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Elongation of α globin chains, does excessive amino acids and helices relate to clinical manifestation?

Research Article

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Summary

Haemoglobin variants in which a disorder results in chain elongation are unusual. For α globin chain, the elongation of haemoglobin is believed to relate to the clinical manifestations such as those in hemoglobin H diseases. Although the primary structures of Hb disorders with elongated α globin chains are well-known the secondary structure of them is not well documented. The study on the tertiary structures of the elongated part in those Hb can help explain more in the pathogenesis of the disorders is needed. Here, the author performs a bioinformatic analysis for nanohematology to study the secondary structures of three well described Hb disorders, Hb Pak Num Po, Hb Pakse and Hb Constant Spring with elongated α globin chains. According to the analysis, the trend of increase aberration relating with increased excessive amino acids and excessive helical residues are noted. However, generalization to other Hb disorders, than these 3 disorders, needs further experimental studies..

I. Introduction

Haemoglobin variants in which a disorder results in chain elongation are unusual (Bunn et al, 1975; Wiwanitkit, 2004). The first two well-known disorders are haemoglobin Tak (Wiwanitkit, 2004) and haemoglobin Cranston (Bunn et al, 1975). However, there are other haemoglobinopathies with chain elongation. For α globin chain, the elongation of haemoglobin is believed to relate to the clinical manifestations such as those in hemoglobin H diseases.

Although the primary structures of Hb disorders with elongated α globin chains are well-known the secondary structure of them is not well documented. The study on the tertiary structures of the elongated part in those Hb can help explain more in the pathogenesis of the disorders is needed. Here, the author performs a bioinformatic analysis for nanohematology to study the secondary structures of three well described Hb disorders with elongated α globin chains. Answering this question, a computer-based study for protein structure modeling is performed.

II. Material and Methods

The author used the bioinformatics techniques to perform structure modelings. The four studied Hb disorders with abnormal elongation of α globin chains include Hb Pakse [codon 142 (TAA-->TAT or Term-->Tyr)](Sanchaisuriya et al, 2002), Hb Constant spring [codon 142 (TAA-->CAA or Term-->Gln)] (Steinberg and Adams, 1983; Harteveld et al, 2001) and Hb Pak Num Po [codon 131/132 +T] (Viprakasit et al, 2004a). The primary amino acid sequence of the elongated part in those Hb disorders is used for further structural modeling. Concerning secondary structure modeling, the author performs protein secondary structure predictions from its primary sequence using NNPREDICT server (Kneller et al, 1990). Briefly, this server is the copyright of the University of California (www.cmpharm.ucsf.edu). The best case prediction is 79% for the class of all-αproteins (Kneller et al, 1990).

III. Results

Using NNPREDICT server, the calculation for secondary structure of the elongated part of each disorder was performed. A table showing the number of excessive amino acids and helices is presented (**Table 1**).

IV. Discussion

Here, the author performed a structural analysis for the elongated part of common Hb disorders with elongation of α globin chains. Concerning the secondary structure analysis, the alterations of folds in structure of globin in each structure can be identified.

As shown in **Table 1**, the hemoglobin with more

Table 1. Underlying pathogenesis, the number of excessive amino acids and helices in studied Hb disorders with elongated α globin chains.

Hb disorders	Number of excessive amino acids	Number of excessive helical residue*	Underlying pathogenesis
Hb Pak Num Po	34	14	thymidine insertion after codon 131
Hb Pakse	31	14	codon 142 TAA-->TAT
Hb Constant Spring	31	11	codon 142 TAA-->CAA

*Data from secondary structures prediction

excessive amino acids has more relation to severe clinical manifestation. In this case, the Hb Pak Num Po contains the most excessive amino acids. Indeed, this Hb disorder,resulting frameshift, gives rise to a highly unstable α globin chain (Viprakasit et al, 2004b). This unusual α globin variant clearly causes α thalassemia and have additional effects on red cell physiology (Viprakasit et al, 2004b). Transfusion-dependent Hb H disease is noted (Viprakasit et al, 2004b).

There are two Hb disorders with fewer excessive amino acids, Hb Constant Spring and Hb Pakse. Indeed, these two disorders usually present with transfusion-independent Hb H diseases. Hb Pakse differs from Hb CS by having lysine at 142 instead of glutamine. It also seems to lead to an unstable α globin mRNA and slighter higher Hb H levels (Viprakasit et al, 2002; Turbpaiboon et al, 2004). According to this study, Hb Pakse has more additional helices comparing to Hb CS. This might imply that the disorders with same number of excessive amino acid, one with more excessive helical residues trends to have more severe clinical manifestation. Indeed, the structural aberration relating to the helical residue of the globin chain seems to show some possible correlation to hemolysis. Coleman *et al* studied the molecular basis of transfusion-dependent hemolytic anemia in Hb Medicine Lake and noted that the potentially distorted B helix might provoke further molecular instability including the presentation of mild hemolytic anaemia (Coleman et al, 1995). However, further studies are needed to verify this hypothesis.

In conclusion, according to the analysis, the trend of increase aberration relating with increased excessive amino acids and excessive helical residues are noted. Generalization to other Hb disorders, than these 3 disorders, needs further experimental studies. According to this study, the bioinformatics software analysis can be used to propose a hypothesis regarding predicted protein structures and a biological effect, as was demonstrated in a previous manuscript by the author (Wiwanitkit, 2004).

However, a correlation between predicted structures and disease severity is still insufficient to definite the final conclusion, therefore, additional biochemical analysis is still required.

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