

## Case Report

### A DUPLICATION MUTATION IN *KCNQ1* GENE IN ROMANO-WARD SYNDROME

#### Romano-Ward sendromunda *KCNQ1* geninde bir duplikasyon mutasyonu

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#### ABSTRACT

Romano-Ward syndrome (RWS, Long QT syndrome 1) is a rare familial congenital cardiac disorder characterized by a prolonged QT interval on electrocardiograph. RWS may occur due to the mutations in *KCNQ1* gene. Our case was a 27-year-old male patient with post-exercise syncope attacks and pre-syncope chest pain. QT interval was 660 ms on ECG. The *KCNQ1* gene was sequenced and a heterozygous twelve base duplication was identified that causes a non-frameshift insertion of four new amino acids (QRQK) in the protein chain between amino acids 262-263. The patient was prescribed with metoprolol and cardioverter defibrillator was implanted. The patient was followed-up and he was discharged.

**Keywords:** Long QT syndrome, *KCNQ1*, Romano-Ward syndrome

#### ÖZET

Romano-Ward sendromu (RWS, Uzun QT sendromu 1) EKG’de uzamış QT aralığı ile karakterize bir ailevi konjenital kalp hastalığıdır. RWS *KCNQ1* genindeki mutasyonlarla oluşabilmektedir. 27 yaşındaki erkek hastamızda senkop öncesi göğüs ağrıları ve efor sonrası senkop atakları vardı. EKG’de 660 milisaniyeyi bulan QT intervalleri vardı. Sekans analizinde 262-263. aminoasitler arasına giren 4 (QRQK) aminoasit ile oluşan ve çerçeve kayması yapmayan 12 bazlık bir heterozigot mutasyon tespit edildi. Hastaya metoprolol reçete edildi ve cardioverter defibrilatör implante edildi. Takiplerin ardından hasta taburcu edildi.

#### INTRODUCTION

Long QT syndrome (LQTS) is a rare familial congenital cardiac disorder characterized by a prolonged QT interval on electrocardiograph corrected for heart rate (QTc) and associated with life-threatening ventricular arrhythmias (1). The prevalence of the disease ranged from 1/5000 to 1/2000. Each year 5,000 deaths have been reported due to the LQTS in the United States (2). The characteristic findings of LQTS include torsades de pointes-type ventricular tachyarrhythmias resulting in recurrent syncope, seizure attacks and sudden death in young patients with normal cardiac morphology particularly during the exercise or emotional situations where the sympathetic activity is increased (3).

There are two types of LQTS: the acquired type and the congenital type. Congenital type of LQTS occurs as a result of mutations in genes encoding transmembrane sodium and potassium ion channel proteins in heart muscle cell (4). There are two

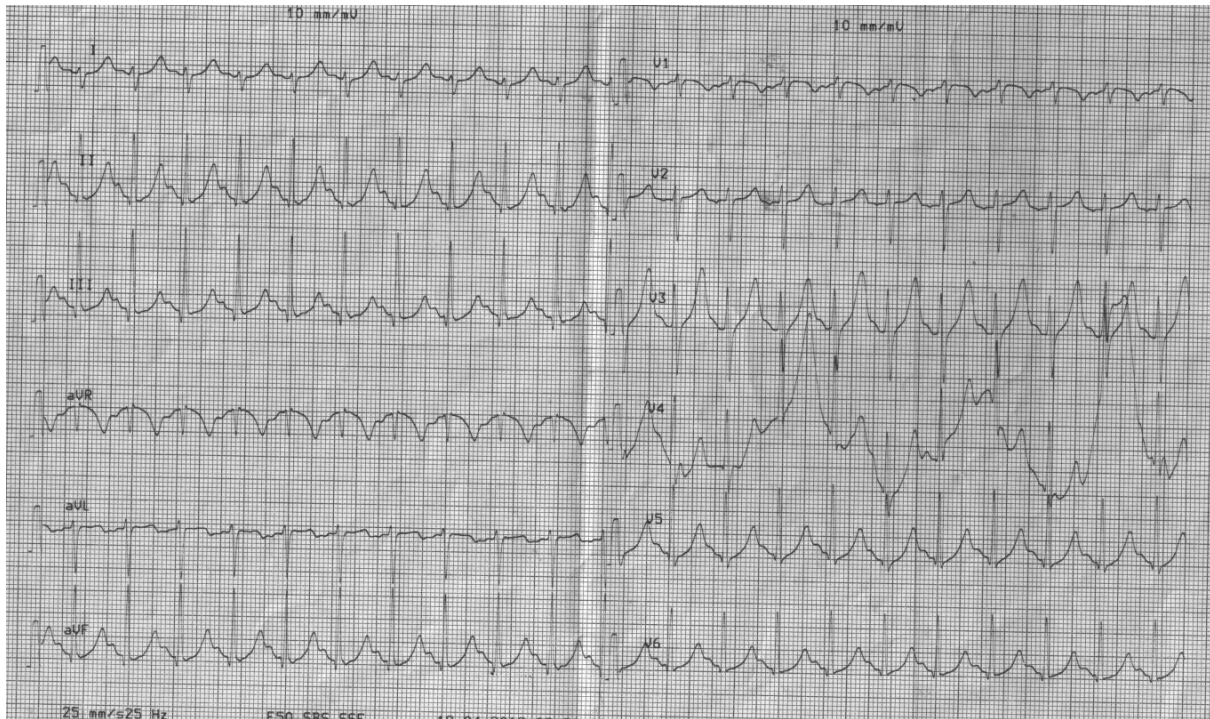
phenotypic variants of the congenital type. The autosomal recessive form Jervelland and Lange-Nielsen syndrome (JLNS) is associated with sensorineural deafness. The autosomal dominant form is Romano-Ward syndrome (RWS) and it is observed more frequent than JNLS (5).

The most common genes related to LQTS are *KCNQ1* (LQT1), *KCNH2* (LQT2), *SCN5A* (LQT3), and the less common genes are *KCNE1* (LQT5), *KCNE2* (LQT6), *CAV3* (LQT9), *SCN4B* (LQT10), *AKAP9* (LQT11), *SNTA1* (LQT12) and *KCNJ5* (LQT13) (<http://omim.org/entry/192500#reference27>).

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In this case, new twelve-base duplication was identified in *KCNQ1* (potassium voltage-gated channel, *KQT-like* subfamily, member 1, NM\_000218.2) gene which has not been described

previously in the literature. In addition, the importance of molecular genetic analysis was emphasized for early diagnosis and treatment of RWS which may cause sudden death.



**Figure 1.** ECG of the patient at the first appointment in the Cardiology outpatient. Sinus rhythm with 660 ms QT interval was observed.

### CASE REPORT

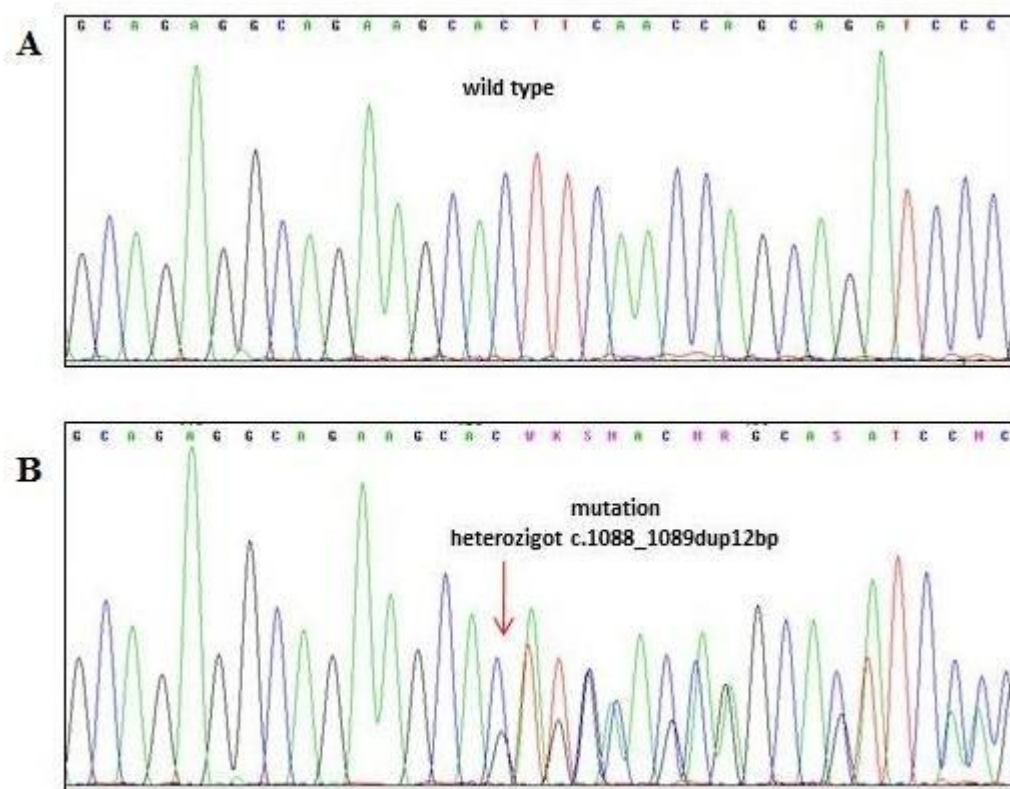
27-year-old male patient with recurrent syncope attacks and restlessness was referred to our cardiology clinic for further examination and treatment. The syncope attacks have been occurred after exercises, and he described pre-syncope chest pain and palpitations. However, he did not describe any other health problem, any drugs or substances that were continuously used in his medical history. His father, brother and nephew have passed away due to the sudden cardiac death at ages of 50, 16 and 3, respectively. An implantable cardioverter defibrillator (ICD) has been implanted in one of his brother.

Physical examination was normal and no pathological findings were observed. His blood pressure was 110/75 mmHg, pulse was 80 beats / min when he admitted to the hospital. The patient's ECG rhythm is sinus and the QT interval was 660 ms (Figure 1). There was no other pathological finding on ECG. Patient's teleradiography, echocardiography, and laboratory tests were normal. Cardiac stress test was performed to identify symptoms and to rule out ischemia. The syncope did not occur during the cardiac stress test, but the results were doubtful for ischemia. Therefore, the patient underwent coronary angiography. Coronary arteries were normal in the coronary angiography. Then, 24-hour rhythm monitoring (holter) was administered, but no rhythm abnormality was detected.

The patient was pre-diagnosed with Long QT syndrome. He was referred to the medical genetics clinic. The absence of deafness or dysmorphic findings and the inheritance pattern that is compatible with the autosomal dominant inheritance, lead us to think about RWS. For this reason, the *KCNQ1* gene mutations were evaluated in DNA extracted from peripheral blood. Sixteen exons were amplified using deep intronic primers and PCR products were sequenced (ABI3500). Heterozygous duplication mutation "c.1088\_1089dupGAGGCAGAAGCA" was detected in exon 8 of *KCNQ1* gene (Figure 2). The patient was prescribed 100 mg of metoprolol succinate tablet daily and ICD was implanted. No problem was seen in the patient's follow-up, and the patient was discharged.

### DISCUSSION

RWS is a familial disorder and often has a higher incidence of sudden cardiac death at younger ages. A wide range of symptoms from dizziness to syncope with loss of consciousness and sudden death are observed in this syndrome. Particularly, it is a cardiac electrophysiologic disorder, characterized by QT prolongation and T-wave abnormalities on the ECG and the ventricular tachycardia torsade de pointes (TdP). TdP is usually self-terminating, but generally leads to recurrent syncope attacks. The syncope attacks occur typically during the exercise, high



**Figure 2.** Automated DNA sequencing result of the *KCNQ1* gene, A. Normal subject B. Patient.

emotional situations, and rarely occur during rest or sleep without any other symptom. In some cases, TdP changes to ventricular fibrillation and causes cardiac arrest or sudden death (6).

Approximately 50% of individuals, who have a disease-causing mutation in one of the genes associated with RWS, usually have one or a few syncope attacks. Special ECG findings, clinical symptoms, family history and molecular genetic analysis results are the key factors for the diagnosis of RWS (6). Thirteen genes, which are associated with RWS, have been identified. The most common genes involved in RWS and their proportional contribution (percentage) to this syndrome are as follows *KCNQ1* (%46), *KCNH2* (%38), *SCN5A* (%13), *KCNE1* and *KCNE2*(7). These genes encode potassium, sodium and calcium ion channels in heart or they encode proteins that interact with these channels. Mutations in these genes may lead to loss of function in potassium channels or gain of function in sodium and calcium channels. Abnormal ion channel function causes to prolongation of cardiac action potential and the susceptibility of cardiac myocytes to early after depolarisations trigger ventricular arrhythmia and TdP (8; 9).

Mutations in *KCNQ1*, the most frequent gene involved in RWS, have been analysed in this patient. The gene is about 400 kb length and located at chromosome 11p15.5-p15.4, and it consists of 16 exons. The gene product (676 amino acids) forms the alpha subunit of the slowly activating delayed rectifier potassium channel (IKs). Abnormal gene product results in reduced IKs function (10). More than 470

mutations including missense, nonsense, splice site, frameshift and deletion/duplication have been reported in *KCNQ1* gene in various databases (11), (<http://www.genomed.org/LOVD/LQTs/home.php>).

This case was heterozygous for the following duplication, c.1088\_1089dupGAGGCAGAAGCA, in exon 8 of the *KCNQ1* gene which is not described in the literature previously. This duplication causes a non-frameshift insertion of four new amino acids (QRQK) in the protein chain between amino acids 262-263. The new amino acids are located in the amino acid chain between the 'ion transport domain,' and 'domain of *KCNQ1* voltage-gated potassium channel'. A program (Mutation Taster) helps to analyse the sequence changes in a virtual digital environment, and provides information whether the sequence changes are pathological or not. This twelve-base duplication may cause mRNA splicing failure resulting in alteration of the amino acid sequence and the features of the protein in translation. Heterozygous point mutations in this region previously associated with RWS. Mutations that detected by sequencing or deletion/duplication analysis of this gene have been found in 46% of the patients with RWS (<http://www.ncbi.nlm.nih.gov/books/NBK1129/>).

These data derived from clinical findings and laboratory test suggest that this case comply with RWS. A future study has been planned to examine the affected and unaffected relatives of the patient and to analyse the related gene to show whether the sequence change segregates to family members with the syndrome. By identifying the new mutations, we will be able to make an early diagnosis, determine the type of

LQTS, give prophylactic treatment and give advice about sports activities and drugs that should be avoided.

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