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Analysis of HBA1 and HBA2 and Their Possible Association with Alpha Thalassemia

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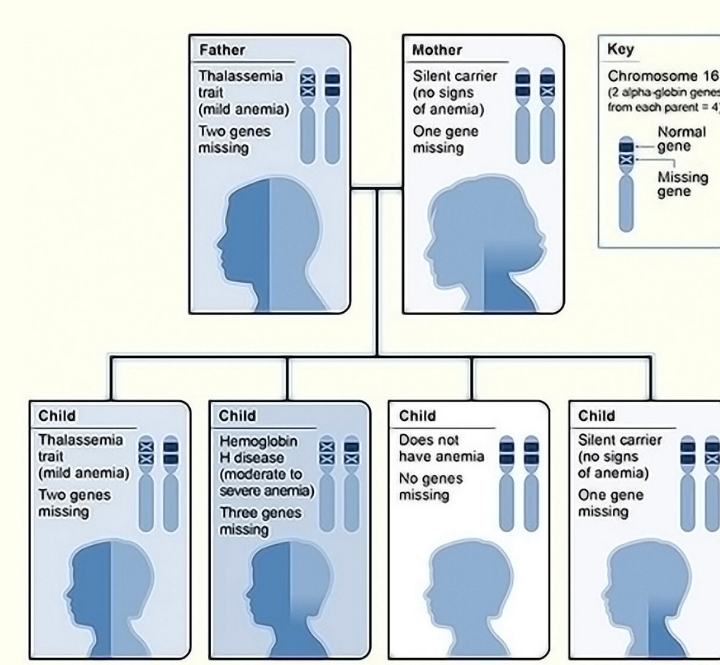


ABSTRACT

Alpha thalassemia is a genetic blood disorder in which the body does not produce enough alpha globin, which is the building block of hemoglobin. Hemoglobin is a protein in red blood cells that carries oxygen throughout the body. It is composed of four protein chains—two alpha globin chains and two beta globin chains. There are four main types of thalassemia including alpha thalassemia silent carrier, alpha thalassemia carrier, hemoglobin H disease, and alpha thalassemia major. The primary objective of this study is to investigate the genes responsible for alpha thalassemia. Simple Clinvar identified two closely related genes that are responsible for alpha thalassemia—HBA1 and HBA2. Simple ClinVar also provided me with a list of variants for each gene. Polyphen2 and SIFT were used to analyze variants of both HBA1 and HBA2. They found various mutations, including Gly60Asp in HBA1 and Met1Thr in HBA2. Both were identified as possibly damaging and pathogenic. Swiss Model was used to illustrate the protein structures for HBA1 and HBA2. Both HBA1 and HBA2 were expressed in three organs including bone marrow, the placenta, and spleen. PolyPhen2 and SIFT found that missense mutations including Gly60Asp and Met1Thr in HBA1 and HBA2 had damaging effects on protein function. These findings demonstrate that mutations in HBA1 and HBA2 may lead to defective chains of alpha-globin due to mutations, leading to alpha thalassemia.

INTRODUCTION

- There are four main types of thalassemia including alpha thalassemia silent carrier, alpha thalassemia carrier, hemoglobin H disease, and alpha thalassemia major. In alpha thalassemia silent carriers, only one gene is missing or damaged and the other three are normal. Individuals with this form of the disease express no symptoms, but can pass it down to their children. Alpha thalassemia carriers only have two of the four genes and express mild anemia. Individuals with hemoglobin H disease only have one working gene and three defective genes, meaning moderate to severe anemia is expressed. Lastly, alpha thalassemia major occurs when all four genes are missing or defective, which causes severe anemia. Fetuses with this condition usually die before birth. Alpha thalassemia is prevalent in Southeast Asian, Middle Eastern, and Mediterranean populations.
- Alpha thalassemia can be diagnosed through clinical evaluation, laboratory testing, analysis of family history, and genetic testing. These tests include CBC (complete blood count), which can give information about the size of red blood cells. Hemoglobin electrophoresis separates various types of hemoglobin present in the blood. Abnormal patterns on hemoglobin electrophoresis can be observed in individuals with this blood disorder. Prenatal testing is also used to determine the status of a child with severe alpha thalassemia, via chorionic villus sampling (CVS). Lastly, peripheral blood smear examines red blood cells under a microscope to observe abnormal RBC morphology.
- HBA1 and HBA2 are two closely related genes found on chromosome 16. Together, each gene contributes two alpha-globin chains, resulting in a total of four alpha-globin chains in the body.

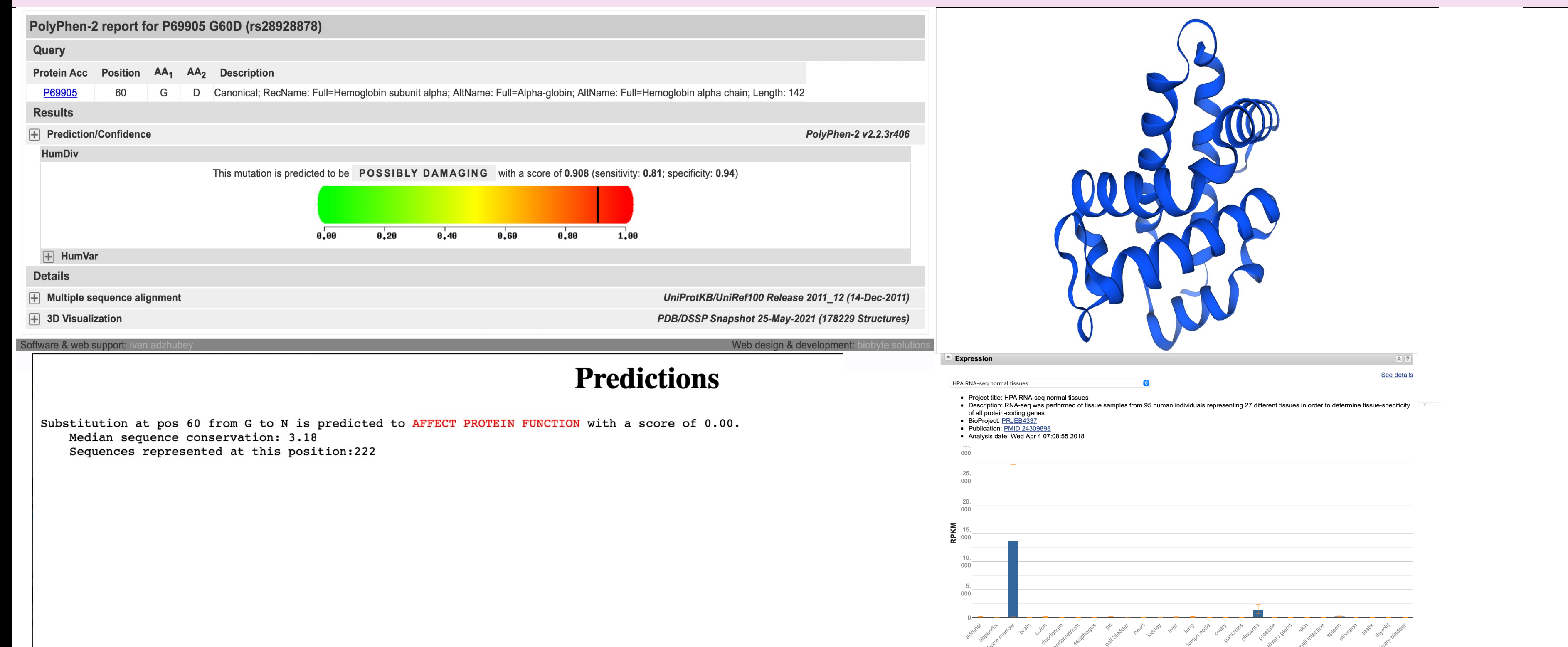


METHODS

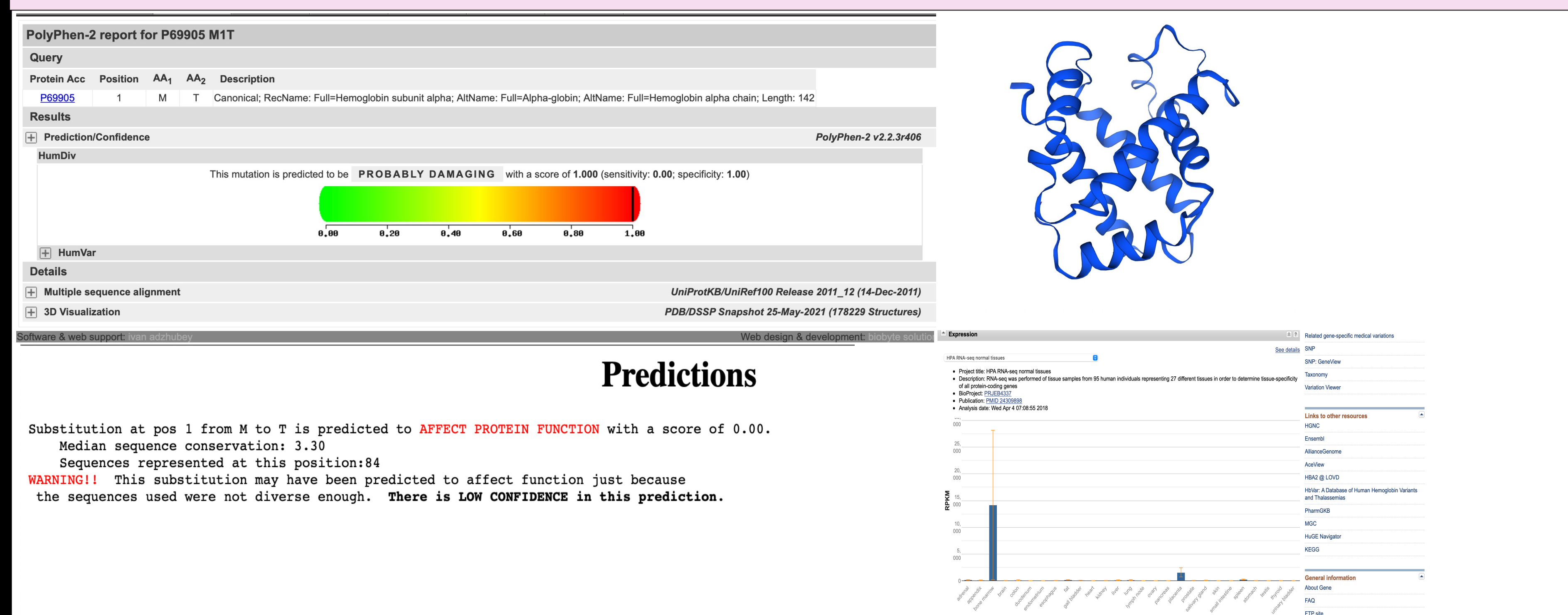
- Simple Clinvar identified two closely related genes that are responsible for alpha thalassemia—HBA1 and HBA2
- Polyphen2 and SIFT were used to analyze variants of both HBA1 and HBA2.
- Swiss Model was used to illustrate the protein structures for HBA1 and HBA2

RESULTS

HBA1



HBA2



Conserved domains on [gi|1690491812|gb|QDE10565|]

alpha-1-globin [Homo sapiens]

Protein Classification

hemoglobin alpha subunit family protein (domain architecture ID 10172381)

hemoglobin alpha subunit family protein is either one of alpha, zeta, mu, theta, or related hemoglobin (Hb) subunits. Hb is the oxygen transport protein of erythrocytes. It is an allosterically modulated heterotetramer. Hemoglobin A (HbA) is the most common Hb in adult humans, and is formed from two alpha-chains and two beta-chains (alpha2beta2). An equilibrium exists between deoxygenated/unliganded/T(tense state) Hb having low oxygen affinity, and oxygenated/Iliganded/R(relaxed state) Hb having a high oxygen affinity. Various endogenous heterotropic effectors bind Hb to modulate its oxygen affinity and cooperative behavior, e.g. hydrogen ions, chloride ions, carbon dioxide and 2,3-bisphosphoglycerate. Hb is also an allosterically regulated nitrite reductase; the plasma nitrite anion may be activated by hemoglobin in areas of hypoxia to bring about vasodilation.

Graphical summary

Query seq. MVLSPADKTNVRAWKVGARHAGEYGRHLEIRNLSFPPTTKTVFPHFLDSHGSQVVGKMKKQVADLTNAVAVYDDHFNALSLSDLAHKLKVDVNFKLLSHCLLVTLAAHPAEFTFPAVHSLDKFLSVSTVLSKYR

Specific hits: Hb-alpha-like, Globin-like superfamily

Name	Accession	Description	Interval	E-value
Hb-alpha-like	cd08927	Hemoglobin alpha, zeta, mu, theta, and related Hb subunits; Hb is the oxygen transport protein ...	3-142	8.64e-85

DISCUSSION AND CONCLUSION

Based on the findings of this study, it can be concluded that mutations in HBA1 and HBA2 experience mutations that can contribute to alpha thalassemia. In HBA1, the data predicted that missense mutations, including Gly60Asp, are possibly damaging and affect protein function. In HBA 2, the data reflected the same conclusion by analyzing mutations such as Met1Thr. The mutations caused in these genes can cause the gene to be defective and inhibit their function. Because the severity of alpha thalassemia depends on the number of nonfunctioning alpha-globin chains, we can infer that the severity of mutations in each gene will determine the status of each alpha globin chain.

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