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Analysis of PTCH-1 Gene in Anemia

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ABSTRACT

Anemia occurs when a lower-than-normal amount of red blood cells circulate in the blood. This disease may also result from low levels of hemoglobin, the protein that transfers oxygen into the blood. The main causes of anemia include inadequate production of red blood cells, blood loss, and vitamin B12 deficiency. Anemia has a wide range of conditions that span from mild and easily treatable, to severe, requiring immediate attention. Individuals who carry the PTCH1 gene have an increased risk of developing iron-deficiency anemia. This study analyzes specific mutations in the PTCH1 gene to determine if it contributes to the development of anemia. A web server database called Simple Clinvar was used to produce information and statistics regarding anemia and the different genetic diseases associated with the disease. The SIFT algorithm was used to predict whether the changes in the amino acid sequence of the PTCH1 gene were deleterious. Another algorithm like this, PolyPhen2, was used to predict and understand the influence amino acid substitutions have on the expression and function of proteins. PTCH1 is part of a cell signaling pathway involved in the formation of tissues and organs, cell growth, and cell division during embryonic development. It provides instructions for producing the patched-1-protein, which functions as a receptor. A substitution at position 997 from I to V is predicted to be tolerated with a score of 0.41. The PolyPhen2 predicts that the mutation is possibly damaging with a score of 0.929. PTCH1 is associated with multiple conditions in addition to anemia including nevoid basal cell carcinoma, also called gorlin syndrome, meningioma, and ovarian tumors. The expression of this gene is proven to be correlated with an increased risk of developing anemia.

INTRODUCTION

Anemia is the most common blood disorder. It is described as a reduction in the proportion of the red blood cells. Therefore, anemia is not a diagnosis but rather an underlying condition. Erythropoietin, which is made in the kidney, is the major stimulator of red blood cell production. The major stimulator of EPO production is tissue hypoxia, meaning that low levels of erythropoietin are inversely proportional to the hemoglobin concentration. To put this simply, an individual who is anemic with low hemoglobin levels has elevated levels of EPO. Anemia affects up to one-third of the global population. The recent advancements in genetic research have shed light on the intricate interplay between PTCH-1 and anemia. The PTCH-1 gene, short for Patched-1, is a crucial component of the Hedgehog signaling pathway, a highly conserved molecular cascade, essential for embryonic development, tissue homeostasis, and cellular differentiation. Originally identified for its role in embryogenesis, PTCH-1's significance extends beyond development, into various physiological processes, including hematopoiesis—the formation of blood cellular components. Mutations/dysregulations in the PTCH-1 gene have been involved in causing hematological disorders that can range from congenital anemia to bone marrow failure.

METHODS

- Simple-Clinvar was used in this study's initial observation of the gene PTCH-1 gene to find its connection to anemia.
- SIFT programming was used to take the sequence homology, which would predict wether an amino acid substitution would effect the protein function
- Modeling methods used in this study include analysis through amino acid substitution to predict the effect of a missense variant using PolyPhen.

RESULTS

GENE IDENTIFICATION

PTCH-1 is a tumor-suppressor gene that prevents cells from proliferating in an uncontrolled way. It works as a negative regulator of the H-H signaling pathway and provides instruction for producing the patched-1 protein, which functions as a receptor.

PolyPhen-2 report for Q13635 I1148V

Query

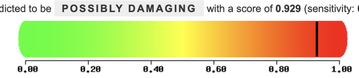
Protein Acc	Position	AA_1	AA_2	Description
Q13635	1148	I	V	Canonical; RecName: Full=Protein patched homolog 1; Short=PTC; Short=PTC1; Length: 1447

Results

Prediction/Confidence — *PolyPhen-2 v2.2.3r406*

HumDiv

This mutation is predicted to be **POSSIBLY DAMAGING** with a score of **0.929** (sensitivity: **0.81**; specificity: **0.94**)

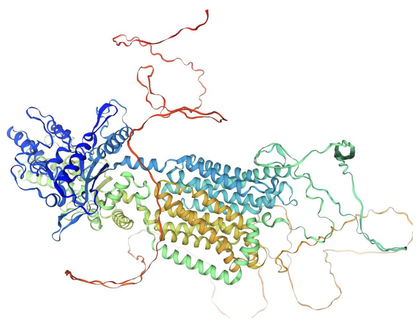


HumVar

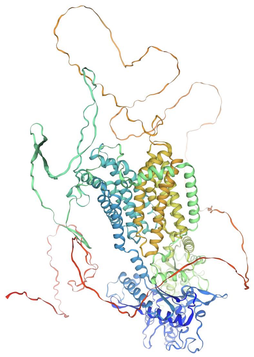
Details

Multiple sequence alignment — *UniProtKB/UniRef100 Release 2011_12 (14-Dec-2011)*

3D Visualization — *PDB/DSSP Snapshot 25-May-2021 (178229 Structures)*



PTCH-1 Mutated Gene



PTCH-1 Normal Gene

Coding Variant Mapping and domain annotation for PTCH-1

DISCUSSION AND CONCLUSION

- PTCH-1 gene's contribution to anemia offers profound insights into the molecular mechanisms governing erythropoiesis and iron metabolism. One of the key findings in understanding PTCH-1's role in anemia is its involvement in hematopoietic stem cell regulation.
- PTCH-1 governs the balance between proliferation, differentiation, and survival of hematopoietic progenitor cells, thereby exerting a significant influence on erythropoiesis.
- Dysregulations of PTCH-1 signaling, either through genetic mutations or aberrant expression, can disrupt this delicate equilibrium, leading to impaired red blood cell production, hereby causing anemia and subsequent anemia. Iron deficiency is a common cause of anemia worldwide, and PTCH-1 plays a crucial role in varying iron uptake, utilization, and recycling processes.
- Dysfunctional PTCH-1 signaling can disturb these iron homeostasis mechanisms, exacerbating iron deficiency anemia or contributing to the development of other anemia subtypes. To conclude, the PTCH-1 gene is an extremely pivotal player in the complex landscape of anemia. It offers a thorough genetic lens into its pathogenesis and explores its impact on iron metabolism.

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CODE
Characterizing Our DNA Exceptions