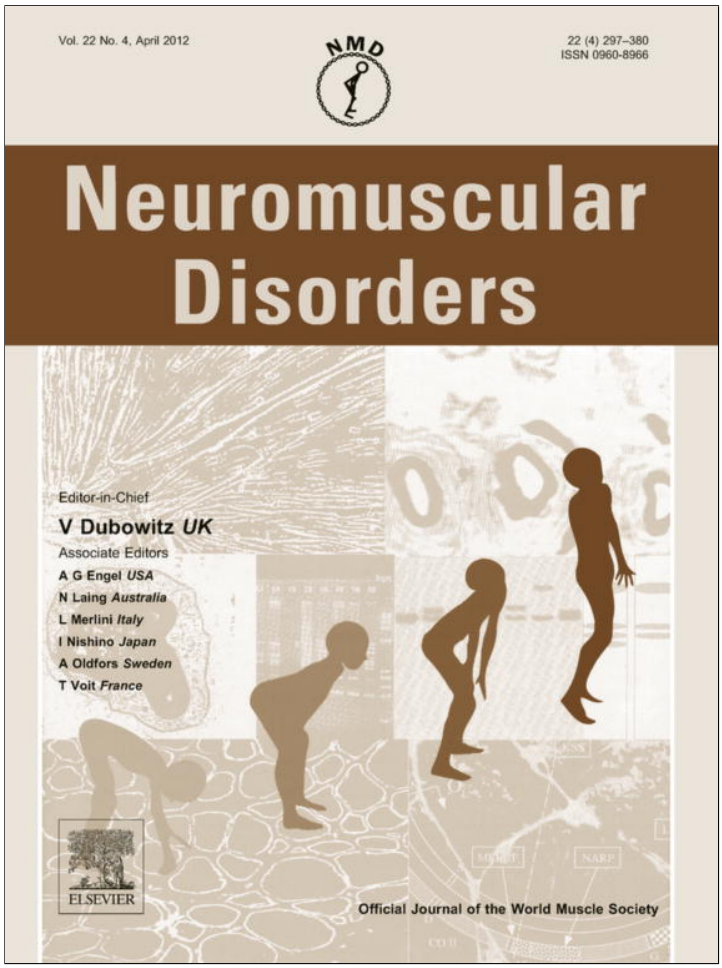

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Case report

A Becker myotonia patient with compound heterozygosity for *CLCN1* mutations and Prinzmetal angina pectoris

Daniel Zielonka [a,*], Karin Jurkat-Rott [b], Paweł Stachowiak [c], Anna Bryl [d], Jerzy T. Marcinkowski [a], Frank Lehmann-Horn [b,1]

[a] *Department of Social Medicine, Poznan University of Medical Sciences, Poland, Rokietnicka Str., 5"C", 60-806 Poznan, Poland*
[b] *Division of Neurophysiology, Ulm University, Germany, Albert-Einstein-Allee 11, 89081 Ulm, Germany*
[c] *Department of Cardiology, Pomeranian University of Medical Sciences, Poland, Powstańców Wlkp. Str., 72, 70-111 Szczecin, Poland*
[d] *Department of Neurology, Municipal Hospital in Poznan, Poland, Szwajcarska Str., 3, 61-285 Poznan, Poland*

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Abstract

Becker myotonia is a recessive muscle disease with prevalence of >1:50,000. It is caused by markedly reduced function of the chloride channel encoded by *CLCN1*. We describe a Polish patient with severe myotonia, transient weakness, and muscle cramps who only responds to lidocaine. In addition, the patient has Prinzmetal angina pectoris and multiple lipomatosis. He is compound heterozygeous for a novel p.W303X and a frequent p.R894X *CLCN1* mutation. *CLCN1* exon number variation was excluded by MLPA. His son with latent myotonia was heterozygeous for p.R894X. We discuss the potential relations of the three rare diseases and the inheritance of p.R894X.

Keywords: Chloride channel myotonia; *CLCN1*-MLPA; Prinzmetal angina

1. Introduction

Myotonia congenita (MC) is an inherited muscle disorder transmitted as an autosomal dominant (Thomsen disease) or autosomal recessive (Becker disease) trait [1,2]. The slowed relaxation after skeletal muscle contraction, defining MC is caused by mutations in *CLCN1* encoding the major chloride channel ClC-1 of skeletal muscle [3]. Mean age of onset, affected muscle groups, concomitant muscle pain, and mild worsening of myotonic symptoms in the cold do not differ between recessive and dominant form of the disease [4]. Myotonic stiffness, transient muscle weakness, diminished reflexes, and muscle hypertrophy are more frequent in the recessive than in the dominant form [4].

The recessive Becker myotonia is caused by nonsense or missense mutations [5] which lead to a loss of function of both gene products which normally form a homodimeric chloride channel complex [3]. The consequence of the mutations is a reduced chloride conductance of the muscle fiber membrane that causes membrane hyperexcitability. It was described by some authors that not only missense but also nonsense *CLCN1* mutations can lead to the dominant Thomsen form. R894X is one of the mutations supposed to exert recessive or dominant effects [6].

Prinzmetal angina pectoris, a coronary spasm considered to be a potassium channelopathy [7,8], has not yet been described in myotonic patients. The exertion independent chest pain is usually extremely severe, leads to ST elevation, and may be accompanied by syncope, related to AV

* Corresponding author. Tel.: +48 504 609 951; fax: +48 618547390.
E-mail address: daniel.zielonka@gmail.com (D. Zielonka).
[1] Frank Lehmann-Horn is responsible for the genetic results.

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block, asystole, or ventricular tachyarrhythmias. The only known risk factor is smoking [9].

Currently, causative treatment of MC increasing Cl^- conductance is not available except acetazolamide, a carbonic anhydrase inhibitor with mild ClC-1 activating properties [10]. In patients who require medication, sodium channel blockers are administered.

Here we describe a familial case of Becker myotonia presenting with very distinctive myotonic symptoms and residual response to the currently available symptomatic treatment. Prinzmetal angina with sudden episodes accompanied the clinical picture of Becker's myotonia. We discuss the potential relation of the three diseases and the effect of the p.R894X mutation.

2. Case presentation

The patient is a 45 year old man, presenting with muscle hypertrophy, muscle stiffness and transient weakness (Fig. 1). Age of onset was 15. At age of 19, stiffness increased in the upper limbs; and speech difficulties due to myotonic stiffness appeared. With continued activity, the myotonia decreased, a phenomenon called warm-up. In the third decade of life, myotonia and transient weakness of lower limbs increased dramatically, and the transient weakness also affected the hand muscles, particularly in winter or on cold days. Since age of 40, a low-amplitude tremor of his fingers occurred during sleep at night.

In age of 40, the patient was admitted to our outpatient clinic because of the transient muscle weakness and stiffness significantly more frequent when he moved quickly. The patient also complained about back pain, and a bone-wrenching muscle pain that occurred twice per hour and lasted few minutes. Its severity and frequency increased on cool days.

The patient had been smoking 10 cigarettes daily for many years. He suffered from recurring lipomas. Due to back and neck pain in forth decade of life, neuroimaging of whole vertebral column was performed. It showed multi-level degenerative changes, lipoma of vertebra Th6 and discs prolapse on level L5/S1 exerting pressure on left spinal nerve explaining the back pain.

The changes of the vertebral column were discussed to be responsible of the muscles cramps that were evoked by forces exerted on the vertebral column by hypertrophic muscles.

At age of 45, the patient experienced several fainting spells. Once he experienced burning or cooling sensations

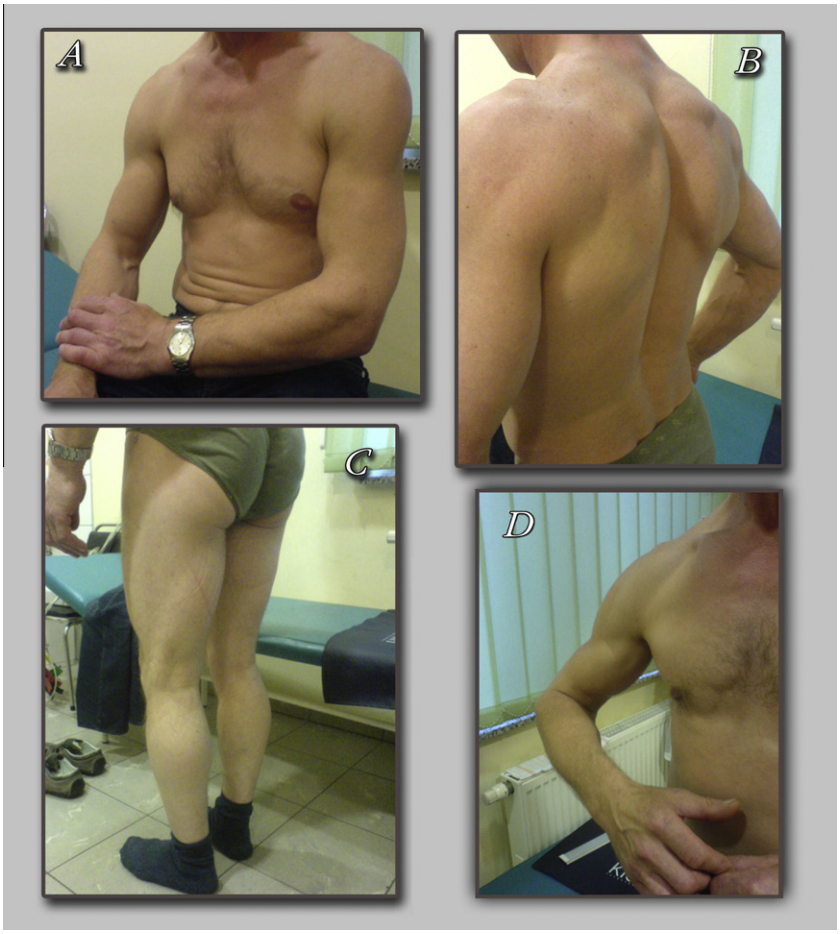

Fig. 1. Muscle hypertrophy (A) frontal view, (B) back view, (C) hypertrophy of leg muscles, (D) arm hypertrophy.

with preceding hidrosis or gooseflesh. When he climbed the stairs he lost consciousness. He recovered completely after seconds. A year later, crushing, acute chest pain with heartburn occurred at rest. An immediately preformed electrocardiogram (Fig. 2A) showed an ST elevation in leads II, III, and aVF, RR: 1360 ms; P: 60 ms; PQ: 160 ms; QRS: 80 ms; QT: 440 ms; QTc: 376 ms; *T* wave height: 0.8 mV (V3) (Fig. 2A); Another ECG (Fig. 2B) was recorded after pain had released shown: RR: 1010 ms; P: 60 ms; PQ: 140 ms; QRS: 80 ms; QT: 380 ms; QTc: 378 ms; *T* wave height: 1.8 mV (V4) (Fig. 2B). The patient denied preceding strenuous exercise or taking any drugs or psychoactive substances.

Laboratory examinations exhibited an increased concentration of heart troponin I with a maximum level of 1.96 μg/l (10^{-6} kg/l). Creatine kinase (CK, 578 U/L) and CK-MB (47 U/L) levels were elevated. Except for increased WBC up to 16.25 G/l, other lab results were normal. Control ECG after 2 h did not show ST elevation, but high *T* waves were present in V4 and V5. The ST-segment became isoelectrical simultaneously to the receding of pain. Echocardiography was normal with an ejection fraction of 65%. Constrictions found in coronarography were hemodynamically not significant whereby a maximum contraction of 50% was observed in the right coronary artery.

The neurological examination revealed generalized myotonia with impressive muscle hypertrophy most eminent in upper limbs and shoulder girdle as well in lower limbs; pectoral and neck muscles where also hypertrophic (Fig. 1). The muscle tone was normal. Weakened tendon reflexes were detected in the upper limbs and normal reflexes in the lower limbs; Babinski sign was negative. Muscle relaxation was slowed while muscle strength was normal. The serum CK level was elevated to 292 U/l when admitted to our clinic. Electrolyte and liver enzyme concentrations were normal. In the ECG high *T* waves in V2–V4 were noted. Needle electromyography indicated normal nerve conduction and spontaneous, abundant myotonic discharges, along with the classic "dive-bomber's sound" in tibialis anterior, biceps brachi and vastus lateralis muscles. After cooling with ice, myotonic discharges increased, and a CMAP decrement of 53% was observed in the short-exercise test.

Genomic DNA was extracted using the salt precipitation method from white blood cells. Polymerase chain reaction (PCR) and direct PCR sequencing of all 23 *CLCN1* exons were performed as described previously [11]. All samples were bidirectionally sequenced. Evaluation of the sequences revealed a novel c.908G > *A* mutation coding for W303X and a second c.2680C > *T* mutation encoding R894X (Fig. 3). The novel mutation was absent in all 200 control individuals. The two mutations were situated on different alleles as verified by the exclusive occurrence of R894X in the son. R894X is found in 28% of all affected persons and has been described as a mutation acting as both dominant and recessive [12]. An additional copy number variation that would not have been identified by PCR was excluded by multiplex ligation-dependent probe amplification (MLPA) as recently described [13].

Patient's parents and siblings, not available for examination, were reported to be unaffected. His son underwent clinical and genetic examination in our department at age

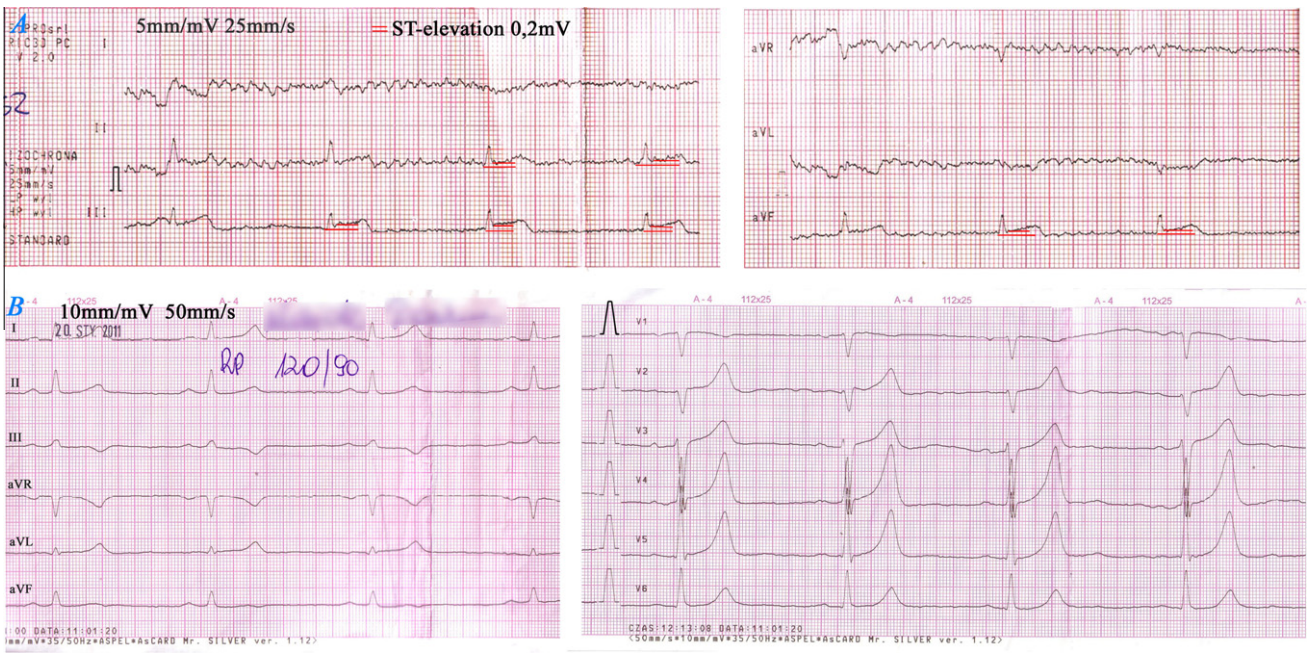

Fig. 2. (A) ECG during chest pain in the emergency room; 25 mm/s; 5 mm/mV; ST-elevation in derivations II, III, aVF (0.2–0.3 mV; the red lines indicate the pathologic alterations in the ECG). (B) ECG after pain had released; 50 mm/s; 10 mm/mV; *T* inversion in III (significant for transient ischemia e.g., after ST-elevation), high *T* wave in V4 (1.8 mV).

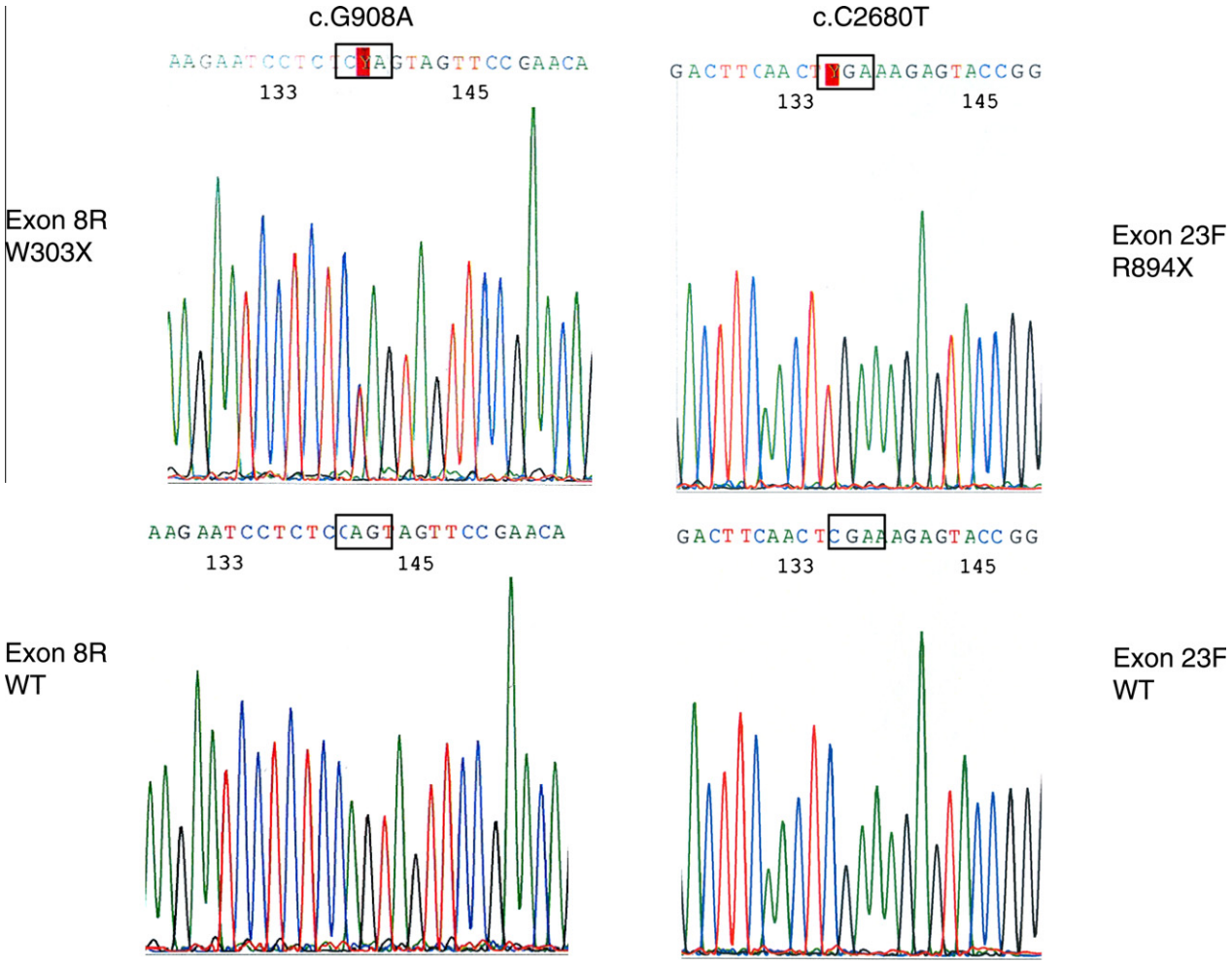

Fig. 3. A comparison of the *CLCN1* sequences of a reverse fragment (*R*) of exon 8 and a forward fragment (*F*) of exon 23 of the patient and from a control (WT). Note that the bases in the reverse sequence are complementary to those in the forward sequence. The novel mutation was absent in all 150 control individuals.

of 19. The examination revealed one lipoma on right wrist, no neurological abnormalities; normal nerve conduction velocities. After cooling, one myotonic discharge, along with the classic "dive-bomber's sounds" was observed in the biceps brachi. After the short exercise test, a CMAP decrement was also not observed. Genetic examination revealed presence of the p.R894X mutation on one *CLCN1* allele.

The patient started treatment for myotonia at age of 40. The patient experienced limited, temporary or no benefit after treatment with mexiletine, phenytoine, carbamazepine, acetazolamide, tetrazepam, tolperisone, tizanidine and baclofen. Currently the patient has been treated with carbamazepine 600 mg/d for 2 years with no effect but serum level of carbamazepine is 0.5 μg/ml and therefore below the therapeutic range (4–10 μg/ml). This could be explained by enzyme induction. To escape enzyme induction in the liver, an intravenous lidocaine test with 300 mg/h was performed. The treatment started with a bolus of 100 mg that markedly improved myotonia and increased joint limitation. The effect disappeared within hours although lidocaine was constantly applied by a pump. After the application has been stopped following 4 h, stiffness slowly increased and reached the pre-test level within few hours.

3. Discussion

Our report describes the coincidence of three independent rare diseases: myotonia, Prinzmetal angina, and multiple lipomatosis. To the patient, the myotonia is the most relevant illness since it is disabling. For genetic counselling, the mode of transmission of this type of myotonia is required. The clinical features such as severe muscle stiffness, transient weakness, and cramp-related muscle pain point to the diagnosis of Becker myotonia. This diagnosis is supported by non-symptomatic parents and the occurrence of two nonsense *CLCN1* mutations on different alleles. However, one of the two mutations, R894X, has been reported to exert recessive or dominant effects [6]. To clarify the effect of this mutation in this family, we tested the patienťs son who is clinically unaffected although he harbours R894X on one allele and although typical age

of onset has long gone. He displayed latent myotonia like the muscles of other heterozygeous recessive *CLCN1* mutation carriers [14,15]. This is in agreement with a moderately reduced chloride conductance by about 50% [16]. Therefore we conclude that p.R894X exerts recessive effects in the patient and that he has recessive Becker myotonia as the additional novel W303X stop mutation should also exert recessive effects like all other stop mutations. Moreover we have shown that the two mutations are situated on different alleles and therefore fulfil the criteria of compound heterozygosity.

The pathologic CMAP decrement in the short exercise test observed in the cooled muscle is also in agreement with the diagnosis of Becker myotonia [17]. Therapy of the myotonia has been turned out problematic in this patient because of enzyme induction of the usual sodium channel blockers administered as antimyotonic drugs. These drugs did not aggravate the Prinzmetal angina pectoris of our patient. Moreover ranolazine, a new sodium channel blocker, was recently reported to have beneficial effects on angina pectoris patients [18]. Hence this drug might be a new option for our patient.

Multiple lipomatosis is a rare autosomal dominant disorder described in some families as related to mutation located on chromosome 12 [19]. Gene *HMGA-2* encodes a factor involved in vasculogenesis, lipomagenesis and development of mesenchymal tumours, is suggested to be responsible for this disorder [20]. It was never described any relationship of MC and multiple lipomatosis therefore it was recognised as an independent concomitant disorder.

Cardiac involvement into MC was reported very rarely [21–23]. Cardiac arrhythmia was described in 2 cases of Thomsen disease and one case of Becker myotonia. Prinzmetal angina in a myotonic patient has never been described before. *KCNJ8* has been suggested as a candidate gene for Prinzmetal angina based on the phenotype of the Kir6.1KO mouse, but human mutations have yet to be identified [8]. If we consider each event independently, the concurrence of Becker myotonia (prevalence of 1:23,000) and Prinzmetal angina (prevalence of 1:20,000–1:50,000) is highly improbable ($1/23{,}000 * 1/50{,}000 \sim 5 * 10^{-5} * 2 * 10^{-5} = 10^{-9}$ to $1/23{,}000 * 1/20{,}000 * \sim (5 * 10^{-5})^2 = 2.5 * 10^{-9}$). Nevertheless there is no known link between the two disorders. The responsible genes are located at different chromosomes (*CLCN1* on chr 7q and *KCNJ8* on chr 11p11.23). Chest pain accompanied by an increased troponin I level and normal echocardiography, good general condition, no abuse of drugs and psychoactive substances, pain at rest but not while exercising, transient ST-segment elevation and insignificant changes in coronarography allow us to diagnose variant angina, known as Prinzmetal's angina. In this condition, the spasm of smooth muscles located in walls of small coronary arteries appears [24]. K_{ATP} channels of smooth muscles play a crucial role in the pathophysiology of Prinzmetal angina how it was described in Kir6.1-null mouse model of this disease [7].

Acknowledgments

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