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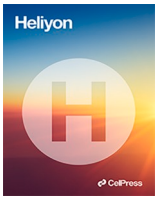

Research article

Identification of specific injury-related SNPs in high-level athletes of Arab origin: A pilot study

Evdokia Varamenti [a,*], Samuel A. Pullinger [b], Pavlos Kollias [c], Vasiliki Chini [d]

[a] Sports Science Department, Aspire Academy, Doha, Qatar
[b] Sport Science Department, Inspire Institute of Sport, Vidyanagar, Dist. Bellary, 583275, India
[c] Section of Statistics and Operational Research, Department of Mathematics, Aristotle University of Thessaloniki, 54124, Thessaloniki, Greece
[d] Diagnostic Genomics Division, Dept of Laboratory Medicine & Pathology, Hamad Hospital, Qatar

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ABSTRACT

Valuable insights for preventing sports injuries in athletes have been achieved through advancements in genetics. This study aimed to determine the allelic frequency of distinct single nucleotide polymorphisms (SNPs) in a group of high-level athletes of Arab origin and to explore whether any significant relationship exists between specific genotypes in the selected SNPs with the prevalence and severity of non-contact soft tissue injuries (NCSTIs) and stress fracture injuries (SFIs). A cohort of 30 Arab male adult athletes trained at the same Sports excellence Centre from various individual sports was recruited and genotyped for collagen type 5 alpha 1 (*COL5A1*) rs12722 and vitamin D receptor (*VDR*) rs10735810 variants. The injury data of participant athletes were collected over two training seasons and categorized according to the site and type (muscle, tendon, ligament, or stress fracture) and severity (mild, moderate, or severe). For the *COL5A1* rs12722, the examined genotypes were not related to the NCSTIs occurrence, while for *VDR* rs10735810, the CT and TT genotypes showed a prevalence for increased stress fracture injuries (RR = 7.72; 95 % CI: 1.66–35.87; $p = 0.011$ and RR = 9.93; 95 % CI: 2.83–34.89; $p < 0.001$, respectively), and increased odds for severe stress fractures (OR = 10.91, 95 % CI: 1.34–126.92, $p = 0.033$). This pilot study indicates a possible association between specific genotypes in the examined polymorphisms and the prevalence and severity of NCSTIs and SFIs. Given the constraints of the small sample size in the current study, additional research is required to gain a comprehensive understanding of this specific population.

1. Introduction

High-level athletes are continuously exposed to numerous training sessions and competitions during the training season, which highly vary in training load and intensity. Various sports-related injuries can occur because of tremendous physical, psychological, and loading demands. Recent studies have shown that sports teams or individual athletes that can avoid injuries demonstrate great success during competitive seasons [1,2,3,4,5]. Furthermore, injuries related to sports can have adverse impacts on an athlete's performance, financial gains, and overall physical and mental well-being, due to prolonged recovery and delayed return to training.

NCSTIs, which are non-contact soft tissue injuries, are commonly seen in football players and account for 20%–30 % of all sports-

* Corresponding author. ASPIRE, Academy for Sports Excellence, PO, Qatar Box: 22287, Doha, Qatar.
E-mail address: evdokia.varamenti@aspire.qa (E. Varamenti).

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related injuries [6,7,5]. NCSTIs occurrence is not related to casualties or external blows in connective tissues such as muscles, tendons, and ligaments. Instead, these injuries can result from a complex partnership between intrinsic and extrinsic factors such as predisposition, somatotype, biomechanical properties, competition level, and turf/ground surface [8,9,10].

Younger athletes often experience stress fractures (SFIs) in the tibia area, which make up approximately 20 % of competitive sports-related injuries [11,12]. A stress fracture is also perceived as an "overuse" injury that occurs because of cumulative bone fatigue and can lead to partial or complete bone rupture from inadequate tolerance to constant and subthreshold applied stress [13]. Athletes in disciplines like endurance sports, gymnastics, and the military are more susceptible to SFIs [14].

Phenomenal progress has been made lately in recent years in the field of genetics and sports-related injury prevention [15]. A comprehensive genetic analysis of an athlete can be used as a highly effective prognostic tool. Sports physicians and physiotherapists can expedite recovery for athletes, both professional and recreational, by incorporating genetics into current examination methods, enabling more efficient injury diagnosis and treatment.

Studies on NCSTI-related genes showed that *Bst*UI variant of the collagen type 5 alpha 1 [*COL5A1* rs12722 C/T (c.*267C > T)] gene could affect the severity of chronic Achilles tendinopathy. Several studies have indicated that athletes and individuals with the CC genotype are less prone to NCSTI [16,17]. In addition, other studies have also shown a strong correlation between *COL5A1* rs12722 polymorphism and anterior cruciate ligament tears in professional soccer players of various ethnicities (Polish and South African) [18,19]. In contrast, the presence of mutant TT genotype of *COL5A1* rs12722 has been linked to improved endurance performance in several long-lasting running events, such as the 42.2-km Ironman triathlons and 56-km ultramarathon running races [20,21,22,23].

There is evidence from current surveys showing a significant association between vitamin D receptor (VDR) polymorphisms and the severity of stress fracture scars. The relationship between various VDR polymorphisms (*Fok*I, *Bsm*I, *Apa*I, and *Taq*I) and SFIs has been widely studied [24,25]. The results of these studies suggest that an association between *Fok*I polymorphism [*VDR* rs10735810 c.2T > C (p.Met1Thr)] and increased risk of SFI among military staff is present. Homozygotes of the rare allele (T) showed a distinct correlation with SFIs compared to that of the common allele homozygotes (C) [25]. There is insufficient research on senior Arab athletes despite the growing interest in genetics and injury. Enhancing understanding can ensure athletes' safety and improve support methods.

Therefore, the study aimed to determine the prevalence of specific single nucleotide polymorphisms (SNPs) in high-level male adult athletes of Arab origin and to explore whether any significant relationship exists between specific genotypes of examined SNPs with prevalence and severity of non-contact soft tissue injuries (NCSTIs) and stress fracture injuries (SFIs).

2. Materials and methods

2.1. Study participants

Thirty high-level Arab male adult athletes from the Middle East were randomly selected. All athletes trained at the same sports centre in Qatar and competed in various international events like the Asian Games and World Cups or Championships. Moreover, the sports that volunteers engaged in included athletics (sprints, endurance, throws), squash, and table tennis. The athletes had a mean age of 19.8 ± 1.5 years, training experience of 7.6 ± 1.5 years, mean height of 173.7 ± 10.6 cm, and body mass of 65.8 ± 8.5 kg.

2.2. Ethics approval

The ethics approval was obtained from the Ethics Committee of the University of Staffordshire, (UK). The study was performed in accordance with the Declaration of Helsinki and subsequent revisions. All participants provided written informed consent to participate in the study and for their data to be published. Moreover, they were notified of voluntary participation before sample collection and of the benefits and possible risks pertaining to their participation. Confidentiality of participants' personal information was upheld during data analysis.

2.3. Saliva sample collection and DNA extraction

Saliva samples were collected from athletes under resting conditions using the Oragene-DNA OG 600 kit (DNA Genotek, Inc., Ottawa, Ontario, Canada) on the first day of their scheduled monitoring. The athletes were not allowed to eat, drink, or chew gum for 30 min before sample collection. DNA was extracted from 30 saliva samples using the prepIT•L2P kit (catalogue # PT-L2P, DNA

Table 1
Information about selected SNPs.

Gene	Encoded protein	Protein function	Alleles and rs number	Location	MAF	SNP type
COL5A1	Pro-a1(V) chain	Major component of type V collagen	C/T rs12722	chr9:134,842,570	C:0.426	Transition substitution, intragenic, 3′-UTR section
VDR	Vitamin D receptor	Protein with greater or lesser affinity to transcription factor II B (TFIIB)	C/T rs10735810	chr12:47,879,112	T:0.347	Missense mutation, transition, substitution, intragenic

*MAF = Minor allelic frequency for Qatari population.

Genotek, Inc.) following the manufacturer's instructions. The extracted DNA was purified using ethanol precipitation. The extracted DNA was assessed for yield and purity, and stored at −20 °C in Tris-EDTA buffer until further analysis.

2.4. Selected gene polymorphisms

The allelic frequencies of the following two SNPs of *COL5A1* and *VDR* genes were determined to examine their correlation with the occurrence of NCSTIs and SFIs. Information about the selected polymorphisms can be seen in "Table 1".

1. *COL5A1* rs12722 (*BstUI*) (c.*267C > T)

Forward primer, F: 5′-GCAGTCAGCAGCGTGGGTCTGGTTATCT-3′ and reverse primer, R: 5′-TTTGGGGTGGCACTTGCAG-CACTGGTCG-3′. VIC and FAM targeted T and C alleles, respectively.

2. *VDR* rs10735810 (*Fok*I) (c.2T > C (p.Met1Thr))

Forward primer, F: 5′-AGCTGGCCCTGGCACTGACTCTGGCTCT-3′ and reverse primer, R: 5′-ATGGAAA-CACCTTGCTTCTTCTCCCTC-3′. VIC and FAM targeted T and C alleles, respectively.

2.5. SNP genotyping

The sample DNA concentration was determined using NanoDrop US/UV 2000/2000c spectrophotometer (Thermo Fisher Scientific, USA). The SNPs were genotyped in 96-well plates using real-time PCR allelic discrimination TaqMan assays on a 7500/7500 Real-Time PCR System (Applied Biosystems, Thermo Fisher Scientific), according to the manufacturer's instructions.

2.6. Polymerase chain reaction - PCR

PCR was performed in a 25-μl reaction volume containing 50 ng DNA and all four dNTPs according to the manufacturer's instructions (Applied Biosystems user manual to TaqMan® Genotyping Master Mix, PN 4371131). The revised protocol requires for purified genomic DNA concentration between 1 and 20 ng in a total volume of 11.25 μl. The following thermal cycling conditions were applied: enzyme activation (95 °C for 10 min, 1 cycle), denaturation (95 °C for 15 s, 40 cycles), and annealing/extension (60 °C for 1 min, 40 cycles).

2.7. Data on sports injuries

Data on participant athletes' injuries were collected during two training seasons (2017–2019). The NCSTIs were categorized as muscle strains and tendon-ligament injuries, with the most frequent being hamstring and quadricep strains, as well as rotator cuff and patellar tendinopathies. For the SFIs, the medial tibial stress syndrome was considered. The classification suggested by Pruna et al. [4, 5] was utilized in this study. Consequently, injuries were classified into three grades depending on how long athletes were absent from training: Grade 1, mild (1–15 days).

2.8. Statistical analysis

Statistical data of the primary demographic variables of the study population (mean ± standard deviation) were determined. The allelic frequencies of both SNPs were assessed for compliance with Hardy-Weinberg equilibrium (HWE) using the proposed equation, $q\hat{}2 + 2qp + p\hat{}2 = 1$, where q and p, are the minor and major allele frequencies. Three Poisson regression models with robust standard errors were used to calculate the effect of both SNPs on the prevalence of muscle strain, tendon - ligament and stress fracture injuries. The SNP genotype levels (CC, CT, and TT) were coded with dummy variables, and the common allele homozygotes CC was specified to be the reference level. For each Poisson regression model, the estimated exponentiated coefficients are reported as risk ratios (RR) along with their 95 % confidence intervals. The ordinal regression model was used to determine the influence of the variant alleles on the severity of the injury (mild, moderate or severe) and odds ratios (OR) along with their 95 % confidence intervals are reported. Statistical significance was set at $p \leq 0.05$. All statistical analyses were performed using R version 4.2.2.

3. Results

3.1. Assessment of SNP compliance with HWE

According to the dbSNP/NCBI database, the minor allele frequencies (MAFs) for rs12722 in the Qatari population were C = 0.426 and T = 0.574 (Global HapMap C = 0.709 and T = 0.291), which implies a higher progeny (57 % vs 29 %) of the Qatari population to inherit T allele. The MAF for *VDR* rs10735810 are T = 0.347 and C = 0.653 (Global HapMap T = 0.370 and C = 0.630). In this current examination, the χ^2 and p values for *COL5A1* rs12722 and *VDR* rs10735810 were 1.4748 and $p = 0.224$ and 10.429 and $p = 0.01$, respectively, denoting a consistent with Hardy-Weinberg equilibrium only for the *COL5A1* rs12722.

3.2. Injury related data

All data relating to the sports injuries of participants retrieved from the sports centre medical database are displayed in Table 2. Six out of 30 participants were injury free. A total of 71 injuries were recorded over two years which were classified according to the site/type (muscle strains, tendons, ligaments, and stress fractures) and severity (mild, moderate, and severe). Most recorded injuries were hamstring and quadricep strains, rotator cuff and patellar tendinopathies, and medial tibial stress syndrome.

Table 3 shows the estimated risk ratio (RR) for muscle, tendon-ligament and stress fracture injuries according to the Poisson regression model. The TT genotype of *COL5A1* rs12722 was associated with a decreased number of muscle strains (RR = 0.16; 95 % CI: 0.04–0.67; $p = 0.028$) and tendon-ligament injuries (RR = 0.27; 95 % CI: 0.08–0.91; $p = 0.046$) compared to the homozygotes CC. Regarding *VDR* rs10735810, the CT and TT genotypes were associated with increased stress fracture injuries (RR = 7.72; 95 % CI: 1.66–35.87; $p = 0.011$ and RR = 9.93; 95 % CI: 2.83–34.89; $p < 0.001$, respectively).

3.3. Association between specific genotypes in the two examined SNPs and injury's severity

Furthermore, in order to determine the association between specific genotypes in the two examined SNPs and injury's severity, three ordinal regression models were specified with muscle strains, tendon-ligaments and stress fractures severity (mild, moderate, severe) as the ordinal outcome and both SNPs as the predictor variables (Table 4). The results indicated that the TT genotype of *VDR* rs10735810 was associated with increased odds for a severe stress fracture compared to a moderate or mild injury (OR = 10.91, 95 % CI: 1.34–126.92, $p = 0.033$), while for the *COL5A1 rs*12722, the TT genotype had a negative effect on tendon injury severity (OR = 0.06, 95 % CI: 0.01–0.81, $p = 0.039$), indicating that TT genotype of this polymorphism was associated with less severe injuries.

4. Discussion

The current study aimed to determine the prevalence of specific SNPs in a cohort of high-level Arab male adult from Middle East based and trained in Qatar. Athletes' sports-related injuries were collected over two training seasons, and the relationship between specific genotypes in examined SNPs and the prevalence/severity of reported injuries was studied. Describing this study as a "pilot" suggests that its preliminary results can be a stepping stone for more significant investigations in the future concerning this population.

For the *COL5A1* rs12722 SNP, the CT and TT genotypes were identified among participants (n = 18 and n = 8 athletes, respectively). Based on previously registered data in dbSNP/NCBI, this cohort of the Arab population (Qatari) exhibits increased T allele expression. Although previous studies have discussed the higher risk of sports-related injuries in athletes with the non-favourable T allele in COL5A1 rs12722, this particular population has not been examined in any research to date.

The COL5A1 gene mutation can result in a 50 % decrease in type V collagen production, leading to stiffness and poor connectivity [18]. While studies have explored different ethnic groups like Caucasians, Hispanics, black Africans, and Asians, Arabs have not been thoroughly investigated [16,18,17].

Most of the athletes employed in the current study overexpressed the favourable CC genotype of the *VDR* rs10735810 variant, pursued by the CT genotype (n = 19 and n = 5, respectively). Corresponding to the dbSNP/NCBI database, The Qatari population often

Table 2
Reported injuries per site/type and injury severity in athletes carrying rs12722 and rs10735810 genotypes.

Muscle Strain injuries	Genotype	Mild	Moderate	Severe	Total
COL5A1, rs12722	CC	2	-	4	6 (27.3 %)
	CT	11	2	1	14 (63.6 %)
	TT	2	–	–	2 (9.1 %)
VDR, rs10735810	CC	12	2	1	15 (68.2 %)
	CT	2	–	–	2 (9.1 %)
	TT	1	–	4	5 (22.7 %)
	Total	**15**	**2**	**5**	**22**
Tendon - Ligament injuries	**Genotype**	**Mild**	**Moderate**	**Severe**	**Total**
COL5A1, rs12722	CC	4	–	2	6 (18.7 %)
	CT	18	2	3	23 (71.9 %)
	TT	3	–	–	3 (9.4 %)
VDR, rs10735810	CC	13	2	4	19 (59.4 %)
	CT	4	–	1	5 (15.6 %)
	TT	8	–	–	8 (25 %)
	Total	**25**	**2**	**5**	**32**
Stress fracture injuries	**Genotype**	**Mild**	**Moderate**	**Severe**	**Total**
COL5A1, rs12722	CC	2	–	–	2 (11.8 %)
	CT	4	1	4	9 (52.9 %)
	TT	6	–	–	6 (35.3 %)
VDR, rs10735810	CC	2	1	–	3 (17.7 %)
	CT	3	–	2	5 (29.4 %)
	TT	7	–	2	9 (52.9 %)
	Total	**12**	**1**	**4**	**17**

Estimated risk ratio (RR) for muscle, tendon-ligament, and stress fracture injuries occurrence.

Table 3
Poisson regression risk ratio (RR) and 95 % CI of the relationship between *COL5A1* rs12722 and *VDR* rs10735810 genotypes and type of injury.

	Muscle strains	Tendon - Ligaments	Stress fractures
COL5A1, rs12722			
CC - Reference	–	–	–
CT	0.59 (0.24, 1.50)	1.04 (0.43, 2.48)	1.42 (0.26, 7.74)
TT	0.16 (0.04, 0.67)	0.27 (0.08, 0.91)	2.54 (0.63, 10.21)
***VDR*, rs10735810**			
CC - Reference	–	–	–
CT	0.43 (0.07, 2.75)	0.76 (0.34, 1.70)	**7.72 (1.66, 35.87)**
TT	0.90 (0.30, 2.72)	1.37 (0.68, 2.74)	**9.93 (2.83, 34.89)**

Table 4
Ordinal regression odds ratio (OR) and 95 % CI of the relationship between *COL5A1* rs12722 and *VDR* rs10735810 genotypes and injury severity.

	Muscle strains	Tendon - Ligaments	Stress fractures
COL5A1, rs12722			
CC - Reference	–	–	–
CT	0.35 (0.03, 3.17)	0.29 (0.03, 2.87)	1.23 (0.10, 23.54)
TT	0.09 (0.01, 1.07)	0.06 (0.01, 0.81)	0.54 (0.03, 8.59)
***VDR*, rs10735810**			
CC - Reference	–	–	–
CT	0.17 (0.01, 1.58)	1.35 (0.23, 7.90)	**6.42 (0.73, 66.93)**
TT	0.50 (0.05, 3.62)	0.73 (0.13, 3.80)	**10.91 (1.34, 126.92)**

exhibits the C allele in the 2 exon, resulting in the production of a shorter protein that binds more strongly to nuclear factor II. Enhanced transcription of vitamin D-dependent genes is also a result of this protein's shortened form [26]. A paper investigating the association between the VDR rs10735810 variant and bone fractures in an Arab military staff was discovered after an extensive literature search [27]. Moreover, various studies have highlighted a common occurrence of low vitamin D levels in the Qatari population [28,29]. Thus, more genetic research is required to explore any relationship between low vitamin D levels and specific sports-related injuries.

Previous research on *COL5A1* rs12722 C/T (c.*267C > T) has demonstrated that TT genotype can negatively affect soft tissue injuries, particularly in tendons and ligaments, in distinct ethnic cohorts of athletes of South African, Australian, Caucasian, Polish, and British origin [28,29,19,17]. Controversial results were found in the present investigation, indicating that Arab athletes with the TT genotype of rs12722 had a lower occurrence of tendon-ligament injuries or stains. In addition, the TT genotype was found to have a negative impact on the severity of tendon injuries according to ordinal regression analysis. The latest study findings provide additional evidence to support an earlier examination suggesting that muscle injury severity is not solely determined by COL5A1 polymorphism, but also by IGF2 and CCL2 [4]. Likewise, the injuries suffered by the participants are probably connected to different variants of genes related to collagen synthesis. Controversial results emerged from the present investigation as Arab athletes with the TT genotype of rs12722 displayed fewer stains or tendon-ligament injuries. Furthermore, based on ordinal regression analysis, the TT genotype had a negative effect on tendon injury severity, indicating that TT was associated with less severe injuries. Current study outcomes further support an earlier examination, which suggested that the degree of muscle injuries is related to other than *COL5A1* polymorphism (i.e., Insulin Like Growth Factor 2 (*IGF2*) and C-C Motif Chemokine Ligand 2 (*CCL2*) [4]. Likewise, the referred injuries of prevailing participants are likely related to different variants relevant to collagen synthesis genes; consequently, more research is needed.

There is a scarcity in the literature of studies examining specific polymorphisms related to collagen synthesis or vitamin D genes in athletes of Arab descent. Few studies worldwide have underlined a close link between the mutant T allele and SFIs in military personnel. For example, Chatzipappas et al. [24] showed that the mutant T allele is more prevalent in male military groups than controls ($p = 0.013$). In another significant survey about stress fractures, where several related SNPs were analysed, homozygotes of the rare allele (T) of *VDR* rs10735810 illustrated a considerable relationship to stress fractures in elite athletes [25]. The current study further supports that the CT and TT genotypes of *VDR* rs10735810 were associated with increased stress fracture injuries in the examined athletes, while the mutant TT genotype of *VDR* rs10735810 was associated with increased odds for a severe stress fracture compared to a moderate or mild injury.

Nevertheless, additional analysis is needed to assess the outcomes due to the limited sample size and variations in the sports of the participating athletes. Still, the sample was composed of high-level athletes of Arab origin, a group that has not been thoroughly studied or understood. Moreover, team sports like football or rugby typically dominate the sample of published studies. The current research focused on athletes from individual sports like athletics and racket sports, where there is a scarcity of data. When taking into account a longer career in elite sport, the participants' mean age of 19.8 years can also be considered young. Despite being high-level national team representatives, the athletes had short professional careers and limited exposure to the injuries studied in this research. Until now, there have been no sports-related genetic studies that have incorporated Arab athletes, and only two investigations have included Asian populations [30,31].

The findings of this pilot study suggest a potential link between certain genotypes in the tested SNP variants and the occurrence and

severity of NCSTIs and SFIs. Additional research is needed to confirm these findings for this specific population before sports professionals can utilize them as a preventive measure for sports-related injuries and make changes to exercise programs.

5. Conclusions

There is no evidence of a connection between the examined genotypes of *COL5A1* and the incidence of injuries, NCSTIs and SFIs, while for VDR rs10735810, the CT and TT genotypes showed a prevalence for increased stress fracture injuries. Furthermore, when assessing injury severity, results indicated that TT genotype of *VDR* rs10735810 was associated with increased odds of severe stress fractures. The study's limitations include a small sample size, limited training experience among the athletes, and the specific nature of their sports. Despite that, this study establishes the groundwork for upcoming research on the sports community in this Middle Eastern area. Therefore, further research with larger cohorts and more SNPs is necessary for this particular sport population.

Ethics statement

Ethics approval was granted by the Ethics Committee at the University of Staffordshire, UK (SU_19_50). The study was conducted in compliance with all regulations. Written informed consent was obtained from all participants in the study.

Data availability

All data are available throughout paper.

CRediT authorship contribution statement

Evdokia Varamenti: Writing – original draft, Visualization, Validation, Project administration, Methodology, Conceptualization. **Samuel A. Pullinger:** Writing – review & editing, Writing – original draft, Validation, Methodology, Investigation. **Pavlos Kollias:** Visualization, Validation, Software, Methodology, Formal analysis, Data curation. **Vasiliki Chini:** Writing – original draft, Validation, Supervision, Methodology, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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