Hemoglobin Thionville

EXPLORING THE IMPACT OF HEMOGLOBIN THIONVILLE AS A HUMAN HEMOGLOBIN VARIANT THROUGH STRUCTURAL INSIGHTS AND FUNCTIONAL APPLICATIONS

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Introduction:

Hemoglobin is a paragon of biological function, as with its tetrameric structure (α2-β2), it is designed to bind oxygen with high fidelity and is essential for processes such as cellular respiration and energy production to take place within the body [4]. This paper will delve into hemoglobinopathies, in particular, the variant Hemoglobin Thionville, by examining its functional, structural, and clinical aspects. The paper will uncover the interplay between genetic information and protein expression, enabling a gain in an in-depth understanding of how human health can be impacted by variations in the systems that govern it.

The critical functions of hemoglobin can be attributed to its sophisticated quaternary structure, which is comprised of two alpha (α) and two beta (β) polypeptide chains (subunits). Each subunit is bound to a heme group that functions as a point of attachment for molecular oxygen [1]. Within the circulatory system of the human body, hemoglobin plays an indispensable role in oxygen transport dynamics, carrying oxygen to respiring tissues from the lungs, as well as transporting carbon dioxide back to the lungs for exhalation, all the while shifting between tense (T) and relaxed (R) configurations [5]. A variant, such as Hemoglobin Thionville (Hb Thionville), results from gene mutations that encode for the protein. Hb Thionville, in particular, differs from wild-type human Hemoglobin (Hb A) in that, the N-terminus in the α-chain contains the initiator methionine, which is due to a substitution of valine with glutamate at the NA-1 position. The variance in the mutant form results in decreased affinity for oxygen due to overall changes in the structure of the α-chains [1]. Oxygen binding in hemoglobin is facilitated by four active sites (binding a maximum of 8 oxygen atoms) in hemoglobin, one in each subunit, and they all contain a heme prosthetic group, which is made up of an iron-containing porphyrin ring system (Fe(II) protoporphyrin IX) [6]. Slight changes in the angles and lengths of bonds stabilizing the heme-binding pocket result in noticeable changes in affinity towards oxygen and

the general stability of hemoglobin. Normally, the initiator methionine is released during the processing of the amino acids (via methionine aminopeptidase), and its acetylation is typically inhibited by the valine that sits next to it in the amino acid sequence. In the mutant, however, the cleavage of the initiator methionine is inhibited by glutamate, and conformational changes in the protein structure make it more stabilized in its deoxidized form upon new inter- and intra-subunit connections. The original connections were indirectly made possible through anion effectors (chloride ions), but are displaced in the mutant because of the modified structures having altered positioning within the physical space occupied [1,7].

The Hemoglobin (Hb) Thionville variant was first identified by Corrine Vasseur, et. al in *Hemoglobin Thionville: An a-Chain Variant With a Substitution of a Glutamate for Valine at NA-1 and Having an Acetylated Methionine NH_2 Terminus.* A 78-year-old French diabetic patient was found with Hb Thionville, making up approximately 21% of the total amount of Hemoglobin present, with no hematological abnormalities [1].

Discussion:

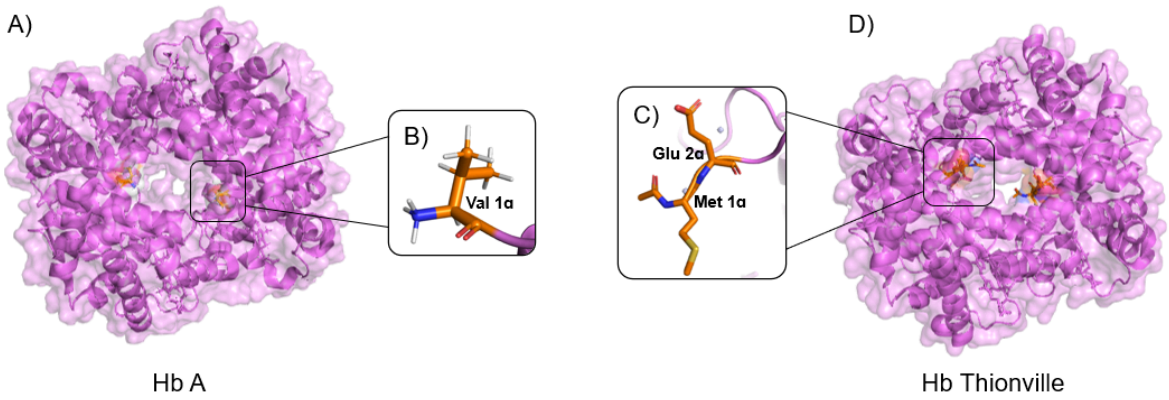

Figure 1. *Visual comparison of the structures of the N-terminal residues in the α-chain of Hb A and Hb Thionville.* (A) Illustrates the quaternary structure of Hb A, highlighting valine residues within the wildtype tetrameric configuration (purple). (B) The atomic composition of valine is color-coded (orange: carbon; blue: nitrogen; red: oxygen; white: hydrogen). (D) Illustrates Hb Thionville's quaternary structure, (C) showcasing the acetylated methionine (contains sulfur (yellow)) and glutamic acid that replaced the valine. (B) and (C) contrast the valine, which is non-polar, with the polar and charged characteristics of glutamic acid. RCSB was used as the source for the protein models of Hb A (PDB: 3KMF) and Hb Thionville (PDB: 1BAB) and were rendered via PyMOL software.

The implications of the Hb Thionville mutation on general structure and function can be deduced through current understanding of hemoglobin variants. The wildtype Hb A consists of a valine residue at the NH_2-terminus of the α-chain, which is integral to the functional binding of oxygen [1]. As illustrated in the visual model, the substitution of valine (Val 1α) for acetylated methionine and glutamic acid (Met 1α, Glu 2α, respectively), showcases a significant deviation from the wildtype profile (Figure 1). In particular, the acetylation of methionine enhances the basicity of the N-terminus through the introduction of new electrostatic and steric components, altering the stability of the tetramer and the interaction of subunits, in the T-state [2].

As described earlier, the comparison of the Hb Thionville mutation with Hb A highlights the differences in the allosteric regulation of oxygen binding. This would assume a clinical manifestation as the mutant is characterized by a lower oxygen affinity. Phenotypic consequences of such mutations are varied, as they could range from asymptomatic to clinically

significant conditions such as cyanosis, underscoring the importance of the α-chain's N-terminus in hemoglobin function [1,3].

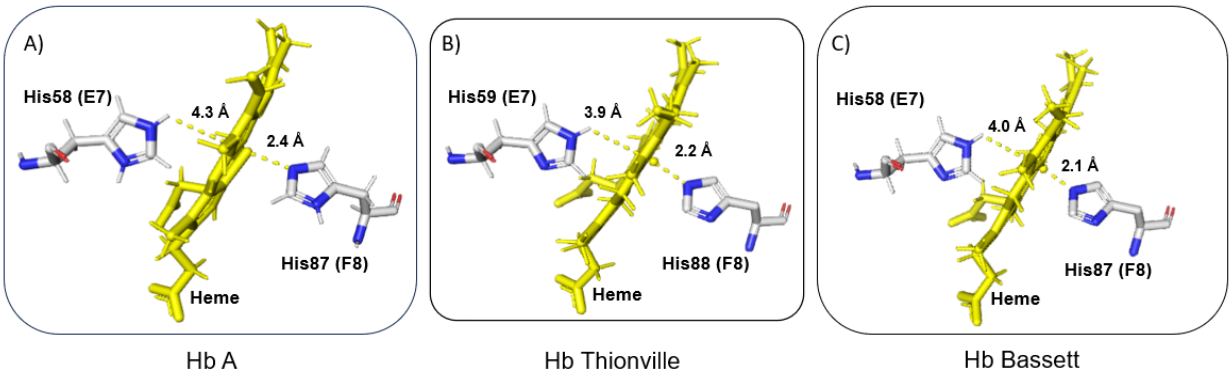

Figure 2. *Visual Comparison of the Heme prosthetic group, and the distances of the proximal and distal Histidine residues from the Fe^{2+} coordination site.* Panels (A), (B), and (C) depict the heme-bound histidine residues in each variant, annotated with the respective amino acid positions and spatial measurements. The dashed line (yellow) on the left, represents the hydrogen bond (distance is measured from hydrogen in histidine to Fe^{2+} in heme) that would be formed by the distal histidine (His59 (E7) in Thionville or His58 (E7) in wildtype and Bassett) (nitrogen: blue; carbon: white) with a bonded oxygen molecule (not shown), and their lengths are provided in angstroms, indicating the potential differences in oxygen affinity in the T-state. RCSB was used as the source for the protein models of Hb A (PDB: 3KMF), Hb Thionville (PDB: 1BAB), and Hb Bassett (PDB: 1R1Y) and they were rendered via PyMOL software.

The observed structural distinctions in the bond lengths between the wildtype Hb A and the variants, Hb Thionville and Bassett, as reflected in their different proximal and distal histidine-iron bond lengths, are pivotal for understanding their oxygen-binding affinities. For Hb A the expected delivery and release of oxygen is due to a delicate balance in bond length that facilitates it. Hb Thionville, with a proximal histidine closer (2.2 Å compared to 2.4 Å in Hb A) and a distal histidine closer (3.9 Å compared to 4.3 Å in Hb A) to the heme iron, suggests altered oxygen affinity, most likely linked to the acetylation of methionine and substitution of valine for glutamate [1,3]. These changes potentially stabilize the T-state over R, influencing the effectiveness of hemoglobin as an oxygen transporter. With a generally smaller heme-binding

pocket in the variants relative to Hb A's heme-binding pocket, oxygen may have more difficulty accessing and binding to heme, hence the lower oxygen affinities [1].

Bond length variations in the heme-binding pocket may not be the only cause and effect for lower oxygen affinity, as the acetylated methionine present in the mutant intrudes the α1-α2 interface, creating new intra- and intersubunit interactions and impeding the binding of heterotropic effectors [1,6]. In particular, some of the chloride ions (anion effectors), which are typically used to decrease oxygen affinity by stabilizing the T state, are displaced by the N-terminal methionine [1,7]. In Hb A, Val 1α does not displace these chlorides, allowing them to interact within the α1-α2 interface during T state, but the further stabilized T state of Thionville would suggest that the new contacts made by the methionine would have a greater effect on maintaining the deoxygenated state [1]. These structural variations highlight the sensitivity of hemoglobin's oxygen-binding capacity to even subtle alterations in the amino acid sequence, reflecting an intrinsic adaptability that, when affected by mutations, leads to significant, physiological consequences [1,3].

To summarize, it is important to integrate the structural and functional nuances that differentiate Thionville from Hb A and other variants like Hb Bassett. The most distinctive feature of Hb Thionville is the acetylated methionine, which alongside glutamic acid, replaces valine at the N-terminus of the α-chain. This modification results in a reduced affinity for oxygen, despite theoretical predictions, illuminating the intricate interplay of hemoglobin's function and structure. This complexity is mirrored in Hb Bassett, exhibiting similar histidine-iron bond lengths and functional characteristics contributing to low oxygen affinity, even though its mutational profile is unlike Thionville [1,2,3]. This discussion encapsulates how

mutations can provide insight into the adaptability and variable function of hemoglobin, for its role in physiological oxygen transport.

Conclusion:

In this exploration of the atomic nuances of hemoglobin variants, the structural elucidations of Hemoglobin Thionville and Bassett offer great insights into the protein's allosteric mechanisms and the kinetics behind oxygen-binding. The subtle shortening in the bond lengths within these variants provides a legitimate illustration of how minute genetic irregularities can culminate in clinical manifestations such as altered oxygen affinities leading to clinical symptoms of cyanosis. The acetylation of Hb Thionville's N-terminus prompts a reevaluation of how it interacts with oxygen, redefining how the interplay between hemoglobin functionality and protein modifications is understood. This study highlights the intricate dependencies within the protein structure, and the observations made here contribute to a greater understanding of hemoglobinopathies and pave the way for future research into tailored therapeutic strategies that could either mitigate clinical outcomes or help in the identification and diagnosis of variants present in the patients. The insights gained here go beyond the molecular scope, informing biological processes and potential interventions.

References:

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