

RESEARCH PAPER

Influence of rs1800172 common gene variation on the structure and function of potassium voltage-gated channel subfamily Q member 1

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Highlights

- Potassium channel KCNQ1 is essential for the proper functioning of some tissues such as the heart and stomach.
- The rs1800172 polymorphism is an important exon variety in the structure of KCNQ1.
- The rs1800172 polymorphism can affect the primary and secondary structure of proteins.

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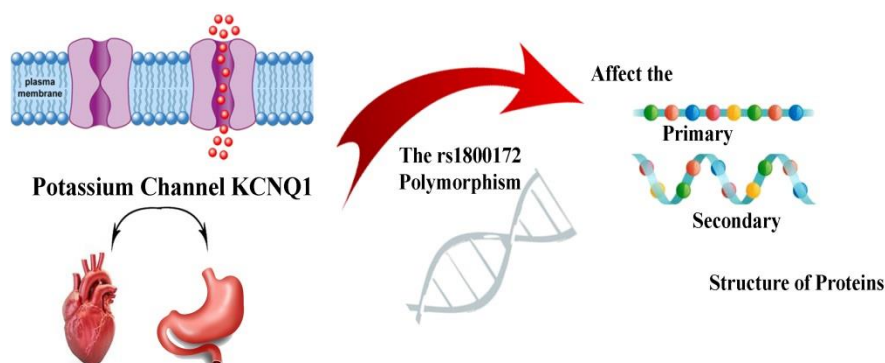
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Graphical Abstract



Abstract

The proper functioning of ion channels is essential for cell survival. One of the important ion channels is potassium voltage-gated channel subfamily Q member 1 (KCNQ), which consists of five genes whose main gene is KCNQ1 and encodes the voltage-gated potassium channel required for the phase of repolarization. KCNQ1 is mainly expressed in the heart muscle, inner ear, stomach, lungs, kidneys, intestines, and pancreas. This channel is essential for the proper functioning of cells in some organs of the body, including the heart and stomach. Thus, mutations and polymorphisms in this gene can alter the risk of some diseases, such as long QT syndrome and gastric cancer. The aim of this study was to investigate the effect of rs1800172 exon polymorphism on the function of the KCNQ1 gene using a bioinformatics approach. The ProtParam server was used to evaluate the primary structure of the protein. The PredictProtein server was used to investigate the effect of mutations on the secondary structure of the protein. Polyphen2 and SNAP2 servers were used to evaluate the effect of rs1800172 variety on overall protein structure and function. RNAsnp online software was used to investigate the effect of mutation on mRNA structure. Our study showed that rs1800172 polymorphism affects the primary and secondary structure of proteins. But this genetic variety did not affect mRNA structure. Investigation of the effect of KCNQ1 gene mutations including rs1800172 can be effective in identifying the pathological mechanisms of KCNQ1.

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Introduction

Ionic channels are essential for the basic functions of the cell and processes involving sensory receptors and intracellular communication in multicellular organisms. Voltage-gated K⁺ channels contribute to the repolarization process in the cell during the action potential, and these channels open in response to membrane repolarization to facilitate potassium ion flow (1). In other motile and immobile cells, where potassium channels are usually active, a relatively constant repolarization force is produced, as well as ion homeostasis and secretory processes. The potassium voltage-gated channel subfamily Q member (KCNQ) family consists of five genes, the main gene of which is KCNQ1, encoding the voltage-gated K⁺ channel required for the phase of repolarization. KCNQ1 is mainly expressed in the heart muscle, inner ear, stomach, lungs, kidneys, intestines, and pancreas (2). KCNQ1 is also involved in the transportation of salt and water in epithelial tissue. KCNQ1 plays a chief role in controlling K⁺ flow in several tissues, including the stomach (3). Also, the location of KCNQ1 in polar epithelial cells is always concentrated on one side (apical) or the other side (basolateral), although its polarity differs between each type of cell (4, 5).

All voltage-dependent ion channels have six domains (S1-S6), of which the S4 domain is voltage-sensitive and passes through the membrane. This domain is composed of alkaline amino acids, which determine the potential of the membrane and respond to alterations in the potential of the membrane. The KCNQ1 protein also contains S4 and can miss its voltage dependence. This channel is the most studied ion channel because it is associated with human diseases and has a great role in cell physiology. KCNQ1 protein can be involved in channel formation with two other proteins, KCNE1 and KCNE2. The KCNQ1 protein can form functional homomeric channels *in vitro*. When the function of the homomeric KCNQ1 channel is expressed heterologously (6), KCNQ1 may be correlated with one or more subunits of KCNE *in vivo*. KCNQ1 molecule does not form heteromers with other subunits of KCNQ, whereas KCNQ2-5 can form heteromer channels together (3). To date, the properties of homomeric KCNQ1 channels have not been shown, while several functional properties of KCNQ1-KCNE heteromers have been shown.

KCNQ1 is located in an area on chromosome 11 (11p15) that is adjacent to the IGF2 gene, which is involved in Beckwith-Wiedemann syndrome (BWS). In this syndrome, imprinting is impaired and people with the disease are overdeveloped and have a higher risk of cancer (7). KCNQ1 is imprinted in most tissues and only its maternal allele is expressed (8). In addition to affecting the activity of KCNQ1 through the electrochemical gradient, extracellular potassium can also inhibit the activity of KCNQ1, the mechanism of which is increased by the ratio of inactivated KCNQ1 channels. In the human body, no other tissue creates a higher concentration gradient for H⁺ than gastric mucosa. Parietal cells pump H⁺ into the lumen of the glands of the gastric, resulting in a million-fold increase of hydrogen ions in gastric acid. Since H⁺/K⁺ ATPase is not able to pump hydrogen ions to the lumen without simultaneously absorbing K⁺. During the secretion of gastric acid, adequate concentrations of potassium ions in the lumen are required (9, 10). Potassium channels have been identified in gastric parietal cells, including the apical KCNQ1-KCNE2 channels, which are highly expressed in gastric parietal cells (11) and can transmit K⁺ into the stomach and this pumping of H⁺/K⁺ ATPase causes the production and secretion of gastric acid. And through this, the H⁺/K⁺ ATPase pump causes the production and secretion of gastric acid (8, 12).

This gene is also involved in the pathophysiology of Long QT Syndrome (LQTS). Long QT syndrome is an atypical property of the electrical system of the heart that could result in a potential arrhythmia that threatens life called torsades de pointes. Torsades de pointes might lead to sudden cardiac death or syncope. More than 600 LQTS-related KCNQ1 mutations have been identified and this number is still growing (13-15). Although progress has been made in describing LQTS-related KCNQ1 functional mutations (16, 17), the mechanical basis of dysfunction of channel is not known for most mutations. The lack of straight experimental information to specify how mutations change the function of the channel has prompted bioinformatics and modeling examinations to predict their pathogenicity (18, 19). Therefore, this study aimed to investigate the effect of rs1800172 mutation on the function and structure of the KCNQ1 gene using a bioinformatics approach.

Materials and Methods

Investigation of KCNQ1 gene and screening of polymorphisms of this gene

First, important genes involved in common non-communicable diseases were identified using a review of reputable scientific databases such as PubMed, Google Scholar, ScienceDirect, SNPedia and some other standard databases. Among these genes, the KCNQ1 gene was selected as an attractive option due to its special structure and channel role in cell membranes. Based on data from the SNPedia database, it was found that there are a large number of single nucleotide polymorphisms (SNPs) in this gene. Since, in theory, exon polymorphisms usually have a greater impact on protein structure and function, coding variants were further evaluated. Polymorphisms were also screened for minor allele frequency (MAF) and polymorphisms with MAF = 0.01-0.1 were considered. The rs1800172 polymorphism, which was located on the last exon of the KCNQ1 gene, was selected. This genetic variant replaces glycine with the amino acid serine at codon 643 of the protein.

Bioinformatics tools used

First, the complete sequence of the KCNQ1 gene coding region was obtained from the NCBI database. The rs1800172 polymorphic locus on the KCNQ1 gene was then identified by Discovery studio software. The KCNQ1 nucleotide sequence was then translated into an amino acid sequence by ExPASy online software (<https://web.expasy.org/translate/>). The primary protein structure characteristics for wild and mutant alleles were calculated using ProtParam online software (<https://web.expasy.org/protparam/>). The secondary structure of the KCNQ1 protein was obtained by PredictProtein software for wild and mutant alleles (<https://predictprotein.org/>). The three-dimensional protein structure was simulated by the Phyre2 server (<http://www.sbg.bio.ic.ac.uk/phyre2/html/page.cgi?id=index>). A hydrophobicity plot for mutant alleles was obtained from ProtScale online software (<https://web.expasy.org/protscale/>). The effect of rs1800172 polymorphism on protein function and structure was deduced by Polyphen2 software (<http://genetics.bwh.harvard.edu/pph2/>) and SNAP (<https://www.rostlab.org/services/SNAP/>). In the next step, the effects of rs1800172 polymorphism on mRNA structure were obtained by RNAsnp software (<https://rth.dk/resources/masnp/>).

Results

Effect of rs1800172 polymorphism on the primary and secondary structure of the protein

Examination of the primary structure of KCNQ1 protein showed that this protein contains 676 amino acids. The primary structure of the protein characteristics was obtained by the ProtParam soft server for both wild and mutant genotypes. The molecular weight of the wild genotype is 74698.60 daltons, while that of the mutant genotype is 74728.62 daltons. The number of negatively charged amino acids for normal and mutant varieties was 53 and the number of positively charged amino acids was 86. The pI value for both mutant and wild varieties is 9.88. The estimated half-life for both varieties was 30 hours. The instability index for the wild genotype was 41.24 while for the mutant genotype it was 41.53. The aliphatic index for wild and mutant varieties was 90.28. The grand average of hydropathicity (GRAVY) was -0.093 for the normal genotype, while it was -0.093 for the mutant genotype. The secondary structure of the protein was obtained by PredictProtein software for both normal and mutant varieties. As shown in [Figure 1](#), the secondary structure of the protein in the wild is different from that in the mutant.

Effect of rs1800172 polymorphism on the tertiary structure of protein and RNA structure

The three-dimensional structure of the protein was obtained by Phyre2 software. After examining the three-dimensional structure of the protein by Discovery Studio software, it was found that most of the protein structure consists of alpha-helix domains ([Figure 2](#)). The protein hydrophobicity plot showed that the degree of hydrophobicity for normal and mutant proteins at the polymorphic site is different ([Figure 2](#)). The effect of

rs1800172 polymorphism on the structure and function of KCNQ1 protein by Polyphen2 software showed that the above polymorphism is benign. Data from SNAP2 also showed that the polymorphism is neutral (Table 1).

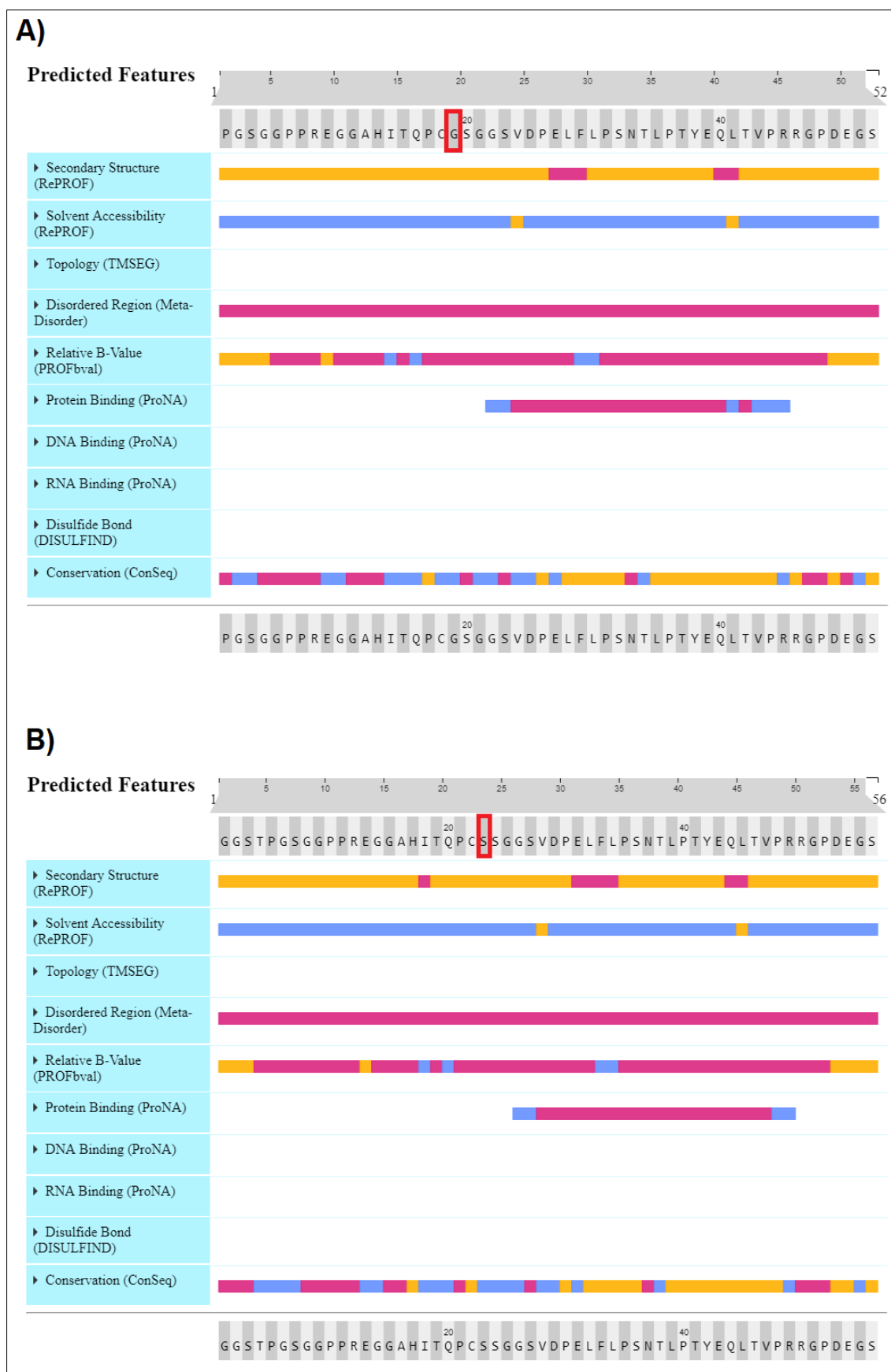


Figure 1. Data from PredictProtein software. Information for wild-type protein (A). Information for protein mutant (B) variety. The polymorphic amino acid is shown in red.

Table 1. Results of SNAP2 online server.

Wild type Amino Acid	Position	Variant Amino Acid	Predicted Effect	Score	Expected Accuracy (%)
G	643	A	Neutral	-47	72%
G	643	R	Neutral	-46	72%
G	643	N	Neutral	-32	66%
G	643	D	Neutral	0	53%
G	643	C	Neutral	-18	57%
G	643	Q	Neutral	-47	72%
G	643	E	Neutral	-23	61%
G	643	G	Neutral	-77	87%
G	643	H	Neutral	-49	72%
G	643	I	Effect	4	53%
G	643	L	Effect	1	53%
G	643	K	Neutral	-28	61%
G	643	M	Neutral	-7	53%
G	643	F	Effect	11	59%
G	643	P	Neutral	-31	66%
G	643	S	Neutral	-70	82%
G	643	T	Neutral	-36	66%
G	643	W	Effect	42	71%
G	643	Y	Neutral	-4	53%
G	643	V	Neutral	-9	53%

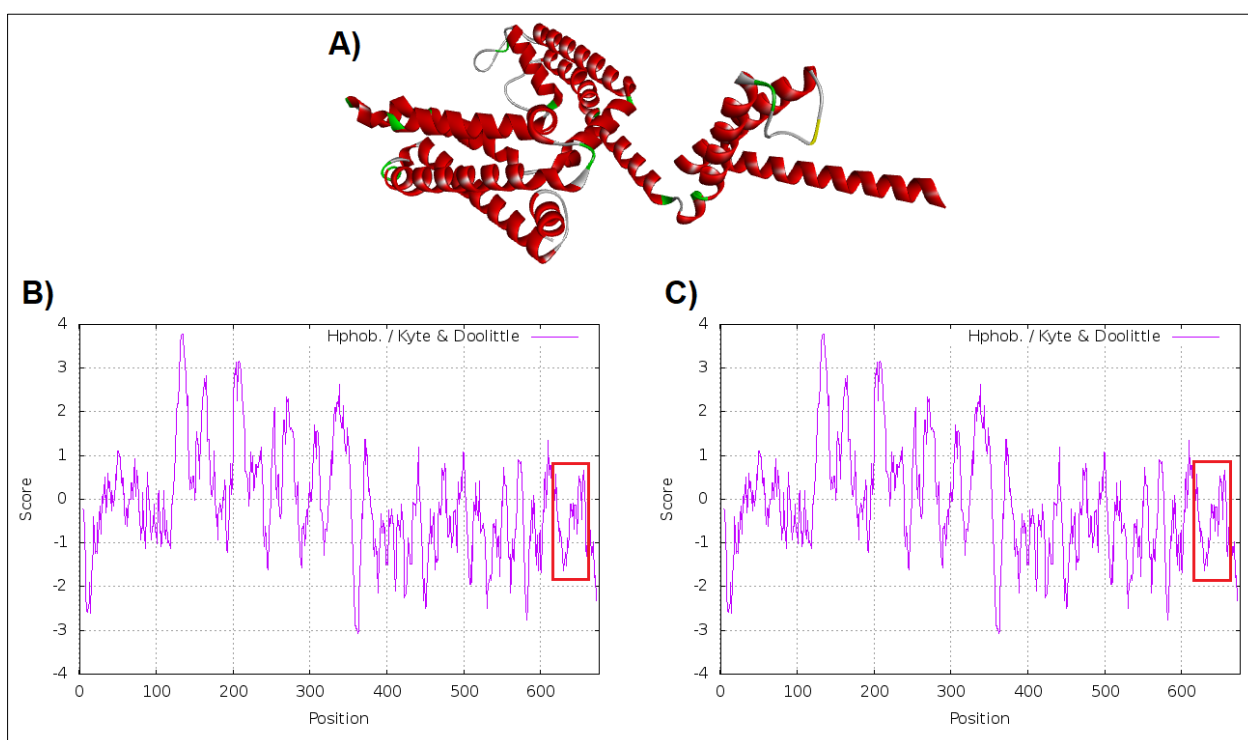


Figure 2. Three-dimensional structure and hydrophobicity plot of the protein. The 3D structure of the protein was simulated by Phyre2 software and most of it appeared as alpha-helix domains (A). Protein hydrophobicity plots for wild (B) and mutant (C) genotypes showed that this index was different for two protein varieties around the polymorphic region.

The effect of rs1800172 polymorphism on mRNA structure was also investigated and the results of this study are shown in Figure 3. As shown in the figure, this polymorphism has no significant effect on the secondary structure of mRNA (Folding Window = 1727-2031, Local region = 1860-1928, distance = 0.0300, $p= 0.6686$).

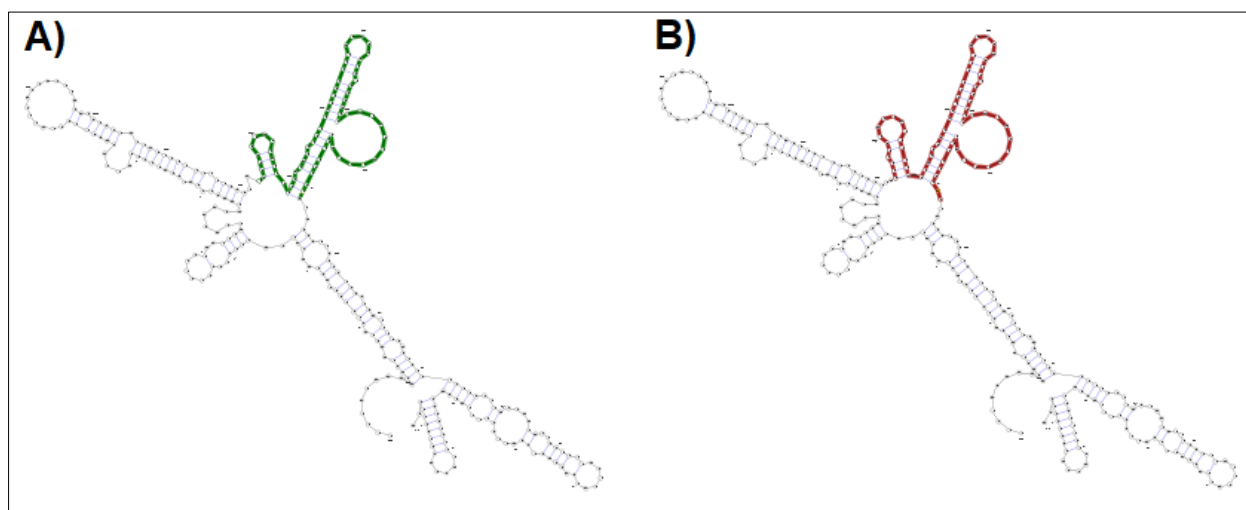


Figure 3. Effect of rs1800172 polymorphism on mRNA structure. Analysis of mRNA structure showed that the polymorphism did not affect the secondary structure of the protein.

Discussion

In this study, we investigated the effect of rs1800172 polymorphism on KCNQ1 gene function. Analysis of our data showed that this polymorphism affects the characteristics of the primary structure of the protein. This polymorphism also affects some protein properties such as secondary structure and protein hydrophobicity plot. Some previous studies have been performed bioinformatically on KCNQ1 gene variants. For example, Li et al. conducted a bioinformatic analysis on this protein in 2017. In their project, we studied 107 functionally determined KCNQ1 variations which were found in a literature. Based on their founded dataset, they established a comprehensive quantitative assessment on the KCNQ1 subdomains and the distribution of the pathogenic variation therein. They observed the conserved subdomains usually are crucial for function of the channel and are supplemented with dysfunctional variations (19).

Long QT syndrome (LQTS) is an inherited syndrome in which most members of family with delayed ventricular repolarization on electrocardiogram appear as prolongation of QT (20, 21). The complaint is correlated with an elevated tendency to sudden arrhythmic death, torsade de pointes, and arrhythmogenic syncope. LQTS is due to mutations that mainly affect ion channels of myocyte, and this single-gene syndrome has an autosomal dominant genetic pattern. Around 85% of existing cases are inherited from one parent, and the other 15% of cases have mutations with de novo source. The disorder is relatively rare and its apparent prevalence is estimated at about 1:3000-1:5000 in the general population. This disorder has changing penetrance. In current studies, two mutations in LQTS were detected in about 10% of LQTS cases (22, 23) and this outcome proposes that this genetic disease may be significantly more common than reports. LQTS cases might be particularly at risk for drug-induced cardiac arrhythmias. Genetic and clinical trainings in LQTS patients have provided helpful insights into major arrhythmogenic and cardiac electrophysiology mechanisms (24, 25). Many studies have been performed on the association of polymorphisms in the KCNQ1 gene and the risk of LQTS. In a study by Duchatelet et al., the T allele of the KCNQ1 polymorphism rs2074238 was introduced as a protective factor in the disease (12). In 1999, Wang et al., examined KCNQ1 mutations in LQTS. Their study showed that mutations in KCNQ1, which are associated with LQT1, are associated with a wide range of dysfunctions in the I(Ks) and KvLQT1 channels (13). Some researchers have also studied the pathogenicity of rs1800172 polymorphism. For example, Koo et al., in 2006 examined the association of a set of exon and intron varieties of

KCNQ1 including the Gly1154Ser variety with LQTS, and their study showed that the association of these genetic variants with disease risk is unclear (14).

As mentioned in the introduction, the KCNQ1 gene is also involved in the physiological function of the stomach (26, 27). Some studies have examined the role of polymorphisms in the KCNQ1 gene and their association with gastric cancer. In a 2015 study by Liu et al., 108 people with metastatic gastric cancer were studied. They examined some polymorphisms including KCNQ1 rs163182 in this patient population. Their study showed that this polymorphism is significantly associated with disease control rate (15). In another study conducted in 2021 by Yang et al., that in this study, 681 patients with gastric cancer and 756 healthy individuals were included in the study (16). In this study, 3 single nucleotide polymorphisms in the KCNQ1 gene and 8 single nucleotide polymorphisms in the KCNQ1OT1 gene were investigated. The results of their study showed that the genotype KCNQ1 rs231348 CT was associated with an increased risk of gastric cancer in individuals older than 55 years and regardless of their gender. The KCNQ1 gene is related to the pathophysiology of some diseases, including LQTS and gastric cancer, and mutations in this gene may alter the risk of developing these diseases (28, 29).

Conclusion

Single nucleotide polymorphisms based on their position on the gene can alter gene function. Polymorphisms upstream of the gene can affect gene expression, while exon polymorphisms affect the structure and function of proteins. In our study, it was found that the rs1800172 polymorphism in the KCNQ1 gene could affect some protein properties. Because this gene is involved in some of the body's physiological functions, the rs1800172 mutation can affect the function of this protein and increase the risk of certain diseases. For example, because this protein is involved in the function of the stomach and heart muscle, the genetic variant rs1800172 may alter the risk of diseases associated with these organs, such as gastric cancer and LQT syndrome. Therefore, the study of mutations in this gene, including rs1800172, can be effective in identifying the pathological mechanisms of KCNQ1.

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