

Drug-induced long qt syndrome



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Long QT (LQT) syndrome is a cardiac arrhythmia diagnosis that is reflective of a description found on the EKG (electrocardiography) as well as patient history and family history. It is an inherited cardiac condition that is characterized by genetically encoded abnormalities in cardiac ion channels, namely through sudden cardiac death, various palpitations, and syncope (temporary loss of consciousness induced by low blood pressure). These abnormalities are characterized by delayed myocardial repolarization that leads to varying degrees of QT prolongation and T-wave abnormalities on an EKG. T-wave abnormalities are represented by longer time from Q wave to the T wave, allowing for longer time for the heart to repolarize.

LQTS is a rare disorder, with about 1 in 7, 000 people possessing the disorder ⁸. This disorder of the heart's electrical activity can cause severe and sudden arrhythmias in response to stress or exercise, as the ion channels on the heart muscle cells may not function effectively or may be present in small amounts, generated by mutations in genes that code for these channels. Though it can be acquired, such as from various medications and drugs, it is typically genetic and exists in different forms, with LQTS 1, 2, and 3 being the main forms of the disease. Essentially, if the disorder goes untreated, more than half of affected individuals with inherited types of LQTS die within 10 years ⁹. However, if identified early on, certain lifestyles changes and medications can lead to a prolonged lifespan and prevent further complications. Such treatments include avoiding strenuous exercise, incorporating more potassium into one's diet, taking beta blocker heart medications, and implanted medical devices can control heart rhythms ¹⁰.

LQT is influenced by three major genes: KCNQ1, KCNH2, and SCN5A. Per Dr. Michael J. Ackerman, he states in ' Genetics of Long QT Syndrome,' that " These genes account for approximately 75% of the disorder" ¹ . Namely, patients with the disorder exhibit mutations in at least one of the three main genes that encode for the alpha (α) subunits and are critically responsible for the cardiac action potential; KCNQ1 and KCNH2 potassium channels (encoded I_{KS} and I_{KR} , and SCN5A sodium channel (encoded I_{NA}). The clear majority of mutations are single nucleotide substitutions or small insert/deletions ² .

LQT1 is is a subtype of congenital cardiac syndrome and is typically inherited in an autosomal dominant manner, as most patients have an affected parent and it is the most common type of LQT syndrome ³ . Each child whose parent carries the autosomal dominant gene of the disease exhibits 50% risk of inheriting the pathogenic variant. Autosomal dominant inheritance of the pathogenic variant occurs when mutation occurs in one of the three major genes, namely KCNQ1. This gene codes for a voltage-gated potassium ion channel that is highly expressed in the heart (KvLQT1) ⁴ . The product of the KCNQ1 gene produces an alpha subunit that interacts with other proteins, such as the mink beta subunit, to generate the I_{KS} ion channel responsible for the delayed potassium rectifier current of the cardiac action potential ⁵ .

The 404 kb long gene codes for a 75-kDa protein containing 676 amino acids and is expressed mainly in the heart, kidneys, pancreas, and small intestine. KCNQ1 subunits contain an NH₂ terminus, six membrane-spanning segments (S1-S6), a pore loop and voltage-sensing domain (VSD and S1-S4),

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two cytoplasmic loops (S2-S3 and S4-S5) and a COOH terminus domain. Majority of KCNQ1 mutations are missense mutations (single nucleotide substitutions) or small deletions/insertions that localize to the S1-S6 transmembrane domains. Mutations in the transmembrane, linker, and pore region of KCNQ1 are typically defined as high-probability disease-causing mutations that cause severe cardiac events in younger ages compared to mutations in the COOH terminal region.

Essentially, genetic background may have an adverse effect on the severity of the disease. Mutation type, specific location, as well as degree of dysfunction play integral roles in the clinical course of LQT1. Moss reported that LQT1 patients with transmembrane mutations and dominant-negative ion current effects had longer corrected QT interval and a higher frequency of cardiac events than individuals with mutations in other regions.

Additionally, hERG (KCNH2) is also another gene that codes for the alpha subunit of a potassium ion channel and mediates the repolarizing I_{KR} current in the cardiac action potential. HERG potassium channels are comprised of four identical alpha subunits, which correspond to the formation of the channel's pore in the plasma membrane. Each subunit is comprised of six transmembrane alpha helices (S1-S6), a pore helix between S5 and S6 transmembrane alpha helices, and is cytoplasmically located between the N and C termini. The S4 helix contains arginine or lysine amino acid residues, which are positively charged and present at every third position. This is believed to act as a voltage-sensitive sensor, thereby enabling the channel to respond to different voltage changes by inducing conformational changes between conducting and non-conducting states. An extracellular " turret"

loop and pore loop exist between the S5 and S6 helices, which loops into the plasma membrane. The pore loop for each of the hERG subunits in a given channel are adjacent to the corresponding loops of the remaining three subunits and collectively yield a region of the channel pore that is selectively permeable. Mutations in this channel that correspond to loss of function can lead to LQT2 while gain of function mutations can lead to short QT syndrome. These clinical disorders are derived from ion channel dysfunction, also known as channelopathies, and can lead to fatal cardiac arrhythmias, due to the disturbances in the repolarization of cardiac action potential. Though these mutations can lead to both long and short QT syndromes, hERG mutations are typically associated with LQTS.

Aside from genetic predisposition of LQT, another way of developing this disorder is for it to be acquired. In particular, LQT is induced by a block of cardiac HERG K⁺ channels as a side effect of certain prescribed drugs. Induced LQT drugs include: methanesulforanilide (MK-499) which suppresses abnormal cardiac rhythms, cisapride which relieves gastrointestinal symptoms such as acid reflux, and the allergy condition treatment terfenadine. These unfortunate discoveries has become a major factor amongst researchers who are trying to develop new and safe drugs.

In regards to induced LQT, the major findings through this research presents that there could be a structural reasoning to why medications that are normally used block HERG but not other channels such as voltage gated channels. An alanine scanning mutagenesis was used to define the the structural ground for the drug block of the HERG channels induced by the MK-499 drug. The binding site is constituted of the amino acids G648, Y652,

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and F656 on the transmembrane domain surface and pore helix T623 and V625 of the HERG subunit¹² that are adjacent to the channel's cavity. It was also concluded that though other compounds are structurally unrelated to the drug, they induce LQT and were studied as well. This includes the antihistamine terfenadine as well as cisapride, (a gastrointestinal prokinetic drug) and were observed to interact with transmembrane domain amino acids Y652 and F656, yet not with amino acid associated with pore helix, V625. It was noted that the amino acids that were expressed interacted with the aromatic residues of the S6 transmembrane domain, and these residues are specific to eag/erg potassium channels¹³. It was also noted that other voltage-gated channels have two different amino acids in the analog positions: isoleucine and valine (Ile and Val respectively). Essentially, these findings point towards possible explanation as to how many frequently used medications block and disrupt HERG's function, while other potassium channels remain unaffected.

To study the effects of the various drugs on HERG potassium channel function, John S. et al induced mutations through site-specific mutagenesis. Using SP6 Cap-Scribe¹⁶, complementary RNA sequences were generated after linearization expression constructed with restriction enzyme, EcoRI. *Xenopus* oocytes were isolated and maintained, as well as cRNA injections were performed. Moreover, to measure and record the membrane currents in the oocytes approximately four days after cRNA injection and to account for chloride currents, Cl⁻ was replaced with Mes. Lastly, the molecular model was accounted for by the retrieved 1BL8 KcsA structure from the Protein Data Bank. The structure was utilized as a template structure for the

homology model and sequence alignment was utilized to generate the homology model. The first model was utilized for the docking of MK-499, as only slight differences were observed. Essentially, one hundred conformations (low-energy) of MK-499 were generated and other high-scoring dockings exhibited very similar strong π stacking interactions with F656 and Y652 (see images below).

References

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