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Original Research

Hubungan Polimorfisme Gen ACTN-3 (R577X) dengan Daya Ledak Otot pada Siswa Sekolah Sepakbola di Medan

Association of ACTN-3 Gen Polymorphism (R577X) and Muscle Explosion in Soccer School Students in Medan

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ABSTRAK

Gen ACTN-3 merupakan gen yang mengkode sebuah protein sarkomer yang hampir secara keseluruhan diekspresikan dalam serat otot cepat dan menghasilkan daya ledak otot. Daya ledak (*power*) adalah kemampuan otot untuk mengatasi tahanan beban dengan kekuatan dan kecepatan tinggi dalam suatu gerakan yang utuh. Daya ledak merupakan komponen penting dalam olahraga sepakbola. Variasi genotif (polimorfisme) ACTN-3 (R/X) cenderung memiliki daya tahan yang lebih baik. Tujuan penelitian ini untuk menganalisis hubungan antara varian genotif ACTN-3 (polimorfisme) dan daya ledak otot. Subjek penelitian ini adalah siswa sekolah sepakbola berusia 11-14 tahun yang berjumlah 33 orang. Daya ledak otot diukur menggunakan tes *standing broad jump*. Varian genotif (polimorfisme) gen ACTN-3 diidentifikasi menggunakan PCR-RFLP dari sampel sel bukal. Uji *Fisher Exact* digunakan untuk mengetahui hubungan antara polimorfisme gen ACTN-3 dengan daya ledak otot. Hasil studi menunjukkan varian genotif ACTN-3 yang memiliki alel R cenderung menunjukkan daya ledak otot kategori diatas rata-rata dan tinggi, sementara varian genotif yang memiliki alel X lebih banyak menunjukkan daya ledak otot dalam tingkat rata-rata. Penelitian ini menunjukkan bahwa secara statistik ada hubungan signifikan antara polimorfisme gen ACTN-3 dengan daya ledak otot pada siswa sekolah sepakbola kota Medan ($p<0,001$) dengan kekuatan korelasi kuat ($c=0,623$).

Kata Kunci: ACTN-3, daya ledak otot, polimorfisme, tes *standing broad jump*

ABSTRACT

ACTN-3 gene is a gene that encodes a sarcomere protein that is almost expressed entirely in fast muscle fibers and produces muscle explosive power. Power is an ability of the muscles to overcome load resistance with high strength and speed in a complete motion. Explosive power is an important component in soccer. Genotypic variations (polymorphisms) of ACTN-3 (R/X) tend to have a better endurance. The purpose of this study was to analyze the relationship between ACTN-3 genotype variant (polymorphism) and muscle explosive power. The subjects of this study were students of football schools aged 11-14 years, as many as 33 people. Muscle explosive power was measured using standing broad jump test. The genotype variant (polymorphism) of ACTN-3 gene was identified using PCR-RFLP from a buccal cell sample. Fisher Exact test was used to determine the relationship between ACTN-3 gene polymorphism and muscle explosive power. The results of the study show that genotypic variant of ACTN-3 which has an R allele tends to show muscle explosive power above the average and high categories, while the genotypic variant that had X alleles show more muscle explosive power on an average level. This study shows that statistically there is a significant relationship between ACTN-3 gene polymorphism and muscle explosive power in soccer school students in Medan ($p<0.001$) with strong correlation ($c=0.623$).

Keywords: *ACTN-3, muscle explosive power, polymorphism, standing broad jump test*

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INTRODUCTION

The interest of the Indonesian citizens towards football game is so high, but it is not compensated with the achievements in the international football level. Speed, power, and strength are vital components to achieve good performance during a match (1). Explosive power is the ability of the muscle to overcome load resistance with high strength and speed in a single complete motion (1). Blast bursts are needed because soccer is a high-intensity ball game involving sprints, rapid changes in direction, jumps, and kicks. Professional soccer players carry out changeable activities 1,200 to 1,400 times, accumulating 150-250 short duration attacks in high intensity. Glycogen depletion occurs as a result of high-intensity acceleration, deceleration, and sprints during a match (2). In addition to techniques and tactical skills, soccer players must be able to develop and maintain high aerobic and anaerobic conditions, speed, agility, strength, and explosive power to become professional players (3,4).

The concept that genetic traits are strongly connected to human physical performance has been widely accepted. Genetic inheritance in athletes is estimated to be around 66%. Knowing the genetic profile early and precisely will contribute to develop the athlete's talent, so it can improve the athlete's performance and achievements (5,6). The human map gene identifies more than 200 genetic variations potentially associated with physical performance phenotypes or responsive training (7,8).

One gene that is related to the athlete's elite performance is the α-actinin-3 (ACTN-3) gene, a gene located on the human chromosome 11q13.2 consisting of 21 exons. This gene encodes sarcomere proteins which are almost entirely expressed in fast muscle fibers (fast glycolytic/type II) which play an important role in the speed and contraction of full muscle strength or muscle explosive power generation (7,9). ACTN3's genotype is related to the speed and phenotype of power (10-12).

About 16% of the population in the world experiences polymorphism in the ACTN-3 gene (fully ACTN-3 deficient), and this is caused by homozygous premature stop codon polymorphisms in the ACTN-3 gene (9). The occurrence of nonsense mutation in the ACTN-3 gene, namely substitution of one cytosine base (C) into tymine (T) at position 1747 (C1747) exon 16 (CGA codon becomes TGA) thus forms stop codon (X) in amino acid arginine (R) at the protein chain position 577, which results in the formation of inactive proteins (13). Individuals with the 577XX genotype do not have ACTN-3 on white muscle fibers (fast-twitch fibers). The base version of cytosine (R) produces the ACTN-3 gene that is fully functional to produce a large number of alpha actinin proteins. Several studies have shown that elite sprint athletes significantly have higher R allele frequencies (9-11). The base version of tymine (X) produces a non-functional ACTN-3 protein. ACTN3 protein deficiency does not show a disease phenotype or a muscle functional disorder (7,14,15).

The absence of ACTN-3 in fast muscle fibers is compensated by ACTN2 upregulation and other enzymes that take part in anaerobic metabolism (16). ACTN-3 deficiency shows a metabolic change, that is an increase in the activity of both glycolysis enzymes and aerobic metabolism and also a maximum decrease in the metabolic activity of the anaerobic enzyme (7). Quinlan (14) showed an increase in glycogen, an increase in GS (glycogen synthase), and a decrease in GPh (glycogen phosphorylase) in the mouse model of ACTN-3 deficiency, and this situation will be the same in humans. This is due to the interaction of GPh with ACTN-3. ACTN-2 upregulation that interacts with proteins on the Z line shows structural changes that become the beginning of metabolic changes. Because ACTN-2, ACTN-3, and GPh are attached to the Z line, losing ACTN-3 alters the 3-dimensional conformation of the Z line, which changes the GPh availability for phosphorylation and activation (9,14).

The purpose of this study was to determine the association between the ACTN-3 gene polymorphism towards muscular power in soccer students in Medan.

METHOD

This study used a cross sectional study conducted at Sejati Pratama Soccer School, University of North Sumatra Soccer School, and the Integrated Laboratory Faculty of Medicine University of North Sumatra (FK USU). Ethical approval was obtained from the ethics commission of the Faculty of Medicine, University of North Sumatra number 270/TGL/KEPK FKUSU-RSUP HAM/2017.

Sample

The study sample was 33 students, aged 11-14 years, underwent regular training at least 3 times a week at the Soccer School, did not suffer from lung disease proved by the spirometry results that showed no restrictions or obstruction.

Buccal cells were taken using buccal-brush. DNA isolation from buccal cells was carried out at the Integrated Laboratory Faculty of Medicine University of North Sumatra. Materials used for DNA isolation were Proteinase K (100µg/mL), PrestoTM Buccal Swab gDNA Extraction Kit (Geneaid), 10x Tris-Acetate-EDTA (TAE) Buffer (Vivantis). Nanophotometer was used to measure the concentration and the purity of DNA. The primers from the GenBank Sequence Database-NCBI (accession number NG_013304.2, GeneID: 641451071) used for amplification were the primary forward 5 '-CTG TTG CCT GTG GTA AGT GGG-3' and reverse primer 5'-TGG TCA CAG TAT GCA GGA GGG -3 '. The PCR reaction consisted of primary forward 1.0 µL, reverse primer 1.0µL, GoTaq (R) Green Master Mix (Promega, USA) 12.5µL, DNA samples 2.0µL and Nucleus Free Water volume 8.5µL to 25 µL. The PCR program used was initial denaturation 95°C for 3 minutes, denaturation 95°C for 30 seconds, annealing 53°C for 20 seconds, extension 72°C for 18 seconds, carried out for 35 cycles, and the last was final extension 72°C for 10 minutes. The PCR product obtained was 291bp, then cut by Dde1 retention enzyme with the following composition: NE 10x Buffer as much as 1.0µL, Acetylated BSA 0.1µL, Dde1 restriction enzyme 0,2µL, Nucleus Free Water 3,7µL, and PCR product 5.0µL and then incubated at 65 °C for 30 minutes. The PCR-RFLP results were then electrophoresed using TAE solution and 4% agarose gel under 100 Volt for 50 minutes and visualized using etidium bromide staining.

Examination of muscle explosive power using the Standing Long Jump test or often called the Standing Broad Jump test (17). The jumping distance will be interpreted as

explosive muscle power. Interpretation of the results of Standing Broad Jump was categorized as high category (above 75 percentile), above average category (50-75 percentile), average category (25-50 percentile), low category (5-25), and very low category (below 10 percentile) (17).

The Fisher's statistical analysis test was used to find out whether there was a significant relationship between the ACTN-3 genotype variant and muscle explosive power, and a contingency coefficient correlation test was used to test the correlation between the ACTN-3 genotype variant and the leg muscle explosive power.

RESULTS

The research subjects were male soccer school students aged 11-14 years, underwent soccer practice routinely at least 3 times a week for 6 months guided by a coach, not having a history of lung disease as evidenced by the spirometry results that showed no restrictions and obstruction.

Table 1 shows that the highest percentage of RX genotype variation with the number of X alleles (0.61%) were more than the R allele (0.39%).

Table 1. Distribution of ACTN3 gene polymorphisms, number, and frequency of R and X alleles

Polymorphisms Gen ACTN-3	Total	Percentage (%)
RR	6	18,2
RX	14	42,4
XX	13	39,4
R allele	26	0,39
X allele	40	0,61
Total of Alel R dan X	66	

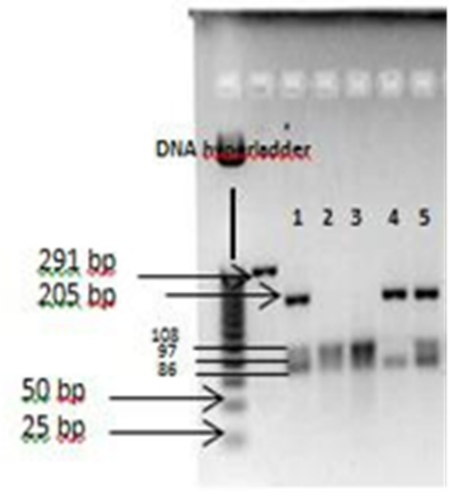

Figure 1 Results of Electrophoresis PCR-RFLP products ACTN-3 gene (Lane 1, 5: RX; Lane 2,3: XX; Lane 4: RR)

Figure 1 shows the PCR-RFLP results obtained by 3 types of ACTN-3 genotype variants namely RR (2 bands) in Lane IV, RX (4 bands) in Lane I, V, and XX (3 bands) in Lane II, III.

Table 2. Analysis of the ACTN-3 bivariate variant genotype (polymorphism) with muscle explosive power

ACTN-3 Genotype	Muscle explosive power		p
	Height n (%)	Average /Above average n (%)	
RR	1(3,03)	5 (15,15)	
RX	6 (18,18)	8 (24,24)	*0,000
XX	2 (6,06)	11 (33,33)	

Note: * Fisher test sig <0.05

The results of the muscle explosive power examination showed the muscle explosive power of soccer school students were 9 students with high explosive power ((27.27%) and 24 students with the average explosive/above an average power (72.73%). In this study there were no students with low explosive power and very low muscle explosive power. Subjects with the RX genotype variant that had high explosive muscle power were 6 students (18.18%) and the average/above average explosive muscle power were 8 students (24.24%). While subjects with XX genotype variants that had high explosive muscle power were 2 students (6.06%), and the average/above average explosive muscle power were 11 students (33.33%). The results of the statistical analysis test used the Fisher's test (p <0.001) showed a significant relationship between the ACTN-3 gene variant and muscle explosive power. The correlation test of the contingency coefficient between the ACTN-3 gene variants with muscle explosive power showed a strong relationship (0.623).

DISCUSSION

In this study, RX genotype had the highest percentage (42.4%) followed by XX genotype (39.39%) and RR (18.2%). Other research on ACTN-3 in Indonesia also obtained the same results as this study. From the research results by Gumilas et al., it was found that the percentage of RX was 57.1%, XX was 24.7%, and RR was 18.2% (n = 68) (18); Ambardini's research (19), RX genotype variant (72.5%), followed by RR (14.9%), and XX (12.6%); Candrawati's research (20) showed the RX genotype variant was 54.9%, XX was 26.8%, and RR was 18.3% (n = 82). In the Polish population, the RX genotype variant showed the highest percentage (43.75%) (6). Ahmetov's study (21) in endurance athletes in Russia also showed 55% of RX genotype and 39.3% of RR genotype (n = 456). Kothari (22) and Fattahi et al. (23) stated that RX genotype was found more than RR and XX in Asian nations. On the contrary, these results differed in Africa (Kenya, Nigeria and South Africa) which found more RR genotypic than RX and XX genotypes (7.24). The frequency distribution of the ACTN3 gene polymorphism is different from each nation (7,23,25). The results of the allele frequency calculation in this study indicate that the number of X allele frequencies (0.61) is higher than the R allele (0.39). XX genotyping frequency differs between ethnic groups, 25% among Asia, 18% among Caucasians, 11% among Ethiopia, 3% among Jamaican and US African-Americans, and Kenyans, and Nigeria whose XX genotype is only 1% (7.25).

In the results of this study, there was no low or very low

category of explosive power among subjects. This is because soccer is intermittent, very intensive, and complex, so the role of basic abilities, especially explosive explosions, strength, kicks, jumps, turns, and runs becomes an important component for possessing the ball (1.3). Being a professional soccer athlete demands to have muscle explosive power above the average because a lot of the activities use explosive power (26). Professional soccer players perform 1,200-1,400 random activities and carry out 150-250 short duration attacks (1-4 seconds) with high intensity (2). Professional soccer players usually have better physical abilities than semi-professionals or amateurs, probably due to higher physical demands in professional soccer matches (27). Healthy living habits of soccer players support high muscle explosive power (3).

Weight training and plyometric are also done to increase explosive power. Plyometric training affects muscle explosive power (28,29). Regular weight training and plyometric might make the subjects in this study did show low and very low muscle explosive power.

The results of this study indicate that there is a significant relationship between the ACTN-3 (polymorphism) genotype variant and muscle explosive power. This study was supported by Gineviciene who showed that there was a significant correlation between ACTN-3 gene polymorphism and explosive power in Lithuana (16). Cieszczyk (30) and Druzhevskaya (10) found a significant correlation between ACTN-3 polymorphism and the status of power athletes in Poland and Russia. On the other hand, Lucia (31) in her study stated that there was no difference in the endurance performance against R577X genotype variant in bicycle athletes. Grenda (32) found that there was no correlation between ACTN-3 polymorphism and sprint swimming activity in swimmers in Poland. Holdys (6) showed that there was no significant correlation between R577X polymorphism in the ACTN-3 gene and the maximum oxygen volume (VO2max), the value of VO2max tends to be higher in individuals with XX and RX genotype (6).

Subjects with RR and RX genotype variants have high explosives and are average/above average. Among subjects who have XX genotype variants, only 2 students have high explosive power. The study on Brazilian soccer athletes by Pimenta stated that athletes with RR genotype had faster sprinting and higher jumping abilities compared to athletes with XX and RX genotypes (33). While, for Olympic sprinters there were no athletes who had XX genotype variants in the ACTN-3 gene. Elite sprint athletes have more RR frequencies and endurance athletes have higher XX frequencies. The presence of the R allele indicates the high performance capacity of muscle strength (high power) contraction both with RR and RX genotype variants and on the other hand X alleles affect better endurance in sports. The ACTN-3 gene with RX genotype variant has an R allele which indicates strong power contraction and has an X allele that has a long durability and a stable supply of ATP which makes oxidative fibers more resistant to fatigue. The success of an athlete's explosive power depends on the proportion of slow-twitch muscle fibers compared to fast-twitch muscle fibers to the muscles trained (in sprinter athletes; fast-twitch is majority). This shows that genotype RR is one of the genetic markers in anaerobic ability (muscle explosive phenotype) while X allele is a genetic marker for aerobic ability (34,35).

This study shows that there were as many as 11 subjects (33.3%) with XX genotype variant that had average/above average muscle explosive power. Research conducted by Gineviciene (16) on Lithuana elite athletes (n = 193) found that XX genotypic variant had higher muscle explosive power than RR genotype variants. This may occur because the absence of ACTN-3 (XX genotypic variation or X allele) in fast muscle fibers is compensated by upregulation of ACTN2 and other enzymes that take part in anaerobic metabolism (16). ACTN-2 is the only sarcomeric α-actinin isoform expressed in muscles in the ACTN-3 deficiency state, increased calcineurin signaling is the result of calcineurin releasing from calsarcin-2 inhibition effect thus activates slow muscle fiber programs and alter the metabolic phenotype of fast muscle fibers (IIB) into slow muscle fibers (7,14). On the other hand, ACTN-3 deficiency or X allele (X genotype) is associated with injury markers after performing eccentric exercises compared to the R allele (36). The Z line becomes less stable during contractions with an increase in ACTN-2 concentration (37).

Examining the combination of more effective genetic polymorphisms such as the combination of the ACTN-3 and ACE genes or several other gene combination candidates can be used to see the potential talent in sports (16). Human physical abilities are very complex and influenced by multifactorial involvement of phenotypes of various genes (involving several genes) and environmental factors (gene interactions with the environment) (8).

Based on the results of statistical analysis (Fisher test) there is a significant correlation between the ACTN-3 genotype variant and muscle explosive power which proves that the R allele indicates strong power contraction or muscle explosive power in both the RR and RX genotype variants. RX genotype is one of key genotypes of being success in football which is a combination of aerobes and anaerobes.

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