

Association of functional genetic variants of A-kinase anchoring protein 10 with QT interval length in full-term Polish newborns

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Submitted: 30 July 2012

Accepted: 13 November 2012

Arch Med Sci 2015; 11, 1: 149–154

DOI: 10.5114/aoms.2013.34172

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Abstract

Introduction: A-Kinase Anchoring Proteins (AKAPs) coordinate the specificity of protein kinase A signaling by localizing the kinase to subcellular sites. The 1936G (V646) *AKAP10* allele has been associated in adults with low cholinergic/vagus nerve sensitivity, shortened PR intervals in ECG recording and in newborns with increased blood pressure and higher cholesterol cord blood concentration. The aim of the study was to answer the question of whether 1936A>G *AKAP10* polymorphism is associated with the newborn electrocardiographic variables.

Material and methods: Electrocardiograms were recorded from 114 consecutive healthy Polish newborns (55 females, 59 males), born after 37 gestational weeks to healthy women with uncomplicated pregnancies. All recordings were made between 3rd and 7th day of life to avoid QT variability. The heart rate per minute and duration of PR, QRS, RR and QT intervals were usually measured. The ECGs were evaluated independently by three observers. At birth, cord blood of neonates was obtained for isolation of genomic DNA.

Results: The distribution of anthropometric and electrocardiographic variables in our cohort approached normality (skewness < 2 for all variables). No significant differences in anthropometric variables and electrocardiographic traits with respect to *AKAP10* genotype were found. Multiple regression analysis with adjustment for gender, gestational age and birth mass revealed that QTc interval in GG *AKAP10* homozygotes was significantly longer, but in range, when compared with A alleles carriers (AA+AG, recessive mode of inheritance). No rhythm disturbances were observed.

Conclusions: Results demonstrate possible association between *AKAP10* 1936A>G variant and QTc interval in Polish newborns.

Key words: A-kinase-anchoring protein 10, electrocardiograph, genetic polymorphism, newborns, QT interval.

Introduction

Quantitative non-invasive measures of cardiac electrical activity recorded in electrocardiographic (ECG) studies are widely available in community-based samples and have been found to be predictive of cardiovascular events including sudden cardiac death [1, 2]. Aggregation of these meas-

ures within families suggests a heritable component. The electrocardiographic PR interval has reported heritability estimated at 34% [3]. The RR interval, or its inverse – heart rate (HR) – has been observed to have a heritability ranging from 32% to 40% in family studies [4] and 54% to 77% in twin studies [5]. Genome-wide association studies have found, for example, that infants with a QTc > 460 ms in the first month of life (and with prolonged QT remaining at 1 year) have a 90% chance of carrying one of a list of mutations from various genes, including *KCHN2* and *KCNQ1* [6]. The heritability of electrocardiographic QT interval duration, a measure of myocardial repolarization, has been reported to be approximately 35%, indicating that 35% of the variability in adjusted QT interval duration is attributable to heritable factors [7]. The heritability of ECG suggests there is a significant genetic component to the determination of these measures of myocardial repolarization, sinus node function, atrioventricular conduction, and autonomic function.

The cAMP-dependent protein kinase (protein kinase A – PKA) is responsible for modulating a vast number of cell physiological processes [8]. A-kinase-anchoring proteins (AKAPs) coordinate PKA signaling by localizing PKA to subcellular sites through binding to the N-terminus of the R subunits [9]. AKAP10 binds both type I and type II R subunit isoforms of PKA. In a comparison of ~6500 single-nucleotide polymorphisms located in approximately 5000 genes between age-stratified, healthy, European-American individuals, Kammerer *et al.* found that only the 1936A>G transition in the gene encoding AKAP10 (*AKAP10*), causing the substitution of isoleucine by valine at position 646 (I646V, G alleles), was statistically significantly less frequent in older subjects for both men (60 to 79 years) and women (60 to 69 years) [10]. The I646V polymorphism enhances by threefold binding of AKAP10 to PKA R1 α and the targeting of the R1 α subunit to the mitochondria [10]. Analysis of 417 white twin pairs from the adult twin registry at St. Thomas Hospital, London, indicated that the I646V variant was associated with a significant decrease in the electrocardiogram PR interval [10]. Further studies revealed that 1936A>G *AKAP10* was associated in adults with increased basal HR and decreased heart rate variability (HRV), which are markers of low cholinergic/vagus nerve sensitivity [11, 12] – one of the factors responsible for increased cardiovascular risk [13].

Therefore, it raises the question whether the 1936A>G *AKAP10* transition is associated with electrocardiographic intermediate phenotypes in full-term Polish newborn infants. Note that it was of importance to measure QTc as early as possible (after the 2nd day of life to avoid maximal QT variability) because a large prospective study has

shown that some infants with prolonged QT in the first week are prone to sudden death [14]. In addition to the factors mentioned above, it should be noted that phenotype-genotype correlation studies using newborns seem to be more plausible than those with older individuals due to exclusion of confounding environmental influences such as diet, lifestyle, smoking or disease [15] and the possibility of a very early prophylactic procedure.

Material and methods

Study subjects

The study was approved by the local ethics committee and the parents gave informed consent. At the Department of Neonatal Diseases of Pomeranian Medical University in Szczecin, we prospectively recruited 114 consecutive healthy Polish newborns (55 females and 59 males), born after the end of the 37th week of gestation to healthy women with uncomplicated pregnancies in whom ECGs were recorded. Due to artifacts, eleven electrocardiograms had to be excluded. All the recordings were made between the third and seventh day of life in order to avoid the variability of QT interval that is maximal during the first 2 days of life as well [16]. None of the enrolled infants had an episode or history of an acute life-threatening event (including apnea), cardiovascular disease, or disease known to affect the autonomic nervous system. All children were breast-fed and free of medication (i.e. without medicines known to influence heart rate and/or blood pressure). Twins, infants of mothers with preeclampsia, hypertension of any cause, diabetes, autoimmune diseases, history of illicit substance use or antenatal steroid therapy were excluded. Other exclusion criteria were congenital infection, intra-uterine growth restriction (i.e. below the 10th percentile birth mass, length or head circumference), chromosomal aberrations or congenital malformations. At birth, cord blood of neonates was obtained for isolation of genomic DNA. The gender of the newborn, birth mass, body length and head circumference were taken from standard hospital records. Body surface area (BSA) was calculated as the square root of (length (cm) \times mass (kg)/3600) according to Mosteller [17]. Because only healthy children were included in the study blood electrolyte concentrations were not quantified.

Electrocardiography

Between days 3 and 7 of life all subjects underwent a routine standard 12-lead body surface electrocardiogram, recorded at a paper speed of 50 mm/s and at a gain of 10 mm/mV (ACARD 3 apparatus). During the electrocardiographic recording, calm infants were resting in a horizontal recumbent position and breathing freely. If the newborns did not

become quiet by themselves they were given 5% glucose to drink to quieten them. The heart rate per minute and duration of PR, QRS, RR and QT intervals were usually measured in lead II from three non-consecutive beats. If records in lead II were unreadable we used lead V₂ to measure the above-mentioned parameters (as in Cowan *et al.* [18], and Rautaharju *et al.* [19]). The ECGs were evaluated independently by three observers (a child cardiologist and two ECG technicians experienced in child ECG analysis), who were blinded to the infants' identity and to each other's readings. The arithmetic means of the results were compared with results of analysis by a pediatrician, who used a computer program constructed to allow analysis of the scanned electrocardiograms in great detail. There were no significant differences between ECG parameters obtained by all involved investigators. The QTc interval was calculated using the Bazett formula ($QTc = QT/\sqrt{RR}$). We used Bazett's formula because it is recommended by guidelines for the interpretation of neonatal electrocardiograms of the European Society of Cardiology [20]. This formula is applicable if the heart rate is in the range 80–180 beats/min [21] and the heart rate of newborns observed in our study was in the range 97–174 beats/min.

Determination of AKAP10 genotype

Genomic DNA from cord blood was isolated (QIAamp Blood DNA Mini Kit; QIAGEN, Hilden, Germany). To genotype the isoleucine to valine mutation at amino acid 646, caused by an A-to-G transition at nucleotide 1936 of the AKAP10 gene, we used our own PCR-RFLP method as described previously. Briefly, genomic DNA was amplified by PCR with primers flanking the polymorphic region: 5'-TCGGTGTAGGTATCCAGTAGTTG-3' as the sense primer, and 5'-TAAGAAGGTAATCCCCACAGCAGT-3' as the antisense primer. These primers yielded a PCR product of 437 bp in length. Genomic DNA samples (20 ng) were amplified in a final volume of 10 µl, which contained 2 pM of each primer, 0.25 mM of each deoxyribonucleotide (dATP, dTTP, dCTP, dGTP) (Promega), 50 mM KCl, 20 mM Tris-HCl (pH 8.4), 1.5 mM MgCl₂, 10 mg/ml albumin from nuclease-free bovine serum, and 0.25 U of DNA polymerase (*Taq*, Boehringer Mannheim, Penzberg, Germany). The amplification was performed in a gradient thermocycler (Mastercycler, Eppendorf, Warsaw, Poland) using the following conditions: initial denaturation at 94°C for 5 min, then 36 cycles: denaturation at 94°C for 20 s, annealing at 64°C for 40 s, and extension at 72°C for 40 s. The reaction finished with a final extension at 72°C for 8 min. Subsequently, the products of amplification were incubated at 65°C for 3 h with 1 U of restriction enzyme *Tai* I (MBI Fermentas, Vilnius, Lithuania),

and separated using 3% agarose gel electrophoresis, and stained with ethidium bromide. The "wild-type" sequence (1936A allele) was identified by lack of the *Tai* I restriction site, while the 1936G allele was digested into 269 and 168 bp restriction fragments. Results were recorded with photographs of gels under UV light. All samples were independently genotyped using a blind method in duplicate, i.e. all samples were anonymously labeled by one person and then genotyped by the second person.

Statistical analysis

The divergence of AKAP10 genotype frequencies from Hardy-Weinberg equilibrium was assessed using a χ^2 test. The distribution of each quantitative variable was tested for skewness. Quantitative data were presented as means \pm SD. Association between AKAP10 genotype and each outcome variable was assessed by one-way ANOVA. In addition, electrocardiographic intermediate phenotypes (traits), with respect to dominant and recessive mode of inheritance of the 1936G AKAP10 minor allele, were analyzed by multiple regression with adjustment for confounding variables. Statistical significance was defined as $p < 0.05$. All data were analyzed using a data analysis software system (Statistica, version 8.0, StatSoft, Inc. 2007, www.statsoft.com).

Results

All PCR-RFLP samples were genotyped twice and a concordance rate of 100% was attained. There were 41 AA AKAP10 homozygotes (36.0%), 59 AG heterozygotes (51.7%) and 14 GG AKAP10 homozygotes (12.3%). The frequency of the 1936G AKAP10 minor allele was 38.2% (35.6% in newborn males and 40.9% in newborn females). The AKAP10 genotype distribution conformed to the expected Hardy-Weinberg equilibrium. The distribution of anthropometric (Table I) and electrocardiographic variables in our cohort approached normality (skewness < 2 for all variables). Mean body mass was 3409 \pm 530 g, body length 56.2 \pm 3.3 cm, head circumference 33.7 \pm 1.5 cm, body surface area 0.23 \pm 0.02 m². All infants were born in good condition (Apgar score was 8 or higher). No significant differences in anthropometric variables and electrocardiographic traits with respect to AKAP10 genotype were found. Multiple regression analysis with adjustment for gender, gestational age and birth mass revealed that QTc interval in GG AKAP10 homozygotes was significantly longer when compared with A allele carriers (AA+AG, recessive mode of inheritance) (Table II).

Discussion

The results of our study show an association between the 1936A>G (I646V) AKAP10 genotype

Table I. Background characteristics (means \pm SD) of newborns with respect to *AKAP10* genotypes

Variables	Total	Genotype			Value of p_{ANOVA}	Value of p_{DO}
		AA	AG	GG		
Gestational age [weeks]	39.9 \pm 1.0	39.7 \pm 0.9	40.1 \pm 1.0	39.8 \pm 0.9	0.110	0.085
Birth weight [g]	3409 \pm 540	3383 \pm 518	3403 \pm 523	3540 \pm 537	0.613	0.927
Body length [cm]	56.2 \pm 3.3	56.1 \pm 3.4	56.3 \pm 3.1	56.6 \pm 3.3	0.887	0.860
Head circumference [cm]	33.7 \pm 1.5	33.7 \pm 1.6	33.7 \pm 1.4	33.8 \pm 1.5	0.954	0.881
Body surface area [m ²]	0.231 \pm 0.023	0.229 \pm 0.024	0.230 \pm 0.023	0.235 \pm 0.024	0.685	0.968

Multiple regression: p_{DO} for dominant (GG + AG vs. AA); p_{RE} for recessive (GG vs. AG + AA) models of inheritance.

Table II. ECG characteristics (means \pm SD) in newborns with respect to *AKAP10* genotypes

Variables	AKAP10 genotype			Value of p_{ANOVA}	Value of p_{DO}	Value of p_{RE}
	AA	AG	GG			
HR [beats/min]	142 \pm 21	143 \pm 24	142 \pm 15	0.997	0.825	0.999
PR [ms]	122 \pm 13	122 \pm 10	122 \pm 6	0.998	0.707	0.888
PQ [ms]	89 \pm 12	89 \pm 10	91 \pm 9	0.698	0.941	0.567
QRS [ms]	74 \pm 4	74 \pm 5	76 \pm 6	0.683	0.690	0.490
QT [ms]	258 \pm 22	258 \pm 27	266 \pm 15	0.642	0.548	0.397
QTc [ms]	395 \pm 17	393 \pm 20	408 \pm 25	0.077	0.562	0.030

Multiple regression: p_{DO} for dominant (GG + AG vs. AA); p_{RE} for recessive (GG vs. AG + AA) models of inheritance after adjustment for gender, gestational age and birth mass.

and length of the QTc interval in Polish newborns born full term. The observed value of the QTc interval is in accordance with other studies of healthy newborns. In a study performed by Schwartz *et al.* on 43 080 white neonates, the 97.5th and the 50th percentiles, i.e. upper and normal values of QTc, were 443 ms and 364 ms respectively [6]. None of the newborns in our study had a QTc interval longer than the upper normal limit of QTc, which is considered to be 440 ms [14]. Because only 2.5% of normal newborns can be expected to have greater length of this interval, we probably did not observe this due to the small sample size. We do not think that the values observed in our study are of clinical significance and/or require any special monitoring of newborns. However, they should shed some light on the influence of *AKAP10* on the physiology of the developing heart.

This study examined the association of a functional *AKAP10* polymorphism with surface ECG investigation and the association of genetic polymorphism with surface ECG in a cohort of newborns within a few days after birth. Previously, Kammerer *et al.* revealed an association between *AKAP10* polymorphism and shorter PR interval in 97 traits using a sample of 417 white twin pairs [10]. They did not observe any changes concerning the QT interval or T wave.

Żukowski *et al.* reported that during kidney transplantation patients with the 1939A>G *AKAP10* variant had a significantly longer QTc interval, which

declined to a level similar to that in the control group 1 h after the operation [22]. These data suggest that this polymorphism can predict arrhythmia in situations with triggering circumstances such as anesthesia and surgical procedures, even in patients who usually have normal values of the QTc interval. There are some differences between our study and the study of Żukowski *et al.* The QTc interval in our study was measured in healthy newborns, and all conditions which could affect the QTc interval were excluded. Newborns were investigated during rest/sleep and in the first days of life, i.e. during a phase of heart immaturity. The study of Żukowski *et al.* was performed on chronically sick adult patients, who qualified for renal transplantation and had undergone anesthesia and surgery.

Although during the first days of life newborns are also stimulated by a rapidly changing environment, this situation cannot be compared to renal transplantation. Nevertheless, we could consider the hypothesis that the 1939A>G *AKAP10* polymorphism, with increased signaling of PKA, could possibly increase the risk of cardiac arrhythmia under aggravating conditions. *AKAP10* is thought to affect heart rhythm [23]. Tingley *et al.* generated *AKAP10*-mutant mice, with a mutation which has a lower affinity to PKA [11]. *AKAP10*-mutant mice showed many cardiovascular abnormalities including decreased heart rate, pathological sinoatrial and atrioventricular conduction as well as arrhythmias and a higher susceptibility to sudden death. It was

postulated that the observed effects were associated with higher activity of the parasympathetic system in the mutant mice. This could mean that the I646V *AKAP10* variant, responsible for enhanced binding to PKA, could have the effect of actually decreasing the activity of the parasympathetic system, associated with cardiovascular risk. It is interesting that *AKAP10* mutation caused death only in adult mice.

Similar observations confirming increased parasympathetic activity associated with disruption of *AKAP10* binding to PKA were reported by Patel *et al.* [24]. In experiments performed on isolated cardiomyocytes and on isolated heart it was observed that such disruption reduced myocyte shortening and rates of contraction and relaxation. In the isolated hearts the authors observed a decreased heart rate and contractile function. Because the hearts were isolated from neurohormonal activation, the results suggest that the influence of *AKAP10* does not only depend on vagal nerve activation. These experimental observations were confirmed in human studies, which showed that the V646 variant was associated with low cholinergic/vagus nerve sensitivity expressed as increased basal heart rate and decreased heart rate variability [11, 12]. In our study we did not observe arrhythmia and we have not found a significant association between 1939A>G *AKAP10* polymorphism and heart rate in the newborns studied by us. Our observations are in accordance with Żukowski *et al.* [22], who also did not observe arrhythmia, or changes of HR and HRV, in their transplant patients. However, when comparing the results obtained by us and the results from the work of Tingley *et al.* [11] and Neumann *et al.* [12] extreme caution should be taken because of significant differences in the design of the studies. Our study included newborns in whom heart rate was calculated on the basis of standard surface ECG performed during resting/sleeping. Tingley *et al.* used 24 h continuous ECG recording and Neumann *et al.* used 10 min continuous 2-lead electrocardiograms. Both methods allowed the measurement of HR as well as HRV. Moreover, Tingley *et al.* did not present HR results for the genotypes of *AKAP10*, and only showed that carriers of the 1936G (V646) variant *AKAP10* were more likely to have a mean HR (over 24 h) of > 75 beats/min, which is an independent risk factor for sudden cardiac death in the adult population. For our newborns all HR values were > 75 beats/min. Additionally, in the study performed by Neumann the influence of the *AKAP10* polymorphism on HR and HRV was not confirmed in the case of high frequency (HF) HRV. The authors postulated that this *AKAP10* variant may have more influence on basal HR and sympathetic-vagal interactions at the sinus node. In newborns the auto-

nomous system of the heart is not well balanced due to its immaturity. We also have to note that the influence of the sympathetic and parasympathetic system on the QTc interval is not fully elucidated and data are very often conflicting [25]. Due to these circumstances, the results observed by us concerning QTc interval and HR suggest that further studies are needed to propose any deeper conclusion.

In contrast to Kammerer *et al.*, we did not observe an influence of *AKAP10* polymorphism on PR interval in newborns. (The values observed in our study are in the general range found in other literature [14].) The PR interval reflects atrioventricular nodal conduction and can lead to atrial fibrillation. Conduction disturbances associated with *AKAP10* were observed in an experimental study performed by Tingley *et al.* [11], but no human study has confirmed these observations. Taking into consideration our other data, we cannot expect that the observations of Kammerer *et al.* of an adult population could be confirmed in our newborns, as the HR is too fast to observe PR interval shortening using a standard surface ECG. The underlying molecular mechanism for the relationship between the *AKAP10* polymorphism and neonatal surface ECG is unclear. Recently, Eggers *et al.* reported that the RGS domains of *AKAP10* interact with the small GTPases Rab4 and Rab11, which regulate endocytic recycling. Therefore, these authors suggested that the fact that 1939A>G *AKAP10* is associated with disease phenotypes could be the result of altered surface expression of various receptors or channels [26], including adrenergic receptors involved in heart rhythm regulation [27]. It should also be taken into consideration that the PKA-AKAP pathway is involved in water and electrolyte homeostasis, e.g. via modulation of epithelial sodium channel (ENaC) or aquaporin 2 [28].

In conclusion, our results demonstrate a possible association between the 1936A>G *AKAP10* variant and QTc in the aboriginal-European newborn population. However, the results should be interpreted with caution due to the relatively small sample size. The results observed by us have no clinical consequences for newborns and do not require any prophylactic treatments, but they do suggest some influence of *AKAP10* on the physiology of the developing heart.

Conflict of interest

The authors declare no conflict of interest.

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