ORİJİNAL ARAŞTIRMA ORIGINAL RESEARCH

DOI: 10.5336/medsci.2017-54901

The Relation Between the P1A1/A2 Polymorphism of ITGB3 Gene and Myocardial Infarction in Elite Athletes

Profesyonel Sporcularda ITGB3 Genindeki P1A1/A2 Polimorfizmi ile Miyokard İnfarktüsü Arasındaki İlişki

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Geliş Tarihi/*Received:* 23.01.2017
Kabul Tarihi/*Accepted:* 31.03.2017

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ABSTRACT Objectives: P1A1/A2 polymorphism on Integrin Subunit Beta 3 (ITGB3) gene's correlation with increased risk of myocardial infarction (MI) is not clear and various researches have reported contradictory results concerning the P1A1/A2 polymorphism of ITGB3 gene. We have focused on the relation P1A1/A2 polymorphism and MI, 26 male subjects under 45 years old who had MI. Due to the increasing concern of sudden death on athletes, we have compared these subjects with professional athletes. We aimed to investigate the frequency of P1A1/A2 polymorphism, in subjects under 45 years old suffering myocardial infarction (MI) and elite athletes who are at the same age range. **Material and Methods:** Peripheral blood was collected from 26 subjects with MI grouped as positive control, 25 healthy subjects grouped as negative control and 37 subjects as elite athletes. DNA was isolated from totally 88 peripheral blood samples. DNA extraction was followed by the PCR-RFLP method in order to detect the PlA1/A2 polymorphism. Amplified DNA products were digested with HpaII restriction enzyme. We aimed to see two bands, at 81 and 127 bp, after enzyme digestion. Standard descriptive statistical methods were applied to summarize the data. **Results:** Three genotypes could be determined after assessment with bioanalyzer; genotype P1A1/P1A1 (81 and 127 bp fragments), genotype P1A1/P1A2 (81,127 and 208 bp fragments) and genotype P1A2/P1A2 (208 bp). Heterozygous polymorphic phenotype (P1A1/P1A2) was observed 8%, 7.7% and 17% on positive control group, negative control group, and elite athletes, respectively. Homozygous phenotype (PlA2/A2) was observed in 7.7% of positive control group only. **Conclusion:** Our study highlights the significance of screening on athletes to prevent sudden deaths during sports. For next step, these obtained results will be analysed on larger populations to try to answer the question that "can sudden cardiac deaths (SCDs) be avoided and what should be done?"

Keywords: Myocardial infarction; polymorphism, genetic; ITGB3 protein, human

ÖZET Amaçlar: İntegrin Subünit Beta 3 (ITGB3) genindeki P1A1/A2 polimorfizmi ile miyokard infarktüsü (MI) artan riski ile ilişkisi net değildir ve çeşitli araştırmalar ITGB3 geninin P1A1/A2 polimorfizmi ile ilgili çelişkili sonuçlar bildirmiştir. P1A1/A2 polimorfizm ve MI arasındaki ilişkiye, 45 yaşın altındaki 26 erkek MI hastası üzerinde odaklandık. Atletlerde ani ölümle ilgili artan endişeler nedeniyle, bu örnekleri profesyonel sporcularla karşılaştırdık. Kırk beş yaş altı miyokard infarktüsü (MI) geçirmiş bireylerde ve aynı yaş aralığında elit atletlerde P1A1/ A2 polimorfizm sıklığını araştırmayı amaçladık. **Gereç ve Yöntemler:** Pozitif kontrol grubu olarak MI hastası 26 örnekten, negatif kontrol olarak gruplandırılan 25 sağlıklı örnekten ve elit atlet grubu olarak 37 örnekten periferik kan toplandı. Toplam 88 periferik kan örneğinden DNA izole edildi. PlA1/A2 polimorfizmini saptamak için DNA ekstraksiyonunu takiben PCR-RFLP yöntemi uygulandı. Çoğaltılmış DNA ürünleri HpaII restriksiyon enzimi ile kesildi. Enzim kesiminden sonra 81 ve 127 bç'de iki bandı görmeyi hedefledik. Verileri özetlemek için standart tanımlayıcı istatistiksel yöntemler uygulanmıştır. **Bulgular:** Biyoanalizörle değerlendirme sonrası üç genotip belirlenebilir; P1A1/P1A1 genotipi (81 ve 127 bç fragmentler), genotip P1A1/P1A2 (81,127 ve 208 bç fragmentler) ve genotip P1A2/P1A2 (208 bç). Pozitif kontrol grubu, negatif kontrol grubu ve elit sporcular üzerinde sırasıyla %8, %7.7 ve %17 oranında heterozigot polimorfik fenotip (P1A1 / P1A2) görüldü. Yalnızca pozitif kontrol grubunun %7.7'sinde homozigot fenotip (PlA2/ A2) gözlenmiştir. **Sonuç:** Çalışmamız sporcuların spor esnasında ani ölümlerini önlemek için taramanın önemini vurgulamaktadır. Bir sonraki adım için, elde edilen sonuçlar, "ani kardiyak ölümler (AKÖ) önlenebilir mi ve ne yapılmalıdır?" sorusunu cevaplamaya çalışmak için daha geniş popülasyonlarda analiz edilecektir.

Anahtar Kelimeler: Miyokardiyal infarktüs; polimorfizm, genetik; ITGB3 protein, insan

Polymorphisms are result of small changes in genetic material. These changes distinguished from mutations by their frequency in the population. To be considered as a polymorphism, these small changes should be at least 1% in the population. In all organisms, including humans, polymorphism are resulted of single nucleotide polymorphisms (SNP), microsatellites, insertions and deletion.[1] They can cause disease as a result of influencing promoter activity (gene expression), messenger RNA (mRNA) conformation (stability), and subcellular localization of mRNAs and/or proteins.[2]

Myocardial infarction's (MI) etiologies are multifactorial. Many genes and their polymorphism with different phenotypic expressions and additional risk factors such as smoking, high blood pressure, diabetes, and abnormal heart rhythm cause disease.[3] Atherothrombosis characterized by atherosclerotic plaque disruption with superimposed thrombosis formation, is the main cause of acute coronary syndromes.[4] Platelets are essential for process of forming and extending atherosclerotic plaques, primary hemostasis, repair of the endothelium.[5,6] As most abundant integrin platelet surface, fibrinogen receptors are needed for primary homeostasis by virtue of their part in thrombocyte aggregation and coagulation after damage in tissue and veins.[7] Due to its central role in blood coagulation as principle mediator of acute coronary thrombosis, research on genetic polymorphisms in fibrinogen receptor coding gene are gained importance because of these polymorphisms relation with cardiovascular diseases.[8]

ITGB3 gene is located at chromosome 17, 17q21.32 position, and consists of 15 exons. PlA1/A2 (rs5918) polymorphism is caused by a SNP (thymine to cytosine conversion (T⇒C)) which is located at exon 3 at 196th nucleotide of ITGB3 gene.[9,10] As a result of this conversion, GPIIIa, as high polymorphic protein, have leucine to proline change at 59th amino acid which alters the protein conformation and spatial orientation of the ligand-binding region of the protein.[11] The most common allelic isoforms of GPIIIa are platelet antigen 1 (PlA1) and 2 (PlA2).[12] In 1996, when compared to homozygous for the P1A1 allele, to P1A2 allele of GPIII was reported to be associated with mycocardal infarction. In addition to this, a recent meta-analysis study has shown the significant relationship between increased MI risk and PlA2 polymorphism risk under 45 years old male patients.[13]

Individuals that have PlA2 allele eventually have overly active thrombin in their blood and shown to have increased levels of coagulations after microvascular injury in muscle tissue.[14] Professional or non-professional athletes are susceptible to vascular injuries due to collisions during sports events and results with blood clotting.[15] Also it is known that more than 3 hours of exercising in a week increases risk of venous thromboembolism, which may lead to myocardial infarction.[16,17]

The clinical effect of P1A2 (rs5918) polymorphism has been investigated in several diseases. In this study, we will investigate PlA1/A2 polymorphism (rs5918) on ITGB3 gene which encoding GPIIIa protein, as a risk factor for myocardial infarction cardiovascular disease patients and we compared this data with professional athletes.

MATERIAL AND METHODS

Ethical approval: The study was approved by the Ethics Committee of Istanbul University (Istanbul, Turkey; project no. 2011/2115-897).

Study population: The study population consisted of 88 Turkish subjects. Twenty six subjects under or equal to 45 years old with heart attack history associated with the MI, were positive control group. Positive control group included 26 male patients, who were diagnosed as acute coronary syndrome in the emergency department and were proven to have coronary artery disease with coronary angiography. Patients, ≤ 45 years old, were chosen in order to decrease influence of conventional cardiovascular risk factors. All patients were male with a mean age of 39 (30-45) years.

The 25 negative control individuals were recruited from healthy individuals and the 37 subjects were selected from the elite athlete. Written informed consent was obtained from the each participant.

DNA isolation: DNA samples were used for genotyping of the PlA1/A2 polymorphism in the ITGB3 gene. Peripheral blood from each individual was protected in tubes contained EDTA and DNA was isolated using a DNA Extraction kit (Agilent Technologies. Inc.. Santa Clara, CA, USA). After DNA extraction, DNA samples were stored at -20°C until the application of polymerase chain reaction (PCR).

Design and information of PCR-RFLP method: PCR-restriction fragment length polymorphism (RFLP) method was used to detect the PlA1/A2 polymorphisms. PlA1/A2 polymorphisms of the ITGB3 exon 3 were amplified with PCR application which performed using forward and reverse primers (Table 1). For the specific genetic analysis, a total amount of 100 ng\µl of genomic DNA was amplified in a total volume of 40 µl reaction mix containing 20 µl of master mix (Hibrigen), 1 µl of each primer, 16 µl Nuclease-free water. PCR was performed at 95°C for 5 min, 35 cycles of denaturation at 95°C for 30 sec, annealing at 58°C for 30 sec and extension at 72°C for 30 sec, and a final extension step for 10 min at 72°C. The accuracy of the genotyping was confirmed by agarose gel electrophoresis, on previously amplified DNA products (205 bp lengths) which stained with ethidium bromide and visualized under ultraviolet light (in the Human Diseases and Diagnosis Laboratory, Istanbul University, Istanbul, Turkey). Amplified DNA products were digested with HpaII restriction enzyme (Eurx, Poland) at 37 °C for 2h. Afterward, the resulted fragments were then detected using bioanalyzer (Agilent 1000; Agilent Technologies, Inc.). Three genotypes could be determined after bioanalyzer; genotype P1A1/P1A1, 81 and 127 bp fragments, genotype P1A1/P1A2 (81,127 AND 208 bp fragments) and genotype P1A2/P1A2 (208 bp).

TABLE 1: ITGB3 primer sequences.

Primer	Sequence
ITGB3 forward	5'-ATGCTCCAATGTACGGGGTA-3'
ITGB3 reverse	5'-ACTCACTGGGAACTCGATGG-3'
ITGB3, integrin beta 3.	

Statistical analysis: Standard descriptive statistical methods were applied to summarize the data. Number and frequency of ITGB3 genotypes in the negative controls, positive control and elite athletes are compared and reported.

RESULTS

Bioanalyzer results: Each genotype of ITGB3 gene is characterized by using the bioanalyzer. Figure 1, shows the bioanalyzer results of digestion the product in heterozygous patients (P1A1/P1A2 genotype). P1A1/P1A2 genotype exhibits three peaks at 82, 128 and 206 bp. Figure 2 illustrates the bioanalyzer results for the homozygous healthy individuals (P1A1/P1A1 genotype). P1A1/P1A1 genotype has only one peak 208 bp. The bioanalyzer results for the homozygous patients (P1A2/P1A2 genotype) are shown in Figure 3 and it can be seen that P1A2/P1A2 genotype shows two bands at 81 and 127 bp.

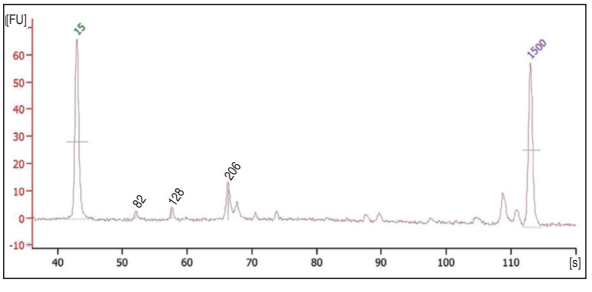

FIGURE 1: Bioanalyzer results of cutting the product in heterozygous patients (P1A1/P1A2 genotype). P1A2/P1A2 genotype shows three bands at 82,128 and 206 bp. [s] indicates base pair size, [FU] indicates fluorescence units.

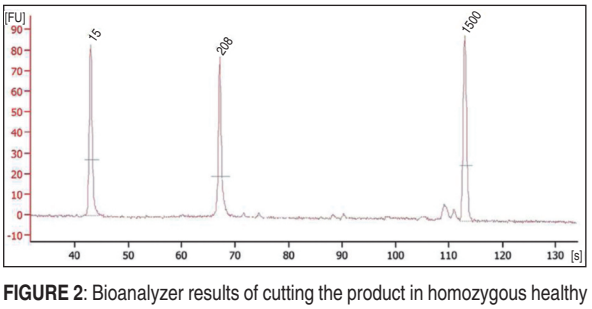

FIGURE 2: Bioanalyzer results of cutting the product in homozygous healthy individuals (P1A1/P1A1 genotype). P1A2/P1A2 genotype shows one bands at 208 bp. [s] indicates base pair size, [FU] indicates fluorescence units.

Genotype frequencies: Comparison of the ITGB3 genotype frequency in all groups (negative control, positive control and elite athletes) is given in Table 2 and Figure 4.

Negative control and positive control

When comparing the negative control and positive control groups, the P1A1/P1A1 genotype is detected at a higher level in the 23 negative control samples (92%). Also, P1A1/P1A2 genotype has relatively higher frequency in the 2 negative control samples (8%). For the P1A2/P1A2 genotype, 2 positive control samples have significantly higher frequency (7.7%) when compared with the negative control.

Negative control and elite athletes

The P1A2/P1A2 genotype is found significantly same for the negative control and elite athletes (0%). As seen in Table 2, P1A1/P1A2 genotype is found significantly higher in 7 elite athletes (19%) than in 2 negative control samples (8%). Additionally, when negative control and elite athletes are compared for the P1A1/P1A1 genotype, it is seen that the frequency is higher in the 23 negative control samples (92% versus 81%, respectively).

Positive control and elite athletes

The P1A1/P1A1 genotype is detected at a higher frequency in the 22 positive control samples (84.6%) than in 30 elite athletes (81%). As seen in Table 3, P1A1/P1A2 genotype is found significantly higher in 7 elite athletes (19%) than in the 2 positive control samples (7.7%). While the P1A2/P1A2 genotype is not detected in elite athletes, the P1A2/P1A2 genotype has 7.7% frequency in 2 positive control samples.

TABLE 2: Number and frequency of ITGB3 genotypes in the negative control, positive control and elite athletes.

Group (n)	Genotype	P1A1/ P1A1	P1A1/ P1A2	P1A2/ P1A2	Total
Negative control	n	23	2	0	25
	Frequency (%)	92%	8%	0%	100%
Positive control	n	22	2	2	26
	Frequency (%)	84.6%	7.7%	7.7%	100%
Elite Athletes	n	30	7	0	37
	Frequency (%)	81%	19%	0%	100%

DISCUSSION AND CONCLUSION

The main focus of this study is the relationship between the PlA2 gene variants and the incidence of major adverse effect of MI. Because, MI is a leading cause of morbidity and mortality worldwide.[18] On the contrary, cardiovascular diseases are leading causes of death in Turkey by 40.3% percent causing 157,965 death at 2015.[19] In addition, the most majority of deaths in athletes over 35 years are caused by coronary artery disease (CAD) or MI.[20]

Recently, this is the first study which aims to compare frequency distribution of P1A1/P1A2 polymorphism in ITGB3 gene among healthy individuals, patients with MI, professional athletes in Turkish population. We found that P1A1/P1A2 genotype has higher frequency in the elite athletes than in the negative control and positive control (Table 2). Also the P1A2/P1A2 genotype in positive control group has higher frequency than in the other groups, any findings in negative control and athletes (Figure 4).

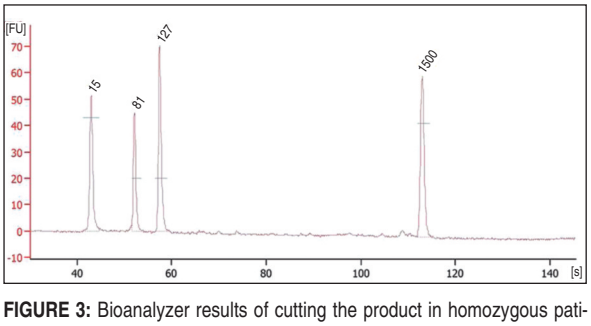

FIGURE 3: Bioanalyzer results of cutting the product in homozygous patients (P1A2/P1A2 genotype). P1A2/P1A2 genotype shows two bands at 81 and 127 bp. [s] indicates base pair size, [FU] indicates fluorescence units.

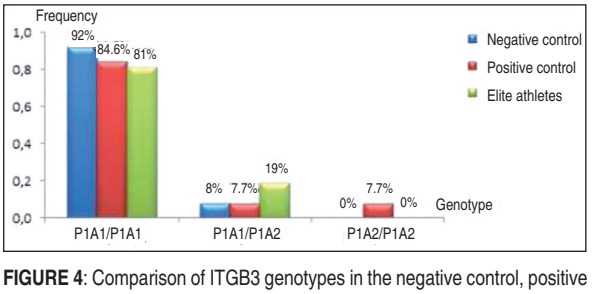

FIGURE 4: Comparison of ITGB3 genotypes in the negative control, positive control and elite athletes.

When comparing the negative control and positive control groups as case-control studies, the P1A2/P1A2 genotype in positive control group has higher frequency (Table 2). Since the study of Weiss et al. is the first study which has reported P1A2 polymorphism as a risk factor for MI, some studies in the literature have been shown inconsistent results.[9,13,21,22] Several studies demonstrated that the P1A2 polymorphism is a strongly associated with MI.[23-25] Rest of studies did not find any results to verify this relationship.[26-28] As seen in Table 2, theP1A2/ P1A2 genotype exists in neither elite athletes nor negative control groups. This result is compatible the findings of Bojesen et al., who reported P1A2/P1A2 genotype was associated with the three fold and four fold risk of MI in young men.[23] The discrepancy of results in literature can be mostly attributed to role of family background of MI and other modifiable risk factors such as diabetes mellitus, smoking and hypertension. Moreover, several factors could contribute to this discrepancy: publication bias toward positive results in small studies, different ethnicity between studies that affects the polymorphisms frequency, differences in study design, and chance factor alone.

P1A1/P1A2 genotype is found significantly higher in elite athletes than in negative control group and positive control group. Compared to the positive or negative group; elite athletes selected randomly, without taking into account whether they have MI in their family or not. Moreover, it would be too difficult to explain inter-individual variations based on genetic inheritance alone because MI is multi factorial disease. However, our results are consistent with the data obtained from the Goldschmidt-Clermont et al. After Olympic gold medalist athlete, Sergei Grinkov's sudden death during training session, Goldschmidt-Clermont et al. proved that he was heterozygous for PlA1/A2 polymorphism and reportedly had severe CAD and died from MI.[29] Therefore, this study implies that having the randomly chosen elite athlete group have higher frequency of PlA2 than negative control group means that they may have greater chance of having CAD resulting with MI.

We cannot totally exclude that our study have limitations such as random sampling, small study size, various population and ethnic groups. We suggest that genetic screening for athletes may be useful for risk assessment and preventing sudden death in athletes. Similar to the Italian government's policy for preventing sudden death in athletes, genetic screening test can be added into health checkups for athletes. Due to low number of samples, our findings need to be extended, we can advise that further studies should be done in experimental groups.

Acknowledgements

This study was supported by the Research Foundation of the University of Istanbul (project no: 53070/2016).

Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Tuba Günel has contributed to ideas, design, consulting, data collection, article writing, critical review, analysis and interpretation. Arzu Antal has contributed to the collection of material, data collection, analysis and interpretation. Tuğçe Şentürk has contributed to ideas, design, source browsing, article writing, material collection, analysis and interpretation. Halil Önder Özbaşak has contributed to ideas, design, source browsing, article writing, material collection, analysis and interpretation. Ece Gümüşoğlu has contributed to design, analysis and interpretation and article writing. Öyküm Esra Aşkın has contributed to the statistical evaluation phase of the study. Mohammad Kazem Hosseini has contributed to material collection and design. Ismail Dölekçap has contributed to the analysis and interpretation. Kılıç Aydınlı has contributed to the consulting, critical review and data collection.

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