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Analysis of RYR1 Variants in Malignant Hypothermia

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ABSTRACT

Malignant Hypothermia is a disease that causes a potentially fatal hypermetabolic reaction of the skeletal muscle. It results in a rapid increase in body temperature and severe muscle contractions when someone receives general anesthesia. Malignant hypothermia is a rare autosomal dominant disorder that affects 1 patient per 5,000 to 100,000 patients. This study utilized Simple ClinVar, UniProt, PolyPhen2, SIFT, and Swiss Model to conduct an analysis and identification of mutations. Simple Clin Var identified the gene RYR1 as associated with malignant hypothermia. The RYR1 gene encodes the major sarcoplasmic reticulum calcium release channel of the skeletal muscle, providing the information needed to make the ryanodine receptor 1 protein. PolyPhen2 and SIFT were employed to predict RYR1 variants lle2435Thr, Thr2206Met, and Arg614Cys as likely pathogenic and damaging to the protein. Based on the analysis using Simple ClinVar, UniProt, Polyphen2, SIFT, and Swiss Model, it is believed that mutations in the RYR1 gene, particularly variants lle2435 Thr, Thr2206Met, ano Arg614Cys, result in decreased calcium channel function, leading to the manifestation of malignant hypothermia during general anesthesia. Calcium channels are structural components that provide a mechanism to modulate the force of contraction. These mutations damage the RYR1 gene which can impact calcium channels leading to malignant hypothermia. These findings could impact the medical community in explaining how the RYR1 variants can cause malignant hypothermia due to their pathogenic significance.

INTRODUCTION

Malignant hyperthermia is a life-threatening reaction to certain anesthesia drugs, causing rapid body temperature increase and muscle rigidity. It's triggered by genetic mutations, notably in the RYR1 gene. Prompt treatment is vital to prevent serious complications, including organ damage or death. The RYR1 gene encodes the major sarcoplasmic reticulum calcium release channel of the skeletal muscle. It provides the information needed to make the ryanodine receptor 1 protein. An RYR1 variant mutation encodes for Thr2206Met which turns threonine to methionine at position 2206.The mutation of threonine to methionine within the ryanodine receptor type 1 (RYR1) gene can lead to malignant hyperthermia, a life-threatening condition triggered by anesthesia. Threonine normally stabilizes the calcium release channel in RYR1, but its substitution with methionine disrupts channel function, causing uncontrolled calcium release in muscle cells. Additionally, glycine, produced through threonine metabolism, inhibits muscle contractions, while L-methionine opens calcium channels, potentially exacerbating calcium dysregulation in malignant hypothermia. Methionine, a nonpolar amino acid, may disrupt the normal interactions and conformational changes required for proper calcium channel function within RYR1. As a result, the mutated RYR1 channel becomes hypersensitive to triggering agents such as volatile anesthetics and depolarizing muscle relaxants, leading to uncontrolled calcium release, muscle rigidity, hypermetabolism, and hyperthermia characteristic of malignant hypothermia. The RYR1 gene is also seen in Congenital Myopathy. This disease is characterized by muscle weakness and hypotonia soon after birth or in early childhood.

METHODS

The tools that were used to conduct the analysis of the RYR1 gene were:

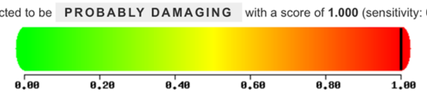
- Simple ClinVar
- PolyPhen2
- SIFT
- Swiss model prot.

Simple ClinVar was used to identify the RYR1 gene in malignant hypothermia. PolyPhen2 and SIFT was used to determine the pathogenicity of the different RYR1 mutations. Swiss model prot was used to construct a 3-D image of the RYR1 gene. All of these tools were used to gain knowledge on the RYR1 mutations to be able to conduct a full analysis of its affect on sideroblastic anemia. Databases like NIH and GeneCards were used to gain a full understanding of RYR1.

RESULTS

Protein Acc	Position	AA_1	AA_2	Description
XP_054177684.1	614	R	C	ryanodine receptor 1 isoform X4 [Homo sapiens]

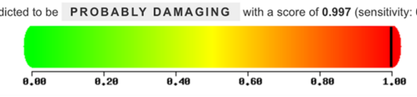
Results
Prediction/Confidence
HumDiv
This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)



HumVar

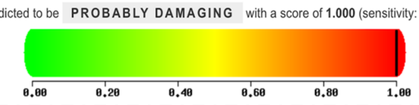
Protein Acc	Position	AA_1	AA_2	Description
XP_054177684.1	2453	I	T	ryanodine receptor 1 isoform X4 [Homo sapiens]

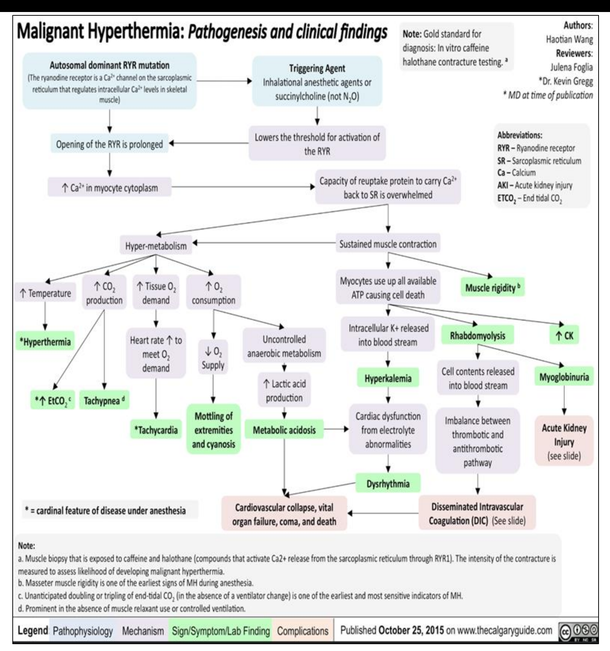
Results
Prediction/Confidence
HumDiv
This mutation is predicted to be **PROBABLY DAMAGING** with a score of **0.997** (sensitivity: **0.41**; specificity: **0.98**)

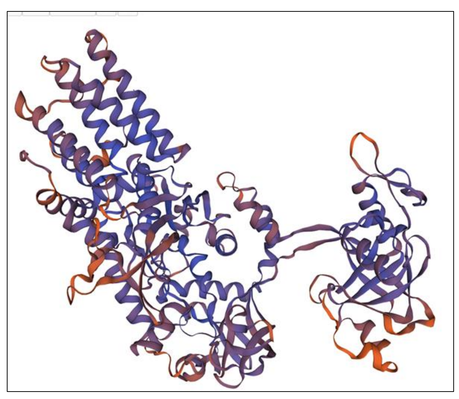


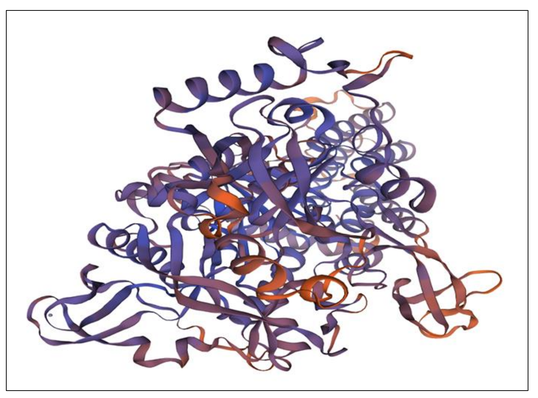
Protein Acc	Position	AA_1	AA_2	Description
XP_054177684.1	2206	T	M	ryanodine receptor 1 isoform X4 [Homo sapiens]

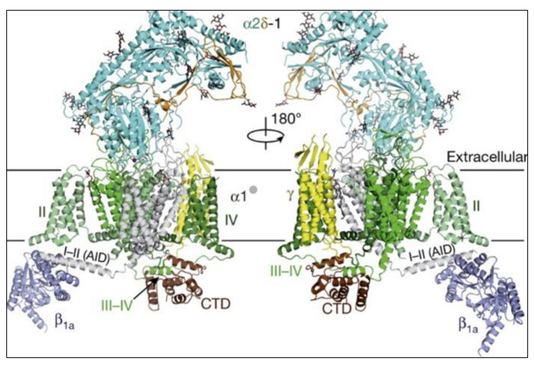
Results
Prediction/Confidence
HumDiv
This mutation is predicted to be **PROBABLY DAMAGING** with a score of **1.000** (sensitivity: **0.00**; specificity: **1.00**)











	Ile2435Thr	Thr2206Met	Arg614Cys
SIFT	0.06	0.00	0.00
Polyphen	0.997	1	1
Simple ClinVar	Pathogenic	Likely Pathogenic	Likely Pathogenic

DISCUSSION AND CONCLUSION

Malignant hypothermia occurs due to an abnormal response of skeletal muscle to specific triggering agents, particularly volatile anesthetics and depolarizing muscle relaxants. This abnormal response is often linked to genetic mutations, particularly in the ryanodine receptor type 1 (RYR1) gene. The mutation of threonine to methionine within the RYR1 gene, along with alterations in glycine metabolism and the effects of L-methionine on calcium channel function, collectively contribute to the pathogenesis of malignant hyperthermia. Methionine's disruption of normal calcium channel interactions leads to hypersensitivity to triggering agents, resulting in uncontrolled calcium release, muscle rigidity, hypermetabolism, and hyperthermia characteristic of malignant hypothermia. Additionally, glycine's role as an inhibitory neurotransmitter and threonine's contribution to calcium channel stability highlight their importance in modulating muscle tone and calcium homeostasis. Dysregulation of these mechanisms, along with aberrant calcium influx through GLR 3.1/3.5 channels, exacerbates calcium dysregulation in malignant hypothermia. These mechanisms collectively contribute to malignant hypothermia development, highlighting the importance of understanding molecular pathways for targeted interventions. Understanding these molecular pathways is crucial for developing targeted therapies to mitigate malignant hypothermia risk and improve patient outcomes. Prompt recognition and treatment are crucial to prevent complications such as organ damage or death. Treatment involves stopping the triggering agents, cooling the body, administering specific medications, and supportive care in a hospital setting.

REFERENCES

Database, G. C. H. G. (n.d.). RYR1. GeneCards is a searchable, integrative database that provides comprehensive, user-friendly information on all annotated and predicted human genes. Retrieved March 10, 2024, from https://www.genecards.org/cgi-bin/carddisp.pl?gene=RYR1

Ducamp, S., & Fleming, M. D. (2019, January 3). The molecular genetics of Malignant Hypothermia. Retrieved March 10, 2024, from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6318428/

Entry - #617021 - hydrops, lactic acidosis, and sideroblastic ... - omim. (n.d.). Retrieved March 11, 2024, from https://www.omim.org/entry/617021

ACKNOWLEDGEMENTS

I'd like to express my heartfelt appreciation to Dr. Elaine Vanterpool for her time and efforts throughout the year. Your helpful advice and suggestions were extremely beneficial to me during the project's completion. In this aspect, I am eternally grateful to you.

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