main abnormality. It is assumed to be due to an insertion of the dinucleotide CA into codon 146 [CACCA(CA)C] which abolishes the normal stop codon at position 147 (Bunn et al, 1975). This abnormality causes a frameshift, which results in elongation of the chain amino acids. Here, the author performs a bioinformatic analysis to study the secondary and tertiary structures of those elongated amino acid sequences. Answering this question, a computer-based study for protein structure modeling is performed. According to this study, the secondary structure analysis of the elongated part of Hb Cranston showed eleven additional helices to the normal globin chains. Based on this information, the main alteration in the Hb Cranston might be due to the additional helices in the elongated part. Concerning the tertiary structure, the increase of folds, accompanied with the aberration in secondary structure of globin in Hb Cranston can be identified.

I. Introduction

Haemoglobin variants in which a frameshift results in chain elongation are unusual (Bunn et al, 1975; Wiwanitkit, 2004). The two well-known disorders are haemoglobin Tak1 and haemoglobin Cranston2. Haemoglobin Cranston (HbCranston) is an unstable haemoglobin firstly described in 1975 (Bunn et al, 1975). Concerning the pathogenesis of HbCranston, this hemoglobinopathy is an unstable variant having an elongated chain due to nonhomologous crossover between two normal chain genes (Bunn et al, 1975).

Pathophysiologically, peptide maps of tryptic digests of the abnormal chain is identical to those of . An except that tryptic peptide 15 (Tyr-His-COOH) was absent and a new peptide was detected, containing equivalent amounts of Ser, Ile, Thr, and Lys. This abnormality results in elongation of the chain by the set on amino acids including Asn, Ser, Ala, Tyr, 2 Phe, and 3 Leu (Bunn et al, 1975). The elongated part of the chain is believed to be the causal factor for the instability of haemoglobin Cranston (Bunn et al, 1975).

Although the primary structure of Hb Cranston disorder is well known the secondary and tertiary structure of Hb Cranston is not well documented. The study on the secondary and tertiary structures of the elongated part in hemoglobin Cranston can help explain more in the pathogenesis of the Hb Cranston disorder is needed. Here, the author performs a bioinformatic analysis to study the secondary and tertiary structures of those elongated amino acid sequence. Answering this question, a computer-based study for protein structure modelling is performed.

II. Material and Methods

The author used the bioinformatics techniques to perform structure modeling.

The primary amino acid sequence of the elongated part in Hb Cranston is “Asn-Ser-Ala-Tyr-Phe- Phe-Leu-Leu-Leu.” Concerning secondary structure modelling, the author performs protein secondary structure predictions from its primary sequence using NNPREPDICTION server (Kneller et al, 1990). Concerning tertiary structure modelling, the author performs protein tertiary structure predictions of from its primary sequence

using CPHmodels 2.0 Server (Lund et al, 2002). The calculated secondary and tertiary structures were presented.

III. Results

Calculated secondary and tertiary structures of the elongated part of hemoglobin Cranston are presented in **Figure 1** and **2**, respectively.

IV. Discussion

Hb Cranston results from an aberration in β globin gene. The chain elongation in Hb Cranston can be explained by the insertion of the repeated pair nucleotide pair AG into β mRNA between the triplet codon of 144 Lysine (AAG) and 145 Tyrosine (UAU) (Bunn et al, 1975). The frameshift mutation is the result leading to an abnormal elongation of the β chain by amino acids- (144) Lys-Ser-Ile-Thr-Lys-Leu-Ala-Phe-Leu-Leu-Ser-Asn-Phe-(157)Tyr- COOH². This variant has firstly been described

in USA (Bunn et al, 1975). The clinical significance of this unstable hemoglobin is the relationship with a compensated hemolytic state due to an unstable hemoglobin variant (Bunn et al, 1975). The main pathogenesis is believed to due to the nature of this abnormal hemoglobin, resulting from the elongation.

Here, the author performed a structural analysis for the elongated part of Hb Cranston (**Figures 1, 2**). According to this study, the secondary structure analysis of the elongated part of Hb Cranston showed eleven additional helices to the normal β globin chains. Based on this information, the main alteration in the Hb Cranston might be due to the additional helices in the elongated part. Indeed, the structural aberration relating to the helix part of the globin chain seems to show some possible correlation to hemolysis. Coleman et al (1995) studied the molecular basis of transfusion-dependent hemolytic anemia in Hb Medicine Lake and noted that the potentially

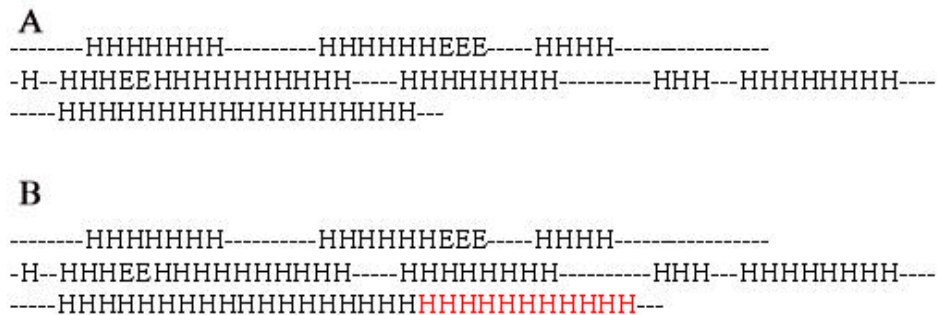


Figure 1. Calculated secondary structures of the elongated part of hemoglobin Cranston (Secondary structure prediction: H = helix, E = strand, - = no prediction). **A.** whole secondary structure of β globin in normal. **B.** whole secondary structure of β globin in Hb Cranston, elongated part is indicated in red

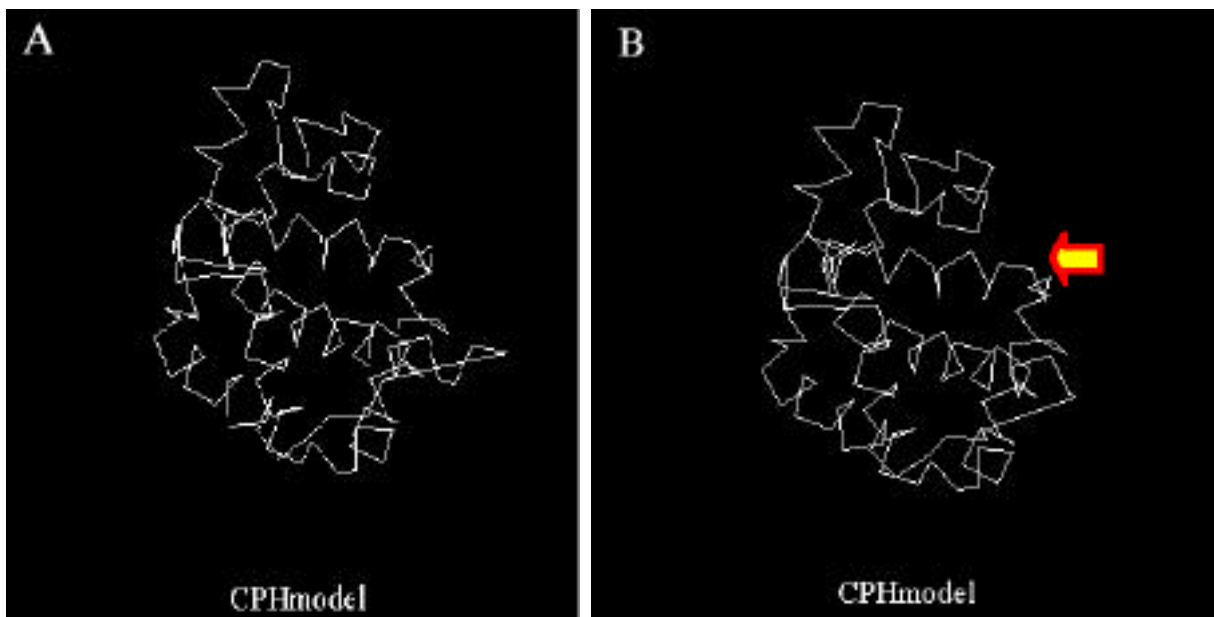


Figure 2. Calculated tertiary structures of the elongated part of hemoglobin Cranston. **A.** whole tertiary structure of β globin in normal. **B.** whole tertiary structure of β globin in Hb Cranston, yellow area indicate the elongated part.

distorted B helix might provoke further molecular instability including the presentation of mild hemolytic anaemia (McDonald et al, 1980).

Although there are some previous studies on kinetic as well as structural properties of Hb Cranston (Shaeffer et al, 1980) and to synthesize of Hb Cranston (Shaeffer et al, 1980) there is no previous study to produce the three-dimensional model of Hb Cranston. Concerning the tertiary structure analysis, the author hereby first generates the model of β globin chain in Hb Cranston using CPHmodels 2.0 Server. Predicted models of β globin chain in normal and Hb Cranston are shown. The increase of folds, accompanied with the aberration in secondary structure of globin in Hb Cranston can be identified. The developed structure can be useful in further study on the molecular and molecular action in this disorder. Although the direct link between structure and gene therapy at the moment is not described knowing more about the basics of this disease may be helpful for the development of future therapies.

In conclusion, the secondary structure analysis of the elongated part of Hb Cranston showed eleven additional helices to the normal β globin chains. Based on this information, the main alteration in the Hb Cranston might be due to the additional helices in the elongated part. Concerning the tertiary structure, the increase of folds, accompanied with the aberration in secondary structure of globin in Hb Cranston can be identified.

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