computational approaches towards the rational design of rescue drugs for hERG mutations

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INTRODUCTION

hERG function and dysfunction

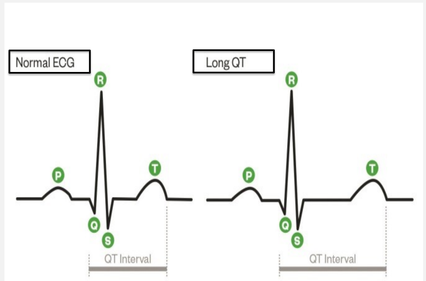
hERG is a potassium selective ion channel expressed in multiple tissues and cell types where it maintains resting membrane potential. [1-3]
The hERG channel, is highly expressed in the heart, and this is where its function and dysfunction is best understood. [1-3]

hERG k+ channels are essential for normal electrical activity in the heart in that they mediate the most important component of the repolarization phase in the cardiac action potential.[1-3]

Dysfunction of the hERG channel was found to cause long QT syndrome (LQTS)

LQTS is a cardiac repolarization disorder characterized by prolongation of the QT interval of the electrocardiogram (ECG) that predisposes affected individuals to arrhythmias that can lead to fainting and sudden death. [1-3]

Dysfunction of hERG channel is a result of:
- Blockage by drugs
- Mutations in the hERG protein



From https://pharmaceutical-journal.com/article/ld/long-qt-syndrome

OBJECTIVE

To study effects of class II trafficking mutations on the hERG protein for the sake of rescuing the defective mutant channels and retrieving their normal function.

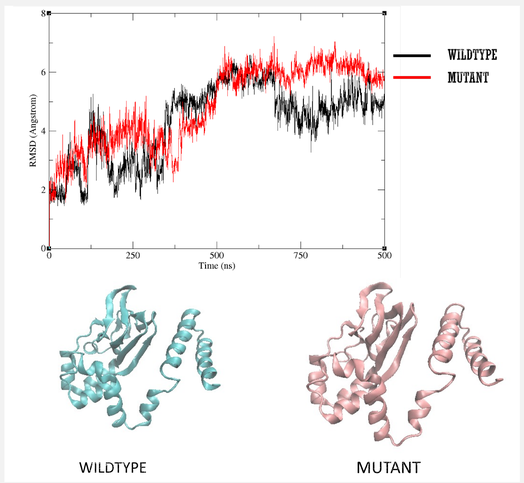
METHODS

- Induce a known mutation in the hERG protein, namely F805C
- Simulate the mutant and the wildtype protein using molecular dynamics simulations for 1 μs
- Analyze the mutant and control: stability of the structural integrity, normal dynamics, secondary structure changes throughout the simulation
- Analyze the cause of the protein misfolding if present. e.g., interactions lost

RESULTS

Backbone stability

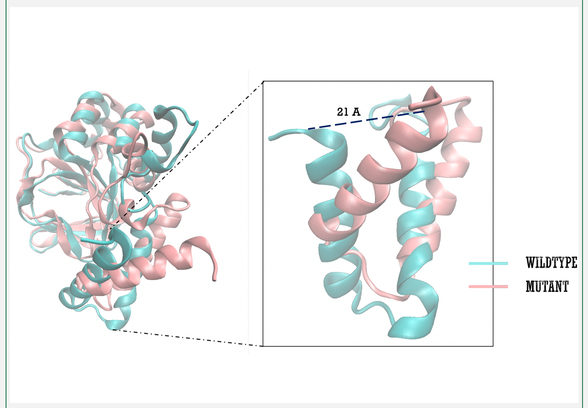
Visual inspection of the simulations and the calculation of the distant deviations of the atom coordinates throughout the length of the simulation was calculated



RESULTS

Local effects

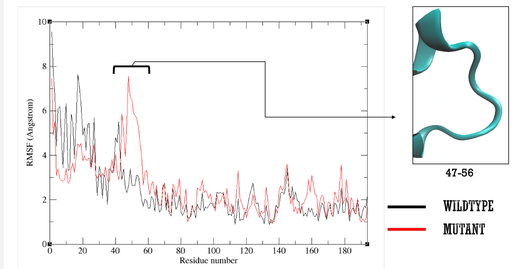
To study the local effects of mutation on protein conformation, the centroids of the top clusters from clustering the two simulations wee superimposed to highlight local changes post mutation.



RESULTS

Effects on normal protein dynamics

To investigate the effect of the F805C mutation on normal protein dynamics, the average positional fluctuations for each amino acid residue was calculated for each simulation



RMSF calculations averaged over each amino acid residue showed comparable fluctuations between the wildtype protein simulation and mutant

One distinct segment of the protein sequence showed higher fluctuations in the mutant simulation compared to that of the wildtype simulation.

Visual inspection of that segment revealed that it's a long loop in the structure of the protein which naturally exabits fewer stable dynamics and increased positional fluctuations

DISSCUSION AND FUTURE DIRECTION

Our results reveal that the F805C mutation located in the intracellular domain of the hERG channel is more likely to induce local misfolding in the structure of the protein rather than unfolding or large-scale denaturation in the protein of the channel.

Our results also reveal that the normal dynamics of the channel protein remains unaffected by this particular mutation.

Including the full-length tetramer of hERG

Follow up work:

- Study the effects of this trafficking mutation (F805C) on the interaction with neighboring domains (study the full sequence of channel).
- Examine the effect of these changes on the folding of the four monomers of the channel.
- Simulate the process of reversing these effects by rescue drugs.

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