

# Connecting KCNQ1 mutants with clinical outcome

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## Abstract

**Purpose:** Mutations in KCNQ1 are linked to long QT and other syndromes. This study reports a method to predict clinical outcome when a mutation at KCNQ1 is found.

**Methods:** We used amino-acid distribution probability to measure KCNQ1 mutants, and cross-impact analysis to couple KCNQ1 mutants with clinical outcome. Then, Bayesian equation was used to calculate the probability of occurrence of long-QT syndrome in the presence of a mutation.

**Results:** Seventy-six mutations were classified into two groups according to whether a mutation increased or decreased amino-acid distribution probability. Cross-impact analysis showed that a mutation that increases the distribution probability has a greater chance of causing long-QT syndrome than a mutation that decreases the distribution probability. Bayesian calculation suggested that a patient would have a 90% chance of developing long-QT syndrome when a mutation is found at KCNQ1.

**Conclusion:** This study details the process of building a quantitative relationship between KCNQ1 mutations and clinical outcome and provides the probability of LQT1 in the presence of a mutation.

Sudden cardiac death in patients without structural heart disease remains a challenge in diagnosis and risk stratification. Genetically determined arrhythmias are a potential cause for primary electrical disease.<sup>1,2</sup> KCNQ1 is the pore-forming subunit of a channel complex whose expression and function have been

well characterized in the heart.<sup>3,4</sup> The majority of mutations are linked to the long QT syndrome.<sup>5,6</sup> A few are linked to Jervell and Lange-Nielsen syndrome, atrial fibrillation type 3 and short QT syndrome type 2.<sup>7-10</sup> It would be helpful to know the chance of occurrence of certain syndromes when a new KCNQ1 mutation is found.

In studying genotype-phenotype relationships, the first step is to determine a protein in relation to a disease, and the second is to build a descriptive quantitative relationship between mutant protein and clinical outcome. Mutations would simply represent a clinical test much as blood glucose concentration is linked with diabetes. Thus, a 20-letter symbolized protein should be converted to a numeric sequence, with each mutation having a different value.

There are several ways to convert a 20-letter symbolized protein to a numeric sequence. Our group has developed three methods to convert a 20-letter symbolized protein into a numeric sequence.<sup>11-14</sup>

In this study, we attempted to couple the mutations in human KCNQ1 with clinical outcome to provide the probability that a patient has long-QT syndrome (LQT1) when a new mutation is found.

**Materials and methods**

Human KCNQ1 with its 76 mutations and documented clinical outcomes were obtained from UniProtKB/Swiss-Prot entry.<sup>15</sup>

We used amino-acid distribution probability to convert human KCNQ1 and its mutants into scalar data<sup>12-14</sup> with the following equation:

$$\frac{r!}{q_0! \times q_1! \times \dots \times q_n!} \times \frac{r!}{r_1! \times r_2! \times \dots \times r_n!} \times n^{-r},$$

where *r* is the number of amino acids, *n* is the number of partitions, *r<sub>n</sub>* is the number of amino acids in the *n*-th partition, *q<sub>n</sub>* is the number of partitions with the same number of amino acids, and ! is the factorial function.<sup>16</sup>

For example, there are nine cysteines in KCNQ1, which is composed of 676 amino acids. These cysteines are positioned at 34, 122, 136, 180, 214, 331, 381, 445 and 642 in KCNQ1. We divided KCNQ1 into nine equal partitions, counted the cysteines in each partition (column 2, Table 1), and used these counts in the equation to obtain the distribution probability of 0.1967. Thus, we converted cysteines into a single value.

When a mutation related to cysteine occurs, the distribution probability changes, to give a value different from normal KCNQ1. For example, a mutation at position 315 changes tyrosine to cysteine.<sup>17</sup> There are nine cysteines in normal KCNQ1 and 10 cysteines after mutation (Table 1). For our equation after mutation, we have *q*<sub>0</sub> = 2, *q*<sub>1</sub> = 6, *q*<sub>2</sub> = 2, *q*<sub>3</sub> = 0, *q*<sub>4</sub> = 0, *q*<sub>5</sub> = 0, *q*<sub>6</sub> = 0, *q*<sub>7</sub> = 0, *q*<sub>8</sub> = 0, *q*<sub>9</sub> = 0, *q*<sub>10</sub> = 0; and *r*<sub>1</sub> = 1, *r*<sub>2</sub> = 2, *r*<sub>3</sub> = 1, *r*<sub>4</sub> = 1, *r*<sub>5</sub> = 2, *r*<sub>6</sub> = 1, *r*<sub>7</sub> = 1, *r*<sub>8</sub> = 0, *r*<sub>9</sub> = 0, *r*<sub>10</sub> = 1. Its probability equals

$$\frac{10!}{2! \times 6! \times 2! \times 0! \times 0! \times 0! \times 0! \times 0! \times 0! \times 0!} \times \frac{10!}{1! \times 2! \times 1! \times 1! \times 2! \times 1! \times 1! \times 0! \times 0! \times 1!} \times 10^{-10} = 0.1143.$$

TABLE 1. Effect of KCNQ1 mutation at position 315 on distribution and probability of cysteines and tyrosines.

Partition	Before mutation		After mutation	
	Cysteine	Tyrosine	Cysteine	Tyrosine
I	1	0	1	0
II	2	1	2	1
III	2	1	1	2
IV	0	2	1	2
V	1	2	2	2
VI	2	1	1	0
VII	0	0	1	0
VIII	0	3	0	4
IX	1	2	0	0
X		0	1	0
XI		2		2
XII		0		0
XIII		1		1
XIV		0		1
XV		2		2
XVI		1		0
XVII		0		0
XVIII		0		1
XIX		1		
Probability	0.1967	0.0895	0.1143	0.0117

This mutation decreases the distribution probability of cysteines, because it is 0.1967 before mutation. On the other hand, there are 19 tyrosines in normal KCNQ1 and 18 tyrosines in the mutant. Their distribution probabilities are 0.0895 and 0.0117 before and after mutation. Thus, the mutation decreases the distribution probability of tyrosines. The overall effect of this mutation leads to a decrease in the distribution probability in the mutant KCNQ1, (0.1143–0.1967) + (0.0117–0.0895) = –0.1602. Each mutation is represented by either increased or decreased distribution probability rather than by changed letters of amino acids. Furthermore, each mutation can be correlated to whether or not a clinical outcome appears, thus we

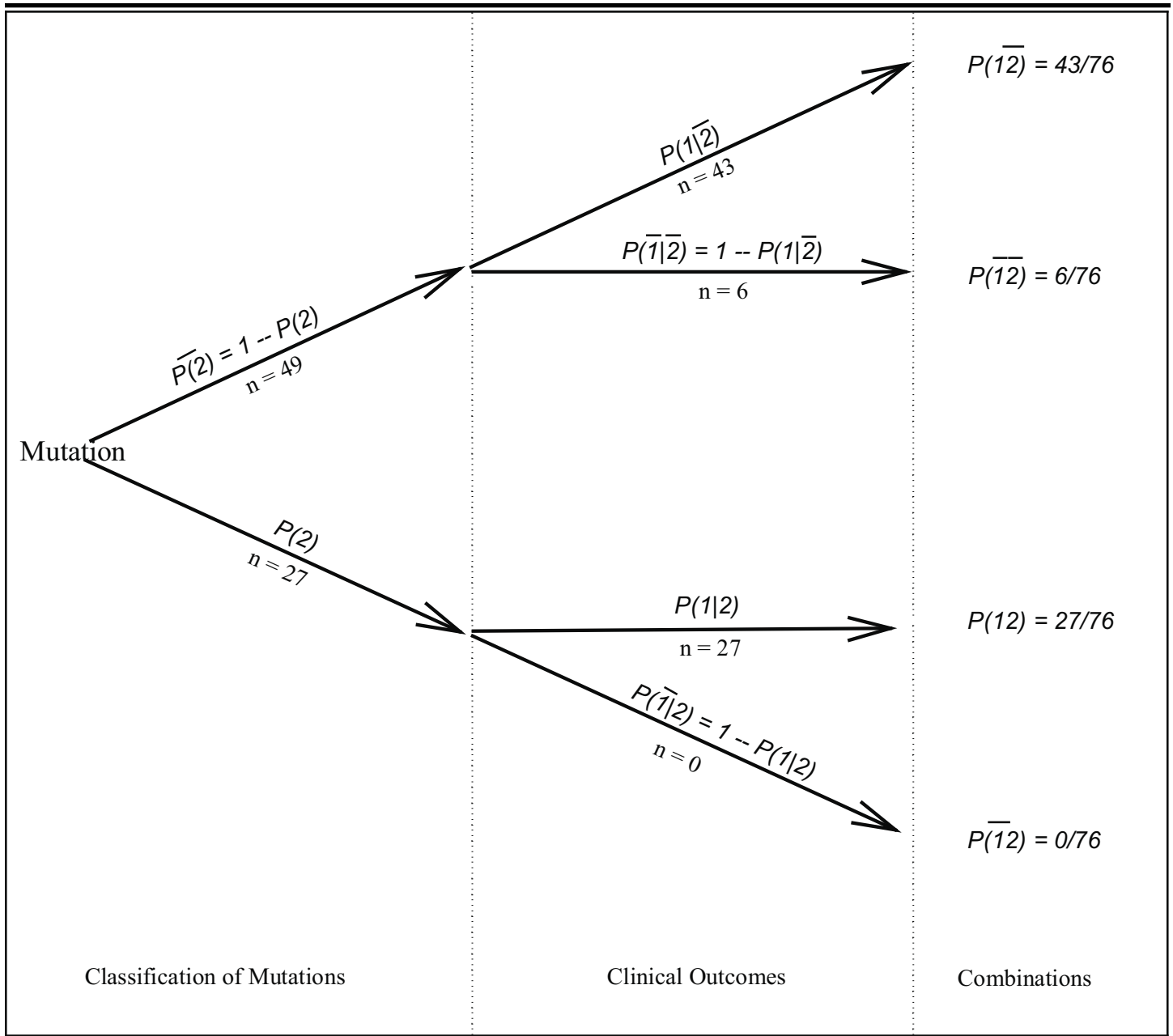


FIGURE 1. Cross-impact relationships among mutations, clinical outcomes, and their combinations.

can use cross-impact analysis to couple both mutation and clinical outcome.<sup>14,18,19</sup> Thereafter, we can use the Bayesian equation to calculate the probability of occurrence of clinical outcome in the presence of a mutation.

**Results**

Of the 76 KCNQ1 mutations, 70 are classified as LQT1, one atrial fibrillation type 3, three Jervell and Lange-Nielsen syndrome, and two short QT syndrome type 2. The cross-impact relationships among KCNQ1 mutations, clinical outcomes and their combinations are shown in Figure 1.  $P(2)$  and  $P(\bar{2})$  are the decreased and increased probabilities led by mutations, and 27 and 49 mutations result in decreased and increased distribution probability, respectively.  $P(1|\bar{2})$  is the impact probability (conditional probability) that LQT1 is diagnosed under the condition of increased distribution probability; 43 mutations have such an effect.  $P(\bar{1}|\bar{2})$  is the impact probability that other diseases are diagnosed under the condition of increased

distribution probability, and 6 mutations operate in such a manner.  $P(1|2)$  is the impact probability that the LQT1 is diagnosed under the condition of decreased distribution probability, and 27 mutations play such a role.  $P(\bar{1}|2)$  is the impact probability that other diseases are diagnosed under the condition of decreased distribution probability, and this category is none. At the level of combinations, we can see the combined results of mutations and clinical outcomes.

The calculated probabilities from Fig. 1 are shown in Table 2, where:

- (i) a mutation has a greater chance of increasing the distribution probability in mutant KCNQ1 as  $P(2)$  is smaller than  $P(\bar{2})$ ;
- (ii) a mutation that increases the distribution probability has far larger chance of causing LQT1 as  $P(1|\bar{2})$  is far larger than  $P(\bar{1}|\bar{2})$ ; and
- (iii) a mutation that decreases the distribution probability has almost full chance of causing LQT1 as  $P(\bar{1}|2)$  is zero.

At this stage, we can use the Bayesian equation,<sup>20</sup>  $P(1|2) = P(2|1) \frac{P(1)}{P(2)}$ , to find the probability that the occurrence of LQT1 under a mutation, which is  $P(1)$ :  $P(1) = \frac{P(1|2)}{P(2|1)} P(2) = \frac{1 \times 0.3553}{0.3857} = 0.9212$  as  $P(2)$  and  $P(1|2)$  have already been defined in cross-impact analysis, and  $P(2|1)$  is the probability that the distribution probability decreases under the condition of being LQT1 ( $P(1|2) = 27/27 = 1$  and  $P(2|1) = 27/(27+43) = 0.3857$ ).

TABLE 2. Probability in Fig. 1.

Classification of Mutations	$P(2) = 27/76 = 0.3553$
	$P(\bar{2}) = 1 - P(2) = 1 - 0.3553 = 0.6447 = 49/76$
Clinical Outcomes	$P(1 \bar{2}) = 43/49 = 0.8776$
	$P(\bar{1} \bar{2}) = 1 - P(1 \bar{2}) = 1 - 0.8776 = 0.1224 = 6/49$
	$P(1 2) = 27/27 = 1$
	$P(\bar{1} 2) = 1 - P(1 2) = 1 - 1 = 0 = 0/27$
Combinations	$P(\bar{1} \bar{2}) = P(1 \bar{2}) \times P(\bar{2}) = 43/49 \times 49/76 = 0.5658 = 43/76$
	$P(\bar{1} \bar{2}) = P(\bar{1} \bar{2}) \times P(\bar{2}) = 6/49 \times 49/76 = 0.0789 = 6/76$
	$P(12) = P(1 2) \times P(2) = 27/27 \times 27/76 = 0.3553 = 27/76$
	$P(\bar{1} 2) = P(\bar{1} 2) \times P(2) = 0/27 \times 27/76 = 0 = 0/76$

**Discussion**

This study shows how to build a quantitatively descriptive relationship between mutations and their clinical outcomes, and how to deduce the probability that a certain clinical outcome appears in the presence of a mutation. In particular, mutations classified as increased amino-acid distribution probability have a closer relationship with LQT1, and the probability that

a patient has LQT1 under a KCNQ1 mutation is about 0.9.

The data in our coupled relationship in Fig. 1 are similar to those used by other groups<sup>21-23</sup> suggesting our data are unbiased. The calculated results fall into the range of clinical findings in literature.<sup>21-24</sup> Our results provide an estimate for clinical outcome with data elaboration. However, the probability obtained in this study is different from those in other genotype-phenotype studies<sup>25-28</sup> indicating that our method is sensitive to different diseases and mutations.

The innovative aspect of this study is that we correlated the mutation-clinical outcome with a quantitative relationship rather than a qualitative relationship. The implication is that we attempt to obtain a probability that provides a clinical estimation. The problem with this type of analysis is that the probability is dependent on the patient population: the probability obtained from Caucasians may not be suitable for Asians. However, this requires more studies in different populations.

In conclusion, this study describes the process of building a quantitative relationship between KCNQ1 mutations and clinical outcomes, and describes the probability that a patient with a mutation exhibits LQT1.

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