JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Internal Medicine

Rapid Communication

Analysis of Clinical Characters of Cantu Syndrome: Etiology and High Penetrance of Cardiovascular Phenotypes

Lijiang Ma, MD, PhD[1*], Ruijun Bao, MD, MS[2]

[1]*Division of Molecular Genetics, Department of Pediatrics and Medicine, Columbia University Medical Center, New York, NY, USA*

[2]*The Children's IBD Center, Mount Sinai Hospital, New York, NY, USA*

**Corresponding author: Dr. Lijiang Ma, Division of Molecular Genetics, Department of Pediatrics and Medicine, Columbia University Medical Center ,New York, NY 10032 ,USA, Tel: 212-851-5318; Fax: 212-851-5306; E-mail: lm2689@columbia.edu*

Received: 06-22-2015

Accepted: 07-08-2015

Published: 07-15-2015

Abstract

Background: Cantu syndrome is characterized by hypertrichosis, distinct facial features, cardiovascular abnormalities and a wide variety of phenotypes in many other organs and systems. This study is to illustrate clinical characters of Cantu syndrome in cardiovascular system and to investigate etiology of this disease. *Methods:* Cantu syndrome cases were searched from PubMed. Clinical data were collected from previous reports. Descriptive analysis was conducted to study clinical characters of Cantu syndrome patients especially in cardiovascular system. Fisher's exact test was used to examine if age of parents played a role in disease occurrence. *Results:* 60 Cantu syndrome patients were studied. 56/60 (93%) had congenital heart disease and/or cardiac diseases, including patent ductus arteriosus, atrial septal defect, coarctation of the aorta, bicuspid aortic valve, aortic stenosis, pulmonary stenosis, aortopulmonary collateral artery, partial anomalous pulmonary venous return, cardiomegaly, hypertrophic/dilated/noncompaction cardiomyopathy, pericardial effusion or heart failure. 10/60 (16.7%) patients developed transient or persistent pulmonary hypertension. Most of the cases were sporadic. More patients were born to father at age>35 when compared with normal population and the result was statistically significant. 3 (5%) patients died in infancy or in childhood while 57 patients were alive during last follow up. More than half of the patients were seen in 0-10 age group. *Conclusions:* The disease presented a wide variety of clinical presentations and different severity. Besides hypertrichosis and osteochondrodysplasia, there was high penetrance of cardiovascular phenotypes. Some of the clinical manifestations resolved spontaneously. Patients were more frequently observed in 0-10 age group in the clinic. Advanced father's age played a role in disease occurrence.

Keywords: Genetics; Cardiovascular; *ABCC9*

Introduction

Cantu syndrome, also called hypertrichotic osteochondrodysplasia, is a rare congenital systemic disease which was first recognized in Mexico in 1982 [1]. More cases were reported to further delineate this genetic syndrome [2,3]. Clinical manifestations were varied and the disease has been mistaken for acromegaloid facial appearance syndrome, hypertrichosis with acromegaloid facial appearance syndrome [4], or hypothyroidism [5]. Most of the patients presented hypertrichosis, coarse face, cardiomegaly and osteochondrodysplasia. Neonatal macrosomia, history of maternal polyhydramnios, psychomotor developmental delay, skin abnormality such as pigmentation or loose skin, abnormal blood vessels, lymph edema, anemia, hepatomegaly, pyloric stenosis and immune deficiency were less frequent presen-

tations [5]. Treatment is supportive. Cantu syndrome is recognized as a rare systematic disease with a few scattered cases reported around the world. Patient clinical characters were described with or without detailed information in literature and the etiology is not fully understood. In this report, clinical characters of Cantu syndrome with emphasis on phenotypes in cardiovascular system were analyzed. Etiology of the disease was investigated according to parameters of patients' clinical data collected from literature. Potential mechanisms were discussed in order to provide hint for future studies in genetics and cardiovascular disorders.

Materials and methods

Subjects

MEDLINE (National Library of Medicine, Bethesda, MD) database was searched using the key word *Cantu Syndrome*. Additional case reports were identified from references of selected articles. The search period was from initial case report published by Cantu in 1982 until current. Duplicated cases, when indicated in the publications, were removed.

Statistics

Data were analyzed using R package (version 3.1.2) for Window. Histogram of patients' age at last follow up was generated by Histo Plot using R. Comparisons of births to parents' age between Cantu syndrome and normal population were assessed by Fisher's exact test. *P* values were for two-tailed tests. A p value<0.05 was considered statistically significant.

Results

There were 63 subjects reported to have "Cantu syndrome" or "Cantu craniofaciofronto digital syndrome" to date. Three subjects from one familial case were not included in this study because the subjects did not have hypertricosis which is a typical feature presented in all other Cantu syndrome patients [6]. A total of 60 cases were analyzed. Different races around the world were affected. Most cases were from Mexico and Europe while others from India, Australia, United States, Japan and Korea. There were 31 female and 29 male patients and gender distribution is almost equal.

Cardiac structural abnormalities and cardiovascular diseases in Cantu syndrome patients

56 (93%) patients had abnormality in cardiovascular structure and/or heart diseases. 41 (68.3%) patients had cardiomegaly, 30 (50%) had hypertrophic, dilated, or left ventricular noncompaction cardiomyopathy mainly affecting left ventricle or septum of the heart. 9 (15%) had different severity of pericardial effusion that were either trace amount or require pericardiocentesis and pericardiostomy. Echocardiography examination showed normal cardiac functions in most of the patients. 4 patients developed heart failure but were responsive to medications.

31 (51.7%) patients had cardiac structural abnormalities. Patent ductus arteriosus (PDA) was observed frequently (19/60, 31.7%). Some of these patients responded to medication while others had large PDA and required surgical ligation. 3 (5%) patients had atrial septal defect and 2 (3.3%) had patent foramen ovale. Bicuspid aortic valve was seen in two subjects. Other cardiac structural abnormalities included 2 aortic stenosis, 2 pulmonary stenosis, 2 aortopulmonary collateral artery, 1 dilated aorta and aortic root, 1 coarctation of the aorta and 1 partial anomalous pulmonary venous return. 5 individuals had cardiac structural abnormality unspecified.

Abnormal development of blood vessels were seen in different organs, such as thoracic aortic aneurysm, pulmonary arteriovenous malformation, meningeal arteriovenous malformation and excessive tortuosity of retinal vessels. One patient had dilated and tortuous intrahepatic arteries and veins as well as tortuous major cerebral arteries including internal carotids, anterior cerebral and middle cerebral arteries. Total 5 (8.3%) subjects had vascular abnormality and this occurred with or without other cardiovascular defects or diseases. Table 1 listed all cardiovascular structural abnormalities and cardiac diseases identified in Cantu syndrome patients. Incidence for each subtype of the disease was indicated as well.

Table 1. Cardiovascular Phenotypes in Cantu Syndrome.

Type of cardiovascular abnormality	Number (Percentage)
Heart diseases	45 (75%)
Cardiomegaly	41 (68.3%)
Hypertrophic/dilated/noncompaction cardiomyopathy	30 (50%)
Pericardial effusion	9 (15%)
Heart failure	4 (6.7%)
Structural abnormality in heart	31 (51.7%)
Patent ductus arteriosis	19 (31.7%)
Atrial septal defect	3 (5%)
Patent foramen ovale	2 (3.3%)
Bicuspid aortic valve	2 (3.3%)
Aortic stenosis	2 (3.3%)
Pulmonary stenosis	2 (3.3%)
Aortopulmonary collateral artery	2 (3.3%)
Coarctation of aorta	1 (1.7%)
Dilated aorta, dilated aortic root	1 (1.7%)
Partial anomalous pulmonary venous return	1 (1.7%)
Structural abnormality in heart-unspecified	5 (8.3%)
Abnormality in blood vessels	5 (8.3%)
Thoracic aortic aneurysm	1 (1.7%)
Pulmonary AV malformation	1 (1.7%)
Excessive tortuosity of retinal vessels	1 (1.7%)
Meningeal AV malformation	1 (1.7%)
Dilated and tortuous intrahepatic arteries and veins, tortuous major cerebral arteries	1 (1.7%)

Abbreviation: AV=arteriovenous

Pulmonary hypertension in Cantu syndrome

10/60 (16.7%) Cantu syndrome patients developed pulmonary hypertension (PH). One subject had transient pulmonary hypertension for two months. A patient had pulmonary arteriovenous malformation. PH was diagnosed at 1 year old and was response to steroids treatment. 1 subject had PH and tracheomalasia. In one subject, PH was diagnosed at neonatal period and patient had bronchopulmonary hypoplasia. Two patients were considered to have secondary PH by the authors: one patient had scoliosis, obstructive apnea and PH was diagnosed at age 36; one patient had partial pulmonary venous obstruction in left lower lobe and PH was diagnosed at 4 month. 4 patients had persistent PH without other associated abnormalities in lung or thoracic cavity. Two patients were died due to cardiopulmonary complications and other eight subjects were alive. Table 2 showed associated abnormalities, age of diagnosis and outcome for each patient who had PH in Cantu syndrome patients.

age between 35 and 50. Average age of the mothers was 30.1 and average age of fathers was 36.8 (data not shown). Data of parents' age for child birth in normal population was collected from US CDC National vital statistics reports in 2013 [7]. There were 310.7 births to mother at age less than 35 and 60.5 births to mother between 35 and 50 years old per 1000 women in normal population. There were 260.4 births to father at age less than 35 and 82.4 births to father at age between 35 and 50 per 1000 men in normal population. Statistical analysis indicated births to mothers at age >35 were not differ between Cantu syndrome group and normal individual (*p* value=0.426). However, analysis showed more babies were born to father between 35 and 50 in Cantu syndrome group when compared with normal population and this is statistically significant (p value=0.018, Table 3).

Table 2. Clinical Characters of Pulmonary Hypertension Patients in Cantu Syndrome, n=10 (16.7%).

Type of PH and associated comorbidity	Gender	Age of dx	Outcome
Transient PH	M	2-4 month	Alive and evaluated at 3.5 yrs old
PH and AV malformation in lungs	F	1 yr	Respond to steroids, alive and last follow up at 12 yrs old
PH and bronchopulmonary dysplasia	F	Neonatal period	Died at 248 days
PH and tracheomalasia	M	Unknown	Alive and last follow up at 6 yrs old
PH, scoliosis and obstructive sleep apnea	F	36 yrs	Alive and last follow up at 50 yrs old
PH and partial pulmonary venous obstruction in left lower lobe	M	4 month	Alive and last follow up at 8 yrs old
Persistent PH	M	Unknown	Died at 4 month
Persistent PH	F	Unknown	Alive and evaluated at 4 month
Persistent PH	F	4 month	Alive and last follow up at 4 month
Persistent PH	F	4.25 yrs	Alive and last follow up at 4.25 yrs old

Abbreviations: PH=pulmonary hypertension; dx=diagnosis; AV=arterial venous; BPD=bronchopulmonary dysplasia; M=male; F=female; yrs=years.

Cantu syndrome occurrence is associated with advanced paternal age

There were 7 familial and 43 sporadic cases. Age of parents when Cantu syndrome subject was born were investigated in sporadic cases. Mother's age was reported in 12 patients and father's age was known in 10 subjects. 9 subjects were born to mother < 35 years old. 3 individuals were born to mother at age between 35 to 39 years old. No subject was born to mother at age equal or greater than 40. 4 patients were born to father < 35 years old and 6 patients were born to father at

Frequency distribution of patient's age at last follow up

Three patients died in infancy/childhood due to cardiopulmonary complications or unknown reasons. All other 57 patients were alive during the latest follow up. The frequency distribution of age of last follow up in Cantu syndrome patients was shown in figure 1. There were 36 individuals in 0-10 group, 12 subjects in 11-20 age group, 5 in 21-30 group, 5 in 31-40 group and 2 in 41-50 group. The highest frequency was observed in 0-10 year's group. Number of subjects decreased significantly in older age groups.

Table 3. Comparison of number of births to parents at different ages between Cantu syndrome and normal population. * p<0.05.

Age group-mother	Cantu syndrome n=12(%)	Births per 1000 women in normal population, n=372 (%)	*p* -value
Born to mother <35 yrs old	9 (75%)	311 (84%)	
Born to mother between 35-50 yrs old	3 (25%)	61 (16%)	0.426
Age group-father	**Cantu syndrome n=10 (%)**	**Births per 1000 men in normal population, n=342 (%)**	***p* -value**
Born to father <35 yrs old	4 (40%)	260 (76%)	
Born to mother between 35-50 yrs old	6 (60%)	82 (24%)	0.018*

Abbreviation: yrs=years. *: A p value<0.05 was considered statistically significant.

Figure 1. Frequency distributions of patients' age at last follow up

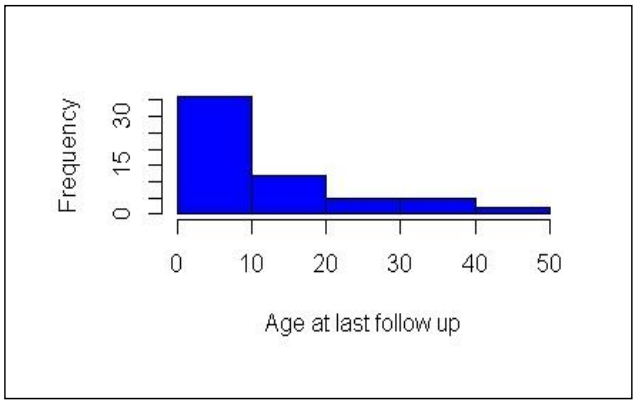

Figure 1. **Frequency distributions of patients' age at last follow up.** Histogram was generated by R. There were 36 patients in 0-10 age group, 12 in 11-20 age group, 5 subjects in 21-30 age group, 5 in 31-40 age group and 2 in 41-50 age group.

Discussion

Cardiovascular structural abnormalities and cardiac diseases were observed in 93% of Cantu syndrome subjects, indicating there is high penetrance of cardiovascular phenotypes in these patients. For treatment, some of the individuals needed surgery while others responded to medication. Two patients had cardiomyopathy evolved by age 5 or by eleven month and 2 patients had cardiomegaly disappeared after several years [8,9]. In one child, pericardial effusion started from third trimester in utero and resolved at 8 month [10]. Pericardial effusion was derived from pericarditis in one patient [1]. Biopsies of heart were performed in two patients and were reported to be normal or had some degree of disorganization of cardiac smooth muscle [11,12]. In one patient, examination of biopsy from pericardium showed pericardial fibrosis and mild focal chronic inflammation [13]. No one died of cardiomyopathy in adult patients and two patients resolved spontaneously. Cardiac functions were normal in most of the individuals.

31/60 (50%) subjects had abnormality in central nervous system. 28 (46.7) patients had psychomotor developmental delay. Enlarged sella turcica was found in 6 individuals. 2 subjects had brain atrophy and 1 had autistic disorder. Intelligence quotient (IQ) is generally normal [11] although some patients had slightly lower IQ and two patient showed high IQ [5]. Cerebral vascular abnormalities were reported in 2 patients. 18 patients had cardiovascular abnormalities but normal in central nervous system (CNS). Most of the patients who had developmental delay were mild and were able to catch up with developmental milestones as they grow up. This suggested that the neural phenotypes were caused by abnormal structure or function of CNS but not secondary to cardiovascular defects because cardiac function was usually normal in these patients.

There were other less frequent clinical presentations in cardiovascular system in Cantu syndrome. 10 (16.7%) patients had pulmonary hypertension. 1 patient had transient PH and 2 patients were considered to have secondary PH [5,10,13]. Persistent PH in other patients were idiopathic. 5 patients had vascular abnormality in different organs. 3 patients had lymph edema [1,14]. Bilateral insufficiency of the lymphatic system, delayed lymphatic drainage and dilated lymphatic vessels were found in one patient which might be the caus-

es of lymph edema seen in Cantu syndrome.

Cantu syndrome is an autosomal dominantly inherited genetic disease [11,15]. Karyotyping was normal and chromosomal imbalances have not been detected [9,11,16]. Studies using whole exome sequencing identified variants in ATP binding cassette, subfamily C, member 9 (ABCC9), which is a regulatory component of ATP sensitive potassium channel complex, as a genetic risk factor for this disease. Total 36 patients from 5 familial and 23 sporadic cases, including new and previously reported subjects, were examined [4,5,10,17-23]. 30/36 (85.7%) individuals had 16 heterozygous missense variants in *ABCC9*. Arg1116His, Arg1154Gln and Arg1154Trp were recurrent variants. 16/30 subjects had de novo variants and 9 individuals were unknown for their inheritance status. In two patients who were negative for *ABCC9*, targeted sequencing of potassium channel, inwardly rectifying, subfamily J, member 8 (KCNJ8), which is a potassium channel protein regulated by ABCC9, identified two de novo heterozygous missense variants. These suggested genes encoding component of ATP sensitive potassium channel played a role in the pathogenesis of Cantu syndrome.

ABCC9 is expressed widely in human tissues including cardiac and skeletal muscles and brain [24]. ABCC9 is highly expressed in heart [25,26]. Although *Abcc9* knockout mice was apparently normal and demonstrated no cardiac phenotypes [27], variants in *ABCC9* were identified in cardiac diseases and Cantu syndrome in human. Missense variant A1513T and a small insertion/deletion variant 4570-4572delTTAinsAAAT were identified in dilated cardiomyopathy patients [28]. Targeted sequencing of candidate genes identified a missense variant M1198I in a patient who had left ventricular non-compaction cardiomyopathy [29]. Whether these variants were inherited or de novo is unknown. Missense variant T1547I was found to confer risk of atrial fibrillation [30]. 16 missense variants were reported in Cantu syndrome and 93% of Cantu syndrome patients had a wide spectrum of cardiovascular diseases, including congenital abnormal structure in heart (CHD), cardiomyopathy, cardiomegaly, abnormal development of blood vessels and pulmonary hypertension, indicating *ABCC9* is involved in cardiovascular development and disease in human. ABCC9 is expressed in almost all over of the human body with abundant expression found in heart and brain [24]. Mechanisms of the high penetrance of cardiovascular phenotypes presented in Cantu syndrome remain unknown.

Mutations in potassium channels, such as potassium channel, subfamily K, member 3 (KCNK3) and potassium channel, voltage gated, shaker-related subfamily, member 5 (KCNA5) [31, 32], were identified less frequently in PH patients. Some of the Cantu syndrome subjects who had mutations in *ABCC9* or *KCNJ8* developed PH, suggesting *ABCC9*/*KCNJ8* might be rare genetic causes for PH. Targeting potassium channel will provide novel therapy for the disease.

Etiology of Cantu syndrome is unknown. Studies have shown that paternal age is associated with de novo mutations [33]. The result in this study showed that advanced paternal age may associated with Cantu syndrome, which is consistent with previous report. Due to the small sample size, larger scale study will consolidate the conclusion. Further investigation in the mechanisms of do novo variants in human genome and significance of these variants in diseases will be informative.

Conclusions

Cantu syndrome is a rare genetic disease that could affect almost every organ and system. Abnormalities in cardiovascular system have been observed in very high frequency and can cause lethality in severe cases. Occurrence of the disease in sporadic cases maybe associated with advanced paternal age.

Acknowledgement

The authors thank Dr. Gijs van Haaften and Dr. Edwin Cuppen for assistance in case information presented in their publication.

Conflict of interests: None

References

1. Cantu´ JM, Garcı´a-Cruz D, Sanchez-Corona J, Hernandez A, Nazara´ Z. A distinct osteochondrodysplasia with hypertrichosis: individualization of a probable autosomal recessive entity. Hum. Genet. 1982, 60(1): 36–41.

2. Garcia-Cruz D, Sánchez-Corona J, Nazará Z, Garcia-Crúz MO, Figuera LE et al. Congenital hypertrichosis, osteochondrodysplasia, and cardiomegaly: further delineation of a new genetic syndrome. Am J Med Genet. 1997, 69(2): 138-151.

3. Concolino D, Formicola S, Camera G, Strisciuglio P. Congenital hypertrichosis, cardiomegaly, and osteochondrodysplasia (Cantú syndrome): a new case with unusual radiological findings. Am J Med Genet. 2000, 92(3): 191-194.

4. Czeschik JC, Voigt C, Goecke TO, Lüdecke HJ, Wagner N et al. Wide clinical variability in conditions with coarse facial features and hypertrichosis caused by mutations in ABCC9. Am J Med Genet A. 2013, 161A(2): 295-300.

5. Scurr I, Wilson L, Lees M, Robertson S, Kirk E et al. Cantu syndrome: report of nine new cases and expansion of the phenotype. Am J Med Genet. 2011, 155A(3): 508-518.

6. Garcia-Gonzalez CL, Garcia-Cruz D, Garcia-Cruz MO, Castañeda-Cisneros G et al. A familial case of Cantu craniofaciofronto digital syndrome. Clin Dysmorphol. 2012, 21(3): 162-166.

7. Martin JA, Hamilton BE, Osterman MJ, Curtin SC, Matthews TJ. Births: final data for 2013. Natl Vital Stat Rep. 2015, 64(1): 1-65.

8. Rosser EM, Kaariainen H, Hurst JA, Baraitser M, Hall CM et al. Three patients with the osteochondrodysplasia and hypertrichosis syndrome--Cantu syndrome. Clin Dysmorphol. 1998, 7(2): 79-85.

9. Engels H, Bosse K, Ehrbrecht A, Zahn S, Hoischen A et al. Further case of Cantú syndrome: exclusion of cryptic subtelomeric chromosome aberrations. Am J Med Genet. 2002, 111(2): 205-209.

10. Hiraki Y, Miyatake S, Hayashidani M, Nishimura Y, Matsuura H et al. Aortic aneurysm and craniosynostosis in a family with Cantú syndrome. Am J Med Genet A. 2014, 164A(1): 231–236.

11. Grange DK, Lorch SM, Cole PL, Singh GK. Cantu syndrome in a woman and her two daughters: Further confirmation of autosomal dominant inheritance and review of the cardiac manifestations. Am J Med Genet A. 2006, 140(15):1673-1680.

12. Nevin NC, Mulholland HC, Thomas PS. Congenital hypertrichosis, cardiomegaly and mild osteochondrodysplasia. Am J Med Genet. 1996, 66(1): 33-38.

13. Kobayashi D, Cook AL, Williams DA. Pulmonary hypertension secondary to partial pulmonary venous obstruction in a child with Cantu syndrome. Pediatr Pulmonol. 2010, 45(7): 727-729.

14. García-Cruz D, Mampel A, Echeverria MI, Vargas AL, Castañeda-Cisneros G et al. Cantu syndrome and lymphoedema. Clin Dysmorphol. 2011, 20(1): 32-37.

15. Lazalde B, Sánchez-Urbina R, Nuño-Arana I, Bitar WE, de Lourdes Ramírez-Dueñas M. Autosomal dominant inheritance in Cantú syndrome (congenital hypertrichosis, osteochondrodysplasia, and cardiomegaly). Am J Med Genet. 2000, 94(5): 421-427.

16. Graziadio C, Rosa RF, Rosa RC, Zen PR, Flores JA et al. Short-term follow-up of a Brazilian patient with Cantú syndrome. Am J Med Genet A. 2011, 155A(5): 1184-1188.

17. van Bon BW, Gilissen C, Grange DK, Hennekam RC, Kayserili H et al. Cantú syndrome is caused by mutations in ABCC9. Am J Hum Genet. 2012, 90(6): 1094-10101.

18. Harakalova M, van Harssel JJ, Terhal PA, van Lieshout S, Duran K et al. Dominant missense mutations in ABCC9 cause Cantú syndrome. Nat Genet. 2012, 44(7): 793-796.

19. Park JY, Koo SH, Jung YJ, Lim YJ, Chung ML. A patient with Cantú syndrome associated with fatal bronchopulmonary dysplasia and pulmonary hypertension. Am J Med Genet. 2014, 164A(8): 2118–2120.

20. O'Brien JJ, Ririe DG. Anesthetic experience in a patient with Cantú syndrome. Paediatr Anaesth. 2008, 18(12): 1255-1257.

21. Robertson SP, Kirk E, Bernier F, Brereton J, Turner A et al. Congenital hypertrichosis, osteochondrodysplasia, and cardiomegaly: Cantú syndrome. Am J Med Genet. 1999, 85(4): 395-402.

22. Cooper PE, Reutter H, Woelfle J, Engels H, Grange DK et al. Cantú syndrome resulting from activating mutation in the KCNJ8 gene. Hum Mutat. 2014, 35(7): 809-813.

23. Brownstein CA, Towne MC, Luquette LJ, Harris DJ et al. Mutation of KCNJ8 in a patient with Cantú syndrome with unique vascular abnormalities - support for the role of K(ATP) channels in this condition. Eur J Med Genet. 2013, 56(12): 678-682.

24. Davis-Taber R, Choi W, Feng J, Hoogenboom L, McNally T et al. Molecular characterization of human SUR2-containing K(ATP) channels. Gene. 2000, 256(1-2): 261-270.

25. Shi NQ, Ye B, Makielski JC. Function and distribution of the SUR isoforms and splice variants. J Mol Cell Cardiol. 2005, 39(1): 51-60.

26. Nichols CG, Singh GK, Grange DK. KATP channels and cardiovascular disease: suddenly a syndrome. Circ Res. 2013, 112(7): 1059-1072.

27. Chutkow WA, Samuel V, Hansen PA, Pu J, Valdivia CR et al. Disruption of Sur2-containing K_{ATP} channels enhances insulin-stimulated glucose uptake in skeletal muscle. Proc Natl Acad Sci USA. 2001, 98(20):11760–11764.

28. Bienengraeber M, Olson TM, Selivanov VA, Kathmann EC, O'Cochlain F et al. ABCC9 mutations identified in human dilated cardiomyopathy disrupt catalytic K(ATP) channel gating. Nat Genet. 2004, 36(4): 382-387.

29. Waldmüller S, Schroeder C, Sturm M, Scheffold T, Imbrich K et al. Targeted 46-gene and clinical exome sequencing for mutations causing cardiomyopathies. Mol Cell Probes. 2015.

30. Olson TM, Alekseev AE, Moreau C, Liu XK, Zingman LV et al. K(ATP) channel mutation confers risk for vein of Marshall adrenergic atrial fibrillation. Nat Clin Pract Cardiovasc Med. 2007, 4(2):110-116.

31. Ma L, Roman-Campos D, Austin ED, Eyries M, Sampson KS et al. A novel channelopathy in pulmonary arterial hypertension. N Engl J Med. 2013, 369(4): 351-361.

32. Pousada G, Baloira A, Vilariño C, Cifrian JM, Valverde D. Novel mutations in BMPR2, ACVRL1 and KCNA5 genes and hemodynamic parameters in patients with pulmonary arterial hypertension. PLoS One. 2014, 9(6): e100261.

33. Campbell CD, Eichler EE. Properties and rates of germline mutations in humans. Trends Genet. 2013, 29(10): 575-584.