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Pathogenic Variants in the *TJP1* Gene are Associated with Cardiac Phenotypes in Endurance Athletes from Oaxaca, México

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Abstract

Background: The sudden cardiac arrest of an apparently healthy athlete is an uncommon but feared event with an unclear incidence in athlete depending on genetic diversity from population and study methodology from screening cardiac disease. In young athletes have an undiagnosed arrhythmogenic cardiomyopathy and other arrhythmias causes of sudden cardiac death. *TJP1* gene is a new candidate gene from association studies in these cardiovascular disease. *E*ncodes for the thigh junction's proteins type 1, which is part from the myocyte lateral membrane between cell-cell due to development the desmosome.

Aim: Was scan detect structural and cardiovascular disease in asymptomatic high performance young's athletes, determinate the association with the genetic variants in the *TJP1* gene.

Materials and methods: Male 167 asymptomatic high-performance athletes usuries come to our center every year for their check-up, were enrolled. We obtained electrocardiography (ECG) from all study participants.

Results: The five probands with the sustained ventricular tachycardia were heterozygote carrier's for the variant rs1038306187 locus by the domain guanylate kinase. 3 left bundle branch block (LBBB), right bundle branch block in two cases, was positive from the gene variation. 986C>T, p.(S329L). The probands with arrhythmogenic dysplasia were carrier from the variant c.793C>T p.(R265W).

Conclusion: The genetic variants in the TJP1 explain the 37.7% cardiovascular problems in asymptomatic endurance athletes, being the SNV rs781148827 the variant more frequently, in the Mexican population.

Keywords: Arrhythmogenic Dysplasia, Right Bundle Branch Block, Ventricular Tachycardia, Young Athletes

Introduction

The sudden cardiac arrest of an apparently healthy athlete is an uncommon but feared event with an unclear incidence in athlete depending on genetic diversity from population and study methodology from screaning cardic enjury. In young athletes an undiagnosed arrhythmogenic cardiomyopathy, ventricular arrhythmias, left ventricular hypertrophy, stroke, and causes of sudden cardiac death [1]. The common genetic variations allelic variants can be causing have been reported to be surprisingly common in athletes with ventricular arrhythmias [2]. However, little is known about this entity and the associated exercise doses, individual susceptibility and risk markers of arrhythmic remodeling in athletes. Also is known about cardiac phenotypes and genetic risk markers or desmosoma of life-threatening arrhythmic events in endurance athletes with ventricular arrhythmia [3].

With these considerations, *TJP1* gene is a new candidate gene from association studies in cardiovascular disease. Certtely *TJP1* encodes for the thight juntions proteins type 1, which is part from the miocyte lateral membrane between cell-cell due to development the desmosome. Also, their variations can be used such as a molecular marker of physical performance, because *TJP1* it has been shown to participate in the absorption of nutrients at the level of intestinal, which favors having better macro and micronutrient reserves, which is a determining factor for endurance performance [4]. Is limited the genetic studies from gene variation of TJP1, in this sense, an interesting marker of the gene, is the polymorphism rs229166, leads to a conformational change in the ZO-1 structure, which is realetd to the albuminuria [5, 6]. Other polymorphism is the SNV rs1038306187 leading to the change of amino acid p. Gln791Glu in the domain guanylate kinase. The domain ZU5 has been

reported 33 genetic variants leading to conformational changes. The variants that affect gene expression by nucleotide changes at the cryptic sites of the alternative splicing are SNV rs781148827, rs5478300017, rs78014403 and rs1020739943 in acceptor region, and rs1029122894 in the donor region, but none of these polymorphisms have been explored for their pathogenic effect in structural heart or cardiovascular diseases. Due to effect on ZO-1 expression, they are a new frontier of research in the also fitness performance [6]. On the other hand, this gene could be very useful too in the detection of arrhythmogenic dysplasia, which are a very important cause of sudden death in many athletes and highperformance athletes [2]. For those the aim of the study was scan detect structural and cardiovascular problems in asymptomatic high performance young's athletes and determinated the association with the genetic variants in the TJP1 gene.

Material and methods

Male 167 asymptomatic high-performance athletes usuries come to our center every year for their check-up from the Center from Research Traslacional and Medical Precision from the Sierra Sur Oaxaca, México, were enrolled. We obtained electrocardiography (ECG) from all study participants and interpreted these according to current international criteries [1, 2]. We classified ECGs in cases with voltage signs of left ventricular hypertrophy. The number of premature ventricular contractions (PVCs) per 24 h was assessed by Holter monitor recordings in the majority of participants. Nonsustained ventricular tachycardia (NSVT) was considerate as 3 or more consecutive PVCs >100 beats/min, self-terminating within 30 s.

Ventricular tachycardia (VT) was defined as sustained when lasting >30 s, and was documented on 12-lead ECG or Holter monitor recordings previously definided [1, 2]. Sustained VTs were classified as left bundle branch block (LBBB)–like with superior or inferior electric axis, right bundle branch block. Life-threatening arrhythmic events were defined as aborted cardiac arrest, sustained VT, ventricular fibrillation previously reported [1, 2].

Doppler echocardiography, was performed in the Usltrasonography Center and Pharmnacy Alpha, from de Sierra Sur, using Vivid 7, E9 or E95 scanners (GE Healthcare) [1, 2]. Was assessed left ventricular (LV) size, ejection fraction, diastolic function, and left atrial. Mechanical dispersion, reflecting contraction heterogeneity, was expressed as the standard deviation of the time from Q/R on surface ECG to peak negative strain in 16 LV segments, previously reported [1, 2].

Molecular study was realized such as previously reported for screening mutations in the *TJP1* gene by Sanger sequencing. Primer pairs were used to amplify the 28 coding exons of TJP1 with flanking intronic sequences based on the published sequence (GenBank accession number NM_003257). The PCR-amplicons were sequenced using the Kit BIG DYE dideoxy terminator chemistry (PerkinElmer, Waltham, Massachusetts) on the sequencer ABI prim 3730XL (PE Applied Biosystems) [2].

This work was approved by the center's ethics and research committee. All included subjects signed the informed consent, from the Center from Research Traslacional and Medical Precision from the Sierra Sur Oaxaca, México.

Results and discussion

From the 167 asymptomatic high-performance athletes usuries come to our center every year for their check-up from the Center from Research Traslacional and Medical Precision from the Sierra Sur Oaxaca, than were enrolled, 23 has been left ventricular hypertrophy, 10 have nonsustained ventricular tachycardia, 5 sustained ventricular tachycardia, 3 left bundle branch block (LBBB), right bundle branch block in two cases, and arrhythmogenic dysplasia in 3 cases.

The molecular results show, than 23 has been left ventricular hypertrophy; ten probands has been carriers heterocigoty from the rs781148827, two probands homcocygote from the genetic variant rs5478300017, eleven probands were heterozygote from the variant rs78014403 in acceptor region. The five probands with the sustained ventricular tachycardia were heterozygote carrier's rs1038306187 in the domain guanylate kinase. 3 left bundle branch block (LBBB), right bundle branch block in two cases, was positive from the gene variation. 986C>T, p.(S329L). The probands with arrhythmogenic dysplasia were carrier from the variant c.793C>T p.(R265W). All those these genetic variants was analyzed in 1300 subjects with Oaxaca ancestry Amerindian, which are negative.

This is the first study from the mutations on the TJP1 gene associated cardiac phenotypes in endurance athletes Mexican. Is the first in reported the frequency from the variants rs781148827, rs5478300017, and rs78014403, which is the acceptor region. The probands with arrhythmogenic dysplasia associated with the variant c.793C>T p.(R265W), was reported, previously [2], but not in the Mexican athletes. Other SNV rs1038306187 leading to the change of amino acid p. Gln791Glu in the domain guanylate kinase, was not previously reported, but has been proposed a candidate marker in neurodegenerative disease [6].

It has been reported that the frequency of cardiovascular problems in asymptomatic athletes is uncertain [1-4]. In this sense, this is the first report in the Mexican population that demonstrates structural cardiac and conduction problems demonstrated with office studies and corroborated with molecular studies, which had a frequency of 37.7%.

The main limitation of the present study is that it was not demonstrated that the pathogenic variants of TJP1 were familial, which will be part of the study object of another work. The fact that mutations were not found in all patients is expected, considering that there are other mutations causing the cardiac phenotypes found in the present cohort [1-3].

Conclusion

The genetic variants in the TJP1 explain the 37.7% cardiovascular problems in asymptomatic endurance athletes, being the SNV rs781148827 the variant more frequently, in the Mexican population.

Declaration conflict interest

The authors declare no conflict of interest.

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