Hereditary hemochromatosis is a rare genetic disease where the body fails to regulate iron properly. In patients with this disease the blood becomes overloaded with iron and organs begin to shut down [1]. To date there is no cure for hemochromatosis; it can only be treated via regular blood donations [2].

Hemochromatosis is caused by mutations in the HFE gene. The HFE protein is a transmembrane protein found in liver and intestinal cells that is important for the regulation of iron. This function occurs via two domains: MHC1 and IgC1. The most common mutation is at amino acid position 282 in the IgC1 domain in which a cysteine is replaced with a tyrosine (C282Y) [3]. This leads to a break in the disulfide bond and a failure for the protein to fold and function properly [4]. Two other mutations exist for hemochromatosis in the MHC1 domain (H63D and S65C), but these mutations do not cause as severe of phenotypes like C282Y [3].

The HFE protein structure has only been loosely characterized and it is unclear why the H63D and S65C mutations, which are found in the MHC1 domain, are capable of causing hereditary hemochromatosis. There has been no research to suggest that the mutations in the MHC1 domain disrupt the structure of HFE. Examining how well conserved HFE human mutation sites are across species will shed light on the global role HFE plays in iron absorption. In addition, this will lead to insight into how important these mutation sites and the MHC1 domain are for HFE function. Finally, as there is no cure for hereditary hemochromatosis it would be beneficial to examine drugs that target the HFE protein and lower iron levels. Knowing more about the structure of HFE, and particularly the role of MHC1 in HFE, would help to select drugs that would likely interact with HFE. Given this, I ***hypothesize*** that the MHC1 domain is important for HFE's function in iron uptake and will be a good target for identifying drugs that interact with HFE.

The ***primary goal*** of this study is to examine the conservation of the mutations in human HFE, particularly H63D and S65C, across species. This will give insight into how important these mutations and the MHC1 domain are for iron uptake. The *secondary goal* of this study is to identify drugs that target HFE directly via the MHC1 domain for the treatment of hereditary hemochromatosis.

Specific Aim 1: **To determine how conserved the known mutation sites in human HFE are between vertebrates and invertebrates.**
Approach: Clustal Omega will be used to align the sequences of several HFE protein homologues.
Hypothesis: The H63D and S65C mutation sites will be conserved across vertebrates indicating the importance of those sites and the MHC1 domain in regulating iron uptake.

Specific Aim 2: **To identify drugs that can modify HFE protein function.**
Approach: A chemical genetic screen will be performed using a diversity oriented library in *C. elegans*.
Hypothesis: Iron levels can be altered by regulating the HFE gene function, possibly by interacting with the protein at the MHC1 domain.

References

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