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Expression of genes KCNQ1 and HERG encoding potassium ion channels Ik_r, Ik_s in long QT syndrome

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Abstract

Background: The KCNQ1 and HERG genes mutations are responsible for specific types of congenital long QT syndrome (LQT).

Aim: To examine the expression of KCNQ1 and HERG genes that encode potassium channels (rapid and slow) responsible for the occurrence of particular types of LQT syndrome. The study also attempted to prove that beta-actin is a good endogenous control when determining the expression of the studied genes.

Methods: The study enrolled six families whose members suffered from either LQT1 or LQT2, or were healthy. Examination of gene expression was achieved with quantitative PCR (QRT-PCR). Expression of the investigated genes was inferred from the analysis of the number of mRNA copies per 1 μg total RNA isolated from whole blood. On the basis of KCNQ1 gene expression profile, the presence of, or absence of, LQT1 could be confirmed.

Results and conclusions: The study revealed a statistically significant difference ($p = 0.031$) between the number of KCNQ1 gene copies in patients and healthy controls. On the basis of HERG (KCNH2) gene expression profile, patients with LQT2 cannot be unequivocally differentiated from healthy subjects ($p = 0.37$).

Key words: long QT syndrome, KCNQ1, HERG, gene expression

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INTRODUCTION

Congenital long QT syndrome (LQT) is a disorder of ion channels characterised by long QT interval (> 450 ms) on ECG, occurrence of polymorphic ventricular tachycardia (torsade de pointes), fainting and sudden cardiac death (SCD) [1]. To date, mutations in 11 genes have been discovered and described as being relevant for this disease. The most frequent are mutations in KCNQ1, HERG (KCNH2) and SCN5A genes which are responsible for the Romano-Ward, Jervell and Lange-Nielsen as well as Brugada syndromes [2]. Clinical symptoms depend on the gene affected by mutation and on individual predisposition [3–5].

The LQT1 type may be caused by mutation in the KCNQ1 gene and is found in approximately 50–60% of cases. Romano-Ward syndrome is an autosomal dominant hereditary disease found in around 99% of LQT1 cases. Jervell

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and Lange-Nielsen syndrome is an autosomal recessive hereditary disease of much rarer occurrence (approximately 1%). Its characteristic features are congenital hearing loss and recurrent syncope, with a high risk of SCD in childhood [6, 7]. Symptoms are usually triggered by excitation of the β-adrenergic system through increased physical effort (mainly swimming) or through strong emotions such as stress, anxiety or fright**.** Women diagnosed with LQT during their puerperium are in categories with the highest rate of lethal cardiac events [8, 9]. LQT1 has a unique ECG pattern characterised by a long QT interval (above 450 ms) and characteristic T wave morphology, which may have a wide base, increase slowly or have a delayed start [6].

The KCNQ1 is mapped to chromosome band 11p15.5. It comprises 16 exons (15 to 19 as the result of alternative splicing) spanning approximately 400 kB [10]. The gene encodes a protein forming the subunit α of the transmembrane slow potassium channel (I_{Ks}), consists of 676 aminoacids; with shorter isomorph 549 aminoacids in the heart [10]. In humans, KCNQ1 gene is expressed in the kidneys, placenta, lungs and heart. Highest mRNA transcript levels of KCNQ1 gene have been observed in heart muscle cells; no expression has been found in the brain, skeletal muscles or liver [6].

The LQT2 type can be caused by mutations in the HERG (KCNH2) gene and is found in 30–35% of clinical cases. It is an autosomal dominant hereditary disorder manifesting itself as Romano-Ward syndrome. The LQT2 can be triggered by strong auditory stimuli such as doorbells, phones ringing, sirens or alarm clocks; it may also occur under the influence of excessive catecholamine secretion [5, 11, 12]. The ECG shows a long QT interval (above 450 ms) and discernible T wave with low amplitude and biphasic overlapping on the descending arm [5, 13, 14].

The HERG (KCNH2) gene, mapped to chromosome 7q35-36, consists of 15 exons (total approximately 19 kB). The corresponding protein product, consisting of 1,159 aminoacids, forms the α subunit of I_{Kr} rapid potassium channel [15, 16], mRNA for HERG gene is found primarily in heart muscle cells. KCNH2 gene has been shown to be important in preventing premature heart stimulation [17, 18].

The principal goal of our study was to examine the expression of KCNQ1 and HERG genes encoding potassium channels that are responsible for the occurrence of LQT1 and LQT2. The study aimed also at the confirmation of LQT among family members of patients diagnosed with this disease. Additionally, the study attempted to answer as to whether and how the expression of the examined genes changes in subjects with clinically diagnosed LQT. Lastly, we sought to verify whether β-actin is a good endogenous control for determining the expression of the studied genes.

METHODS

Gene expression was studied in subjects from six unrelated families. Initial diagnoses were based on such clinical features as altered ECG parameters, personal and family history of syncope and arrhythmia and/or aborted SCD. In total, 23 patients with clinically diagnosed LQT were enrolled in the study; 12 patients with LQT1 and 11 patients with LQT2. The remaining 21 were healthy individuals without clinically confirmed LQT symptoms. Consent to use blood samples taken from patients was obtained from the Bioethics Committee of the Medical University of Silesia.

Total RNA extraction

Total RNA extraction was performed using Fenozol total RNA isolation Reagent Set (A&A Biotechnology) ready-to-use.

Quantitative RT-PCR

Assessment of the transcriptional activity of the investigated genes was carried out using commercial kits (TaqMan Gene Expression Assays Applera for KCNQ1 gene 4331182 Hs00165003m1; for HERG gene 4331182 Hs00542478m1) 5′ end-labelled with FAM and 3′ end-labelled with non-fluorescent quencher. The number of mRNA copies of the investigated genes (KCNQ1, HERG, β-actin) was determined based on kinetics of the QRT-PCR reaction using ABI PRISM™ 7000 sequence detector (Applied Biosystems, CA, USA) and ROX QuantiTect Probe RT-PCR kit containing a fluorescent dye. The QRT-PCR was carried out in one step. The reaction mix contained: 10 μL 2 × QuantiTect Probe RT-PCR Master Mix (HotStarTaq DNA Polymerase, QuantiTect Probe RT-PCR buffer containing Tris-HCl, KCl, $(NH_4)_2SO_4$, 8 mm $MgCl_2$, pH = 8.7, dNTP mix and ROX reference dye) and 0.1 μL QuantiTect RT Mix (QuantiTect Probe RT-PCR kit, Qiagen GmbH, Germany) and 1 μL mix of TaqMan Gene Expression Assay starters and probes (Applied Biosystems), RNA matrix and pyrogen-free water. The reaction mix to amplify β-actin gene DNA standards contained: 25 μL 2 × QuantiTect Probe RT-PCR Master Mix (HotStarTaq DNA Polymerase, QuantiTect Probe RT-PCR containing Tris-HCl, KCl, $(NH_4)_2SO_4$, 5 mm $MgCl_2$, pH = 8.7, dNTP mix, reference ROX) (Qiagen GmbH, Germany) and 0.5 μm sense and antisense starters, β-actin cDNA template and pyrogen-free water. (Applied Biosystems TaqMan Gene Expression Assays for AKT 4331182 Hs 99999903_m1).

The reverse transcription reaction (in two repeats) was carried out at 50°C for 30 min. Following initial activation of HotStar Taq DNA polymerase (95°C/15 min) a two-step reaction was carried out: denaturation at 94°C for 15 s, and starter annealing at 60°C for 60 s (40 cycles). Final elongation of amplification products was carried out at 72°C for 10 min.

A series of QRT-PCR reactions was performed. The electrophoretic analysis of amplimers (length of PCR product for KCNQ1 gene — 78 bp; for HERG gene — 82 bp) and sequence analysis confirmed the specificity of the performed QRT-PCR reaction (data not shown). The results are expressed as the number of mRNA copies of the analysed genes per 1 μg of total RNA.

Statistical analysis

Data was exported from an Excel datasheet to Statistica v.7.1. data analysis software system (StatSoft Inc. 2006). Due to the lack of normal distribution of the investigated parameters (examined with Shapiro-Wilk test) we used a non-parametric Mann-Whitney U-test to analyse the results from the experimental and control groups. Correlation between mRNA copy numbers and clinical parameters was analysed using Spearman rank test correlation. The statistical significance level was set at $p < 0.05$.

RESULTS

Among three families with LQT1 were three asymptomatic mothers and nine children (8 ± 0.5 years), all with typical triggers of cardiac events (exercise and emotional stress). In three families with LQT2 were five adults and six children (7 ± 0.5 years). Three (50%) children and two mothers were symptomatic, triggered by stress, auditory stimuli or during rest or sleep. The twin-mothers with LQT2 presented with recurrent syncope during pregnancy and puerperium, and they had an implanted cardioverter-defibrillator. Their children were younger (3 ± 0.5 years) and without any symptoms. In the standard ECG, the duration of QT corrected using Bazett's formula (QTc) was significantly longer in the LQT2 group (median 0.48) compared to the LQT1 (median 0.4), $p = 0.000082$ (Table 1).

No significant difference was noted between the number of mRNA copies of KCNQ1 gene in patients diagnosed with LQT1 as against LQT2. Similar results were obtained when numbers of mRNA copies were compared for KCNH2 gene in the LQT1 and LQT2 patients. No significant difference between expression levels was revealed. Endogenous control was chosen correctly, as expression levels of the control gene (β-actin) did not differ in both investigated groups (Table 2).

We found a significant difference between the number of mRNA copies of KCNQ1 gene in LQT1 patients and controls ($p = 0.031$). Comparison of expression levels of LQT1 patients and controls for KCNH2 gene revealed no significant differences because there is no candidate gene for this type of LQT (Table 2).

Comparison of expression levels of LQT2 patients and controls for KCNH2 and KCNQ1 genes revealed no significant differences (Table 2). Endogenous control was chosen correctly, as expression levels of the control gene (β-actin) did not differ in both investigated groups ($p = 0.66$).

Differences in expression levels of KCNQ1 gene in patients with both types of syndrome and in controls were of borderline significance ($p = 0.053$). For the KCNH2 gene, no significant differences were revealed between the two groups (Table 2).

We did not find any significant correlation between KCNQ1 and KCNH2 mRNA copy numbers and QTc in patients with LQT1. We found a negative correlation between KCNQ1 mRNA copy numbers and QTc in patients with LQT2 ($p < 0.05$; $r = –0.73$). We did not find any correlation between KCNH2 mRNA copy numbers and QTc in patients with LQT2 ($p > 0.05$).

We found that symptomatic patients had a significantly higher KCNQ1 mRNA copy number than asymptomatic ones ($p = 0.05$). There were no differences beetween KCNH2 mRNA copy numbers in the analysed groups. We observed a trend towards higher expression of KCNH2 in symptomatic patients versus asymptomatic ones (NS).

DISCUSSION

Our study documented a different expression level of KCNQ1 gene in patients with LQT1 and in healthy controls. The other working hypothesis concerning different expression of KCNH2 gene in patients with LQT2 and in healthy individuals was not confirmed, possibly due to the numbers of patients and controls being too small. It is also possible that the disease was not yet expressed at such a young age (most symptomatic patients are young children), and that the molecular expression of LQT syndrome was different, depending on the number of mRNA copies.

To the best of our knowledge, the results described herein have not been reported previously. Published studies have concentrated on a RT-PCR investigation of KCNQ1 and HERG expression levels using mRNA isolated from horse heart muscle (vestibular and ventricular cells) [19]. These studies documented different expression levels of the studied genes in these two particular types of cells. The expression levels found in horse heart cells were similar to those found in rat and ferret. Finley et al. [19] also studied protein products of the genes in question, using antibodies directed against C-terminal epitope fragments.

Franco et al. [20] reported discrepant data concerning the expression of genes that encode potassium channels, at particular stages of murine heart embryonal development. Expression for the studied genes was analysed from the stage of tubular heart development until the full separation of ventricles. At the initial stages, KCNQ1 gene was shown to be expressed at similar levels in all elements of the heart. Expression at comparable level was sustained until the foetal stage of development characterised by full separation of ventricles; elevated expression was found only at the late foetal period. Investigation of another gene, HERG, revealed similar resuls as for KCNQ1.

Lou et al. [21] studied KCNQ1 and HERG expression levels and distribution in tissues, as well as commercially available cell lines (human embryonal kidney cells, heart muscle cells, breast and prostate cancer cells). High levels of expression were confirmed in cells isolated from the heart, pancreas and colon, whereas those in skeletal muscles and breast cancer cells were low. Elevated expression levels of both ge-

Table 1. Clinical data of studied patients

Genotype/control	Age [years]	Gender	QTc [s] Bazett's formula	Cardiac events/triggers
LQT-1	2	Male	0.53	Palpitations, fainting/stress
LQT-1	0.33	Male	0.48	Cardiac arrest/ICD
LQT-1	6	Male	0.46	Palpitations, fainting/exercise
LQT-1	15	Female	0.47	Palpitations, fainting
LQT-1	4	Female	0.46	Palpitations, fainting
LQT-1	32	Female	0.48	
LQT-1	10	Female	0.46	Syncope/exercise
LQT-1	46	Female	0.46	
LQT-1	7	Male	0.47	Fainting/exercise
LQT-1	16	Female	0.50	Fainting/exercise
LQT-1	37	Female	0.48	
LQT-1	15	Female	0.48	Palpitations
Control-LQT1	13	Female	0.42	
Control-LQT1	43	Male	0.39	
Control-LQT1	23	Male	0.38	
Control-LQT1	11	Female	0.39	
Control-LQT1	52	Male	0.4	
Control-LQT1	74	Female	0.40	
Control-LQT1	41	Female	0.32	
Control-LQT1	53	Male	0.40	
Control-LQT1	22	Female	0.44	
Control-LQT1	47	Male	0.39	
Control-LQT1	41	Male	0.40	
LQT-2	2	Male	0.48	
LQT-2	3	Female	0.48	
LQT-2	21	Female	0.55	Palpitations, recidivans syncope/puerperium/ICD
LQT-2	21	Female	0.54	Syncope-arousal/puerperium/ICD
LQT-2	4	Female	0.49	Fainting-stress/absence
LQT-2	6	Male	0.46	Syncope-stress-at rest, night
LQT-2	50	Female	0.53	
LQT-2	29	Male	0.46	
LQT-2	16	Female	0.46	Syncope-stress
LQT-2	11	Female	0.46	
LQT-2	39	Female	0.46	
Control-LQT2	22	Male	0.43	
Control-LQT2	30	Male	0.4	
Control-LQT2	5	Female	0.43	
Control-LQT2	28	Female	0.44	
Control-LQT2	27	Male	0.38	
Control-LQT2	30	Female	0.39	
Control-LQT2	55	Male	0.44	
Control-LQT2	44	Male	0.43	
Control-LQT2	65	Female	0.41	
Control-LQT2	19	Female	0.41	

ICD — implantable cardioverter-defibrillator

nes were found in the right atrium and ventricle compared to the left atrium and ventricle, thus underlining differences in expression levels in individual cardiac chambers.

The distinctive character of this study results from comparing the expression levels of KCNQ1 and KNCH2 genes in subjects with clinically diagnosed LQT1 and LQT2 and in healthy subjects. We found that symptomatic patients with LQT1 have a significantly higher KCNQ1 mRNA copy number than asymptomatic ones. It is possible that in the long QT1 type of syndrome, mRNA copy number is related to the

Table 2. Results of real-time PCR analysis for KCNQ1 and KCNH2 genes in long QT syndrome patients and healthy individuals

Group	KCNQ1*	P	KCNH2*	P
Patients LQT1	108855.2	0.18	16713118.7	0.33
Patients LQT2	80.6		343116.2	
Patients LQT1	108855.2	0.031	16713118.7	0.37
Control LQT1	211857749		164098518	
Patients LQT2	80.6	0.507	343116.2	0.529
Control LQT2	336741.9		18171.8	
Patients LQT1 & LQT2	80308	0.053	8839232.8	0.65
Control LQT1 & LQT2	111117425		85964154	

*Median of mRNA copy numbers per μg total RNA

occurrence of disease. We observed a trend towards a higher expression of KCNH2 in symptomatic patients with LQT2 *vs* asymptomatic ones, but that difference did not reach statistical significance, presumably due to the limited number of subjects.

The present study is also the first to use patients' peripheral blood as the material for the subject investigation. Studies on KCNQ1 and HERG expression reported thus far have been based on animal biopsy material or commercially available cell lines. On the basis of results obtained herein, the effects of KCNQ1 and HERG expression levels on the occurrence of LQT cannot be unequivocally determined.

Detailed analysis of this problem would require further studies involving larger study groups. This would permit a more precise determination of gene expression levels at a population level and would minimise statistical errors. It seems worthwhile to compare expression levels of KCNQ1 and KCNH2 genes in myocyte biopsy specimens from subjectswith diagnosed LQT and from healthy subjects. Cardiomyocytes may prove to be the best study material available because of the direct relationship between the functioning of ion channels in the heart and the occurrence of LQT. However, in the light of the results obtained herein, it could be that gene expression profiles are an additional criterion of differential diagnosis of long QT types. At present, this is an experimental method helpful in LQT diagnosis.

Our results allow a better LQT diagnosis to be obtained, and, possibly, differentiation between its two commonest phenotypes (LQT1 and LQT2). This would lead to a more targeted therapy and prophylaxis, both of which are highly desirable given the deadly nature of this syndrome.

Limitations of the study

The main possible limitation of our study is the fact that gene expression changes are controlled through highly complex, non-linear interactions between proteins, DNA, RNA, and a variety of metabolites. Real-time PCR gene expression analysis measures mRNA levels and this method may only suggest possible changes in protein levels or function rather than demonstrate them. Protein expression may not correlate with mRNA expression. Therefore, although there is a close association between gene expression and protein function, further analysis (e.g. protein analysis) will be necessary to clarify the role of KCNQ1 and KCNH2 expression level in LQT aetiology.

Another limitation is that the gene of interest must be transcribed at detectable levels in available tissue samples. Myocardial biopsy is not routinely performed for LQT diagnosis. The Unigene National Centre for Biotechnology Information and Gene Expression Omnibus suggest that expression of KCNQ1 and KCNH2 genes is largely restricted to the myocardium, and their mRNA transcripts cannot be reliably obtained from lymphocyte cultures. On the other hand, Miller et al. [22] showed that cardiovascular restricted mRNAs can be readily detected in peripheral blood without additional purification steps or cell culture, and then used as the starting material for rapid high-fidelity screening of mutations in genes associated with heart diseases. Replication studies verifying our observations should be performed.

CONCLUSIONS

1. KCNQ1 gene expression profile may be an additional criterion for the presence of, or absence of, LQT1.
2. Patients with LQT2 cannot be unequivocally differentiated from healthy controls on the basis of HERG (KCNH2) gene expression profile.
3. Beta-actin may be of use as an endogenous control in KCNQ1 and KCNH2 expression analysis in patients with LQT.

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Conflict of interest: *none declared*

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Ekspresja genów KCNQ1 i HERG kodujących kanały potasowe IK_R, IK_s w zespole długiego QT

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Streszczenie

Wstęp i cel: Głównym celem pracy było zbadanie ekspresji genów HERG i KCNQ1, kodujących kanały potasowe (szybkie i wolne), odpowiadających za wystąpienie określonego rodzaju zespołu długiego QT (LQTS).

Metody: Do badania włączono 6 rodzin, u członków których zdiagnozowano LQTS1 lub LQTS2, lub zdrowych. Badanie miało na celu udowodnienie, że beta-aktyna stanowi dobrą kontrolę endogenną przy ustalaniu ekspresji badanych genów. Do badania ekspresji genów wykorzystano ilościową analizę PCR w czasie rzeczywistym (QRT-PCR). Ekspresję badanych genów przedstawiono jako liczbę kopii mRNA w przeliczeniu na 1 μg całkowitego RNA izolowanego z krwi pełnej. Dane zostały wyeksportowane z arkusza Excel do programu analizy danych Statistica V.7.1.

Wyniki i wnioski: Na podstawie profilu ekspresji genu KCNQ1 można potwierdzić występowanie zespołu LQTS1. Badania wykazały statystycznie istotną różnicę ($p = 0,031$) między liczbą KCNQ1 kopii genu u osób chorych i zdrowych. Na podstawie profilu ekspresji genu HERG (KCNH2) chorych z LQTS2 nie można jednoznacznie odróżnić od osób zdrowych ($p = 0,37$).

Słowa kluczowe: zespół wydłużonego QT, KCNQ1, HERG, ekspresja genów

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