

## Research Article

# Assessment of fibrillin-2 and elastin gene polymorphisms in patients with a traumatic Achilles tendon rupture: Is Achilles tendon rupture a genetic disease?

Jan Poszepczyński<sup>1</sup>, Michał Pietrusiński<sup>2</sup>, Maciej Borowiec<sup>2</sup>, Marcin Edward Domżański<sup>1</sup><sup>1</sup>Department of Orthopedics and Traumatology, Military Medical Academy Memorial Teaching Hospital, Lodz, Poland<sup>2</sup>Department of Clinical Genetics, Medical University of Lodz, Lodz, Poland

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## ORCID iDs of the authors:

J.P. 0000-0003-2279-8810;

M.P. 0000-0002-9419-6221;

M.E. 0000-0003-2812-5676;

M.E.D. 0000-0003-1915-0773

## ABSTRACT

**Objective:** The study aimed to investigate the polymorphism of fibrillin-2 (FBN2) and elastin genes in patients with Achilles tendon rupture and to compare the results with a control group of participants who did not experience such an injury.

**Methods:** In this prospective study, 106 consecutive patients in whom traumatic Achilles tendon rupture was diagnosed and treated were included. The control group consisted of randomly selected 92 athletes (10 women and 82 men) 85 of whom had practiced sports in the past, aged 40-76 years, who during their sports career did not experience Achilles tendon ruptures. Material for genetic tests was obtained by the swab from the oral cavity epithelium of all the study population.

**Results:** 102 (96%) of patients with traumatic Achilles tendon ruptures were people with polymorphism B or heterozygotes for the elastin gene. 97 (92%) of patients with traumatic Achilles tendon ruptures were people with polymorphism B and heterozygotes for the FBN2 gene. Patients with homozygote A of the elastin gene and homozygote A of the FBN2 gene demonstrated a considerably lower incidence rate of sport-related Achilles tendon rupture. The type of sport that led to the Achilles tendon rupture and the amount of experience practicing it, as well as BMI and drug usage, did not contribute to a higher rate of incidence of any additional musculoskeletal problems or a longer time to return to their pre-injury sports activity. Polymorphisms of the fibrillin 2 ( $P=.0001$ ) and elastin ( $P=.0009$ ) genes impact the occurrence of traumatic injury to the Achilles tendon. However, it does not affect the length of full recovery time ( $P=.2251$ ).

**Conclusion:** Minimally invasive and, above all, safe collection of genetic material from the epithelium of the oral cavity in order to assess the polymorphic state of the FBN and elastin genes may allow the identification of a group of players at risk of Achilles tendon rupture resulting in long-term injury, which will significantly affect their sports career in the future.

**Level of Evidence:** Level II, Prognostic Study.

## Introduction

Achilles tendon rupture is most frequently preceded by histological and molecular lesions within the injury.<sup>1,2</sup> Elastin and fibrillin proteins are crucial elements of the extracellular matrix because they ensure the correct functioning of the musculoskeletal system.<sup>3</sup> Elastin, an insoluble polymer of the monomeric soluble precursor tropoelastin, is the main component of elastic fibers in the matrix tissue, where it provides elastic recoil and resilience to tendons and ligaments.

Fibrillins represent the predominant core of the microfibrils in elastic and non-elastic extracellular matrices and they interact closely with tropoelastin and integrins.<sup>4</sup> According to the literature, the use of fluoroquinolones<sup>2,5,6</sup> and steroids<sup>7,8</sup> increases the risk of Achilles tendon rupture.

In spite of extensive literature, no clear strategy for treating such injury has been developed,<sup>9,10</sup> nor have other factors—including gender, medicine taken in the past and currently, variants of the fibrillin-2, and elastin genes crucial for the prospective return to sports activity—been identified. The study was designed to assess selected polymorphisms of the fibrillin-2 and

elastin genes in patients with traumatic injury to the Achilles tendon. We also analyzed possible correlations between age and BMI on the occurrence of additional (earlier or later) musculotendinous injuries and the time needed to return to pre-injury activity.

The study's secondary outcomes included assessing the fibrillin-2 and elastin gene polymorphisms in patients treated for Achilles tendon rupture and evaluating their prospective impact on the time to full recovery and the incidence of other musculotendinous injuries in adult patients.

## Materials and Methods

### Participants

The study involved all patients admitted consecutively to our hospitals between January 2015 and December 2019 due to Achilles tendon rupture. All of them were prospectively assessed. The inclusion criteria for the study included an age of 18-70 years at the time of injury (a detailed statistical analysis was conducted for each age group), a traumatic, indirect Achilles tendon rupture, lack of systemic disorders, professional activity, and the willingness to participate in the study. All examined patients were representatives of the Central European Caucasian population, which

## Corresponding author:

Jan Poszepczyński

janek24061982@tlen.pl



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in the past had been tested for polymorphisms of the fibrillin-2 and elastin genes.<sup>11</sup>

None of the study participants had symptoms or signs of Ehlers-Danlos syndrome (OMIM 130000), hypermobility, benign hypermobility joint syndrome, or other monogenic connective tissue disorders when their medical examinations were reviewed by a medical practitioner. The Achilles tendon rupture was diagnosed during a clinical test that revealed a lack of tendon continuity with a palpable gap and loss of strength on the plantar flexion and was confirmed by an ultrasound test.

The control group consisted of 92 randomly selected athletes (10 women and 82 men), aged 40-76 years, who had practiced sports in the past and had not experienced Achilles tendon rupture.

### Genetics

Material for the genetic tests was obtained from a swab taken from the oral cavity epithelium on the day after suturing of the Achilles tendon and before the patient was discharged from the hospital. Material for genetic testing was obtained using a dedicated disposable diagnostic kit; the patients were asked not to eat, drink, chew gum, or smoke at least 1 hour before the swab was taken. All the samples were collected by only 1 person involved in the study. They were then coded in order to comply with General Data Protection Regulation (GDPR) regulations. DNA was isolated from buccal cells using a commercial kit for isolating genomic DNA (Sherlock AX, A&A Biotechnology, Gdynia, Poland) according to the manufacturer's instructions. The resulting nucleic acid was suspended in TE buffer and stored at  $-20^{\circ}\text{C}$  for further analysis. The single nucleotide polymorphisms located at the ELN and FBN genes were evaluated. The A/G (rs2071307) of ELN and the C/G of FBN2 (rs331079) gene polymorphisms were determined using TaqMan® SNP Genotyping Assays (Thermo Fisher Scientific, USA). Reactions were carried out using an AriaMx Real-Time PCR thermocycler (Agilent, USA) in 96-well plates with a volume of 20  $\mu\text{L}$ , according to the manufacturer's instructions.

### Clinical assessment

Patients had regular check-ups in the outpatient clinic (2, 6, and 12 weeks and 6, 12, and 24 months after the surgery) and a final survey was performed during the last check-up (after pre-injury fitness level was regained, allowing them to return to work/sports).

Potential confounders affecting the correlation between the occurrence of the genetic variant along with the episode of the Achilles tendon rupture and the length of full recovery time after operational treatment were identified. They may include previous medications, such as fluoroquinolones or glucocorticosteroids, that may cause injuries to the musculotendinous system and, consequently, may complicate and extend the process of returning to pre-injury fitness.

### HIGHLIGHTS

- Elastin and fibrillin proteins are crucial elements of the extracellular matrix and they are critical in maintaining the functionality of the musculoskeletal system. This study aimed to assess polymorphisms of the fibrillin-2 and elastin genes in patients with traumatic injury to the Achilles tendon.
- The results showed that polymorphisms of the fibrillin-2 and elastin genes were associated with the occurrence of traumatic injury to the Achilles tendon. However, these polymorphisms were not associated with the length of full recovery time.
- The results from this study indicate that fibrillin-2 and elastin gene polymorphisms may have an impact on the occurrence of traumatic injury to the Achilles tendon. More studies are needed to clarify the effect of these and other potentially related genes.

The primary outcomes were the occurrence of homozygote A (rs2071307 A/A), homozygote B (rs2071307 G/G), or heterozygote (rs2071307 A/G) in the elastin gene and homozygote A (rs331079 C/C), homozygote B (rs331079 G/G), or heterozygote (rs331079 C/G) in the fibrillin-2 gene. These polymorphisms (rs2071307 and rs331079) were selected because a probe for testing these polymorphisms was available and based on literature data from similar studies in patients with pathologies concerning damage to the musculoskeletal system.

The secondary outcomes were the time needed to return to pre-injury activity (patients with workers' benefits or a disability pension were excluded from enrollment).

### Statistical analysis

The power calculation for this study was conducted using a recessive model and a disease population prevalence of 10%. To detect an allelic odds ratio (OR) of 2.0 at a power of 80% and a significance level of 5%, the authors assumed a 60% risk allele frequency.

For the purposes of statistical analysis, the numerical data of the patients were divided into groups. Age: <45 years (young), 45-60 (pre-elderly), >60 (elderly); BMI: <25 (correct), 25-30 (overweight), >30 (obese); experience practicing a sport: <10 years, 10-30, >30; time needed to return to pre-injury fitness: 6 months, 12, and 24.

Regarding the unmeasurable characteristics, the nonparametric tests needed no checking of the assumptions. Consequently, all the tests conducted in the study were aimed at identifying possible correlations between selected characteristics. As the characteristics were unmeasurable (qualitative), only the numerical size in specific subgroups was analyzed. To study interactions, the authors applied contingency tables and nonparametric chi-square tests in the analysis of dependencies between unmeasurable characteristics. As the analysis included patients about whom all information was provided, there was no need to estimate, supplement, or delete data. Participants were not observed after full recovery. Sensitivity analysis was not applicable in our study.

Approval from the Bioethics Commission at the Medical University of Lodz was obtained (RNN/115/17/KE) for the study's design and for the acquisition of data from medical records; informed consent was obtained from all participants.

### Results

From a total of 124 patients, 106 patients met the inclusion criteria and were enrolled in the study (patients who did not practice their sport at least twice a week were excluded). We were able to collect samples from all participants. The mean age for the entire cohort was 45 years (range: 23-70; SD: 12.6). The participants consisted of 13 women and 93 men.

The mean BMI in the study group was  $27 \pm 4 \text{ kg/m}^2$  (range: 20-38).

The mean time needed to return to pre-injury activity level was  $9.8 \pm 5$  months (range: 6-24).

Concomitant injuries of the musculotendinous system were observed in the patients with traumatic injuries to the Achilles tendon. They included the anterior cruciate ligament (ACL)—13 patients (12%), rotator cuff—8 patients (7.5%), Achilles tendon of the other limb—3

patients (2.8%), biceps brachii muscle—3 patients (2.8%), quadriceps femoris muscle—2 patients (1.8%), and anterior talofibular ligament—1 patient (0.9%). A number of the patients had been treated with medications that contributed to the musculoskeletal injuries or considerably extended the time needed to return to pre-injury activity: glucocorticosteroids—4 patients (3.8%) and fluoroquinolones—3 patients (2.8%).

The most common activities included running—41 patients (38.5%), soccer—34 patients (32%), volleyball—8 patients (7.5%), basketball—6 patients (5.5%), tennis—6 patients (5.5%), and dance—5 patients (5%). The mean age of the athletes at the time of Achilles tendon injury was  $27 \pm 12$  years (range: 1-49).

The mean postoperative follow-up time was  $24 \pm 6$  months (range: 6-48).

**Genetic tests**

Analysis was performed for the null hypothesis (the rate of incidence is the same in both populations) and 2 cases of the alternative hypothesis: 2-tailed, when the rates of incidence are considerably different, and 1-tailed, when the rate of incidence in one population is larger/smaller than that of in the other population. The rates of incidence for each gene were considerably different in the 2 populations (Table 1).

**Table 1.** Rates of incidence of specific variants of the fibrillin-2 and elastin genes compared to a control group

Gene	N	% of subjects, patient group (n=106)	% of subjects, control group (n=92)	2-Tailed P	1-Tailed P
FBN 2 A (C,C)	9	8.5	3.2	.01	.049
FBN 2 B (G,G)	43	40.6	21.7	.001	.0007
FBN 2 hetero (C,G)	54	51	75.1	.0001	.0001
ELN A (A,A)	4	3.8	17.4	.0009	.0004
ELN B (G,G)	85	80.2	32.6	.0000	.0000
ELN hetero (A,G)	17	16	50	.0000	.0000

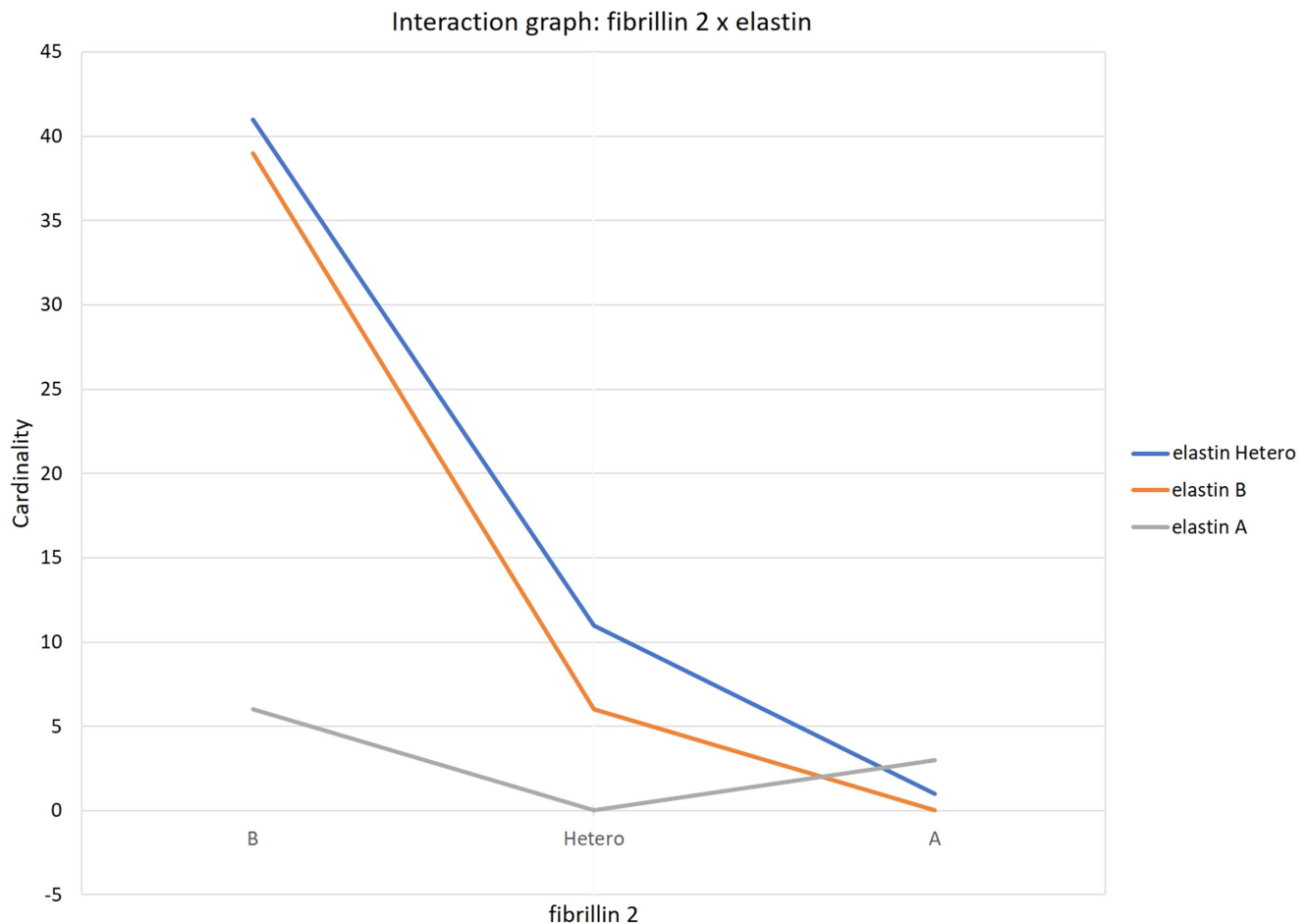
P-value is significant at  $P < .05$ .  
ELN, elastin; FBN, fibrillin-2; N, number of patients.

A statistically significant ( $P=.00003$ ) correlation was observed between the occurrence of gene polymorphisms for fibrillin-2 (Figure 1) and elastin in patients with traumatic Achilles tendon ruptures (Table 2).

**Table 2.** Statistical dependencies between elastin and fibrillin-2 gene variants in patients with Achilles tendon injuries, by age group

Genes/patient's age (years)	<45	45-60	>60
Elastin	0.96	0.33	0.02*
Fibrillin 2	0.12	0.51	0.07

\*Statistical significance ( $P < .05$ ).



**Figure 1.** Correlation between the occurrence of elastin and fibrillin-2 genes in patients with Achilles tendon injury. Y—number of patients with the gene variant; X—classification according to the variant of fibrillin-2. Elastin A—rs2071307 A/A homozygote, Elastin B—rs2071307 G/G homozygote, Elastin hetero—rs2071307 A/G, Fibrillin-2 A—rs331079 C/C homozygote, Fibrillin-2 B—rs331079 G/G homozygote, Fibrillin-2 hetero—rs331079 C/G heterozygote.

**Table 3.** Correlation between occurrence of fibrillin-2 and elastin gene polymorphisms

	Fibrillin heterozygote	Fibrillin B	Fibrillin A
Elastin Hetro	11	41	1
Elastin B	6	38	0
Elastin A	0	6	3

**Table 4.** Correlation between the time needed to return to physical activity, by type of additional injury

	Rotator cuff <i>P</i>	Achilles <i>P</i>	Other <i>P</i>
Elastin	.8087	.2367	.0075
Fibrillin	.4628	.6668	.9754
BMI	.1819	.2411	.4694
Sport	.4337	.0429	.1335

Achilles, injury to Achilles tendon of the other limb; BMI, body mass index; Other, additional musculoskeletal injuries (biceps brachii muscle, quadriceps femoris muscle, anterior talofibular ligament, and anterior cruciate ligament); Sport, type of sport (running, individual, or team sports).

The occurrence of any variant of fibrillin-2 or elastin had no impact on the length of time needed to return to pre-injury physical activity (Table 3).

The type of sport and BMI had no impact on the length of time needed to return to pre-injury physical activity (Table 4).

No statistically significant correlation was observed between the Achilles tendon injury in a specific age group and BMI, pharmacological treatment, sport, or variant of the fibrillin gene.

A statistically significant correlation between the elastin gene variant and Achilles tendon rupture occurred only in the group of patients over 60 years of age. Only in the group of patients under 45 years of age was a statistically significant correlation ( $P=.0156$ ) observed between the length of the return to pre-injury activity and the occurrence of other tendon injuries (Table 5).

Variants of the fibrillin or elastin genes, fluoroquinolone or glucocorticosteroid use, BMI, and age had no impact on the occurrence of concomitant injuries. The type of sport affected the rate of incidence of concomitant injuries in patients with Achilles tendon injuries ( $P=.0399$ ). The odds of Achilles tendon injury were equal in athletes doing individual sports and running, but 1.5 times greater than in those practicing team sports (Table 6).

Regardless of the sport (running, individual, or team), the greatest odds of Achilles tendon rupture with no concomitant injuries were 3, 2, and 3.25 times higher, respectively, than for Achilles injury combined with other injuries.

The analysis of the OR of the injuries in 2 classes revealed that the odds of ACL injury were over 3 times higher in team sports than in

**Table 5.** Correlations between injuries [3 classes of additional injuries: rotator cuff, Achilles tendon of the other limb, and other musculoskeletal injuries (biceps brachii muscle, quadriceps femoris muscle, anterior talofibular ligament, and anterior cruciate ligament)] and selected characteristics (medicine, BMI, sport, length of sporting activity, and length of recovery) by age group

	<45	45-60	>60
Medicine	.9722	.9824	.9583
BMI	.5709	.5613	.8656
Length of sporting activity	.2175	.0461	.5492
Length of recovery	.0156	.6847	.1773
Sport	.1966	.0588	.2589

BMI, body mass index; Length of recovery, time needed to return to pre-injury fitness; Length of sporting activity, length of the sport activity during which damage to the Achilles tendon occurred; Medicine, usage of steroids or fluoroquinolones; Sport, type of sport (running, individual, or team sport).

**Table 6.** Results of tests of independence for classes of specific injuries, by the occurrence of concomitant musculoskeletal injuries

	MSK injury	No MSK injury	<i>P</i>
Medicine	3	9	.8128
Age	29	44	.2602
BMI	27	27	.2962
Length of sporting activity	28	27	.8897
Length of recovery	10	9	.2251
Sport			.0399
Elastin			.3065
Fibrillin 2			.1422

BMI, body mass index; Length of recovery, time needed to return to pre-injury fitness; Medicine, usage of steroids and fluoroquinolones; MSK injury, number of patients with additional musculoskeletal injury; No MSK injury, number of patients with no additional musculoskeletal injury; Sport, type of sport (running, individual, or team sports).

running. Anterior cruciate ligament injuries were not observed in athletes practicing individual sports.

The odds of rotator cuff injuries in runners were nearly 4 times higher than in the athletes playing team sports and nearly 3 times higher than in the athletes practicing individual sports.

The odds of injury of only the Achilles tendon were equal for the athletes doing individual sports and running, while they were 1.5 times higher than in those playing team sports.

## Discussion

Using a safe and minimally invasive method, we found variant B and heterozygotes of fibrillin-2 in more than 92% of the subjects, and variant B and heterozygotes of elastin in more than 96%, which is not reflected in the literature data for the entire Caucasian population.<sup>3</sup> Our study did not take into account other gene polymorphisms (such as TNC and COL27A1) studied in a similar study because they related to Achilles tendon rupture due to chronic tendinopathy.<sup>12</sup>

The analysis was limited to only 2 research centers located in 1 region, which may have significantly diminished the reliability of the study regarding the Polish and global population. The authors chose former players over the age of 40 as a control group and assumed that if an Achilles tendon rupture was to occur, it would be released earlier.

Apart from fibrillin-2 and elastin, our study did not involve the expression of genes tested earlier, such as collagenase, where the outcome depends on the development of chronic symptomatic tendonitis prior to the injury.<sup>13</sup>

All patients were treated surgically, except for 1 J.P. because conservative treatment is common, popular and yields equally good results in Achilles tendon injuries.<sup>14,15</sup> Conservative treatment is preferred especially in centers with well-developed rehabilitation facilities, allowing for early kinesiotherapy.<sup>16,17</sup> All patients in the study were treated with limb immobilization and a prohibition on loading the limb for a period of 6 weeks. This procedure results from an unjustified fear of repeated tendon damage. The literature on the subject does not justify this type of treatment, even with regard to conservative treatment; early loading of the limb after injury reduces stiffness and improves the functional outcome of treatment.<sup>18,19,20</sup> According to the literature, early controlled tension of the sutured Achilles tendon improves its healing and overall functional performance.<sup>9</sup>

The study also did not take into account the type of surgical incision,<sup>21</sup> the selection of which is influenced by the skin vascularity best at the medial surface of the tendon.<sup>22</sup> Since 1977, many surgeons have successfully used various modifications of percutaneous tendon suturing, which were also not taken into account when analyzing the results of our work.<sup>5,23,24</sup>

Unlike in other reports in the literature,<sup>6</sup> we found no statistically significant dependence between Achilles tendon rupture and the use of fluoroquinolone drugs and glucocorticosteroids compared to the control group (which may have been due to the selection of the sample, as only 4 subjects had been treated with glucocorticosteroids and 3 with fluoroquinolones).

The greatest advantage of the study is the minimally invasive and safe method of determining the results, which cannot be said about data obtained from a blood sample.

**Limitations:** For the purpose of generalizing the outcomes, genotyping of fibrillin-2 and elastin genes in a larger group of patients with traumatic Achilles tendon injuries should be performed. Moreover, such analysis should be made in a number of centers located in a larger area. The limitation of this study is that only 2 polymorphisms were taken into account (rs2071307 and rs331079), which resulted from the availability of a probe for testing these polymorphisms and from similar studies in patients with pathology concerning damage to the muscular/tendon system.

Polymorphisms of the fibrillin-2 ( $P=.0001$ ) and elastin ( $P=.0009$ ) genes have an impact on the occurrence of traumatic injury to the Achilles tendon, though it does not affect the length of full recovery time ( $P=.2251$ ), i.e., return to pre-injury fitness and sports activity. Minimally invasively and, above all, safely collecting genetic material from the epithelium of the oral cavity in order to assess the polymorphic state of the fibrillin-2 and elastin genes may help identify the players at risk of Achilles tendon damage resulting in long-term injury, which will significantly affect their future sports career.

**Ethics Committee Approval:** Ethical committee approval was received from the Bioethics Commission at the Medical University of Lodz (Approval no: RNN/115/KE).

**Informed Consent:** Informed consent was obtained from all participants.

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