Association of COA1 with Patellar Tendonitis: A Genome-wide Association Analysis

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ABSTRACT

KIM, S. K., C. NGUYEN, B. H. HORTON, A. L. AVINS, and G. D. ABRAMS. Association of COA1 with Patellar Tendonitis: A Genome-wide Association Analysis. *Med. Sci. Sports Exerc.*, Vol. 53, No. 11, pp. 2419–2424, 2021. **Purpose:** It is unknown why some athletes develop patellar tendinopathy and others do not, even when accounting for similar workloads between individuals. Genetic differences between these two populations may be a contributing factor. The purpose of this work was to screen the entire genome for genetic markers associated with patellar tendinopathy. **Methods:** Genome-wide association (GWA) analyses were performed utilizing data from the Kaiser Permanente Research Board (KPRB) and the UK Biobank. Patellar tendinopathy cases were identified based on electronic health records from KPRB and UK Biobank. GWA analyses from both cohorts were tested for patellar tendinopathy using a logistic regression model adjusting for sex, height, weight, age, and race/ethnicity using allele counts for single nucleotide polymorphisms. The data from the two GWA studies (KPRB and UK Biobank) were combined in a meta-analysis. **Results:** There were a total of 1670 cases of patellar tendinopathy and 293,866 controls within the two cohorts. Two single nucleotide polymorphisms located in the intron of the cytochrome *c* oxidase assembly factor 1 (*COA1*) gene showed a genome-wide significant association in the meta-analysis. **Conclusions:** Genetic markers in *COA1* seem to be associated with patellar tendinopathy and are potential risk factors for patellar tendinopathy that deserve further validation regarding molecular mechanisms. **Key Words:** PATELLAR TENDINOPATHY, PATELLAR TENDON, GENE, GENETIC TESTING, COA1, CYTOCHROME C OXIDASE ASSEMBLY FACTOR 1

Patellar tendinopathy, also known as jumper's knee, is a common condition that presents with anterior knee pain localized to the patellar tendon, typically its origin just inferior to the patella (1). The disorder is considered an overuse injury and is most common in athletes participating in sports that involve jumping (such as basketball and volleyball) but can be seen in other sports (such as running) (2–5). The development of patellar tendinopathy is most commonly initiated by mechanical overload of the tendon, leading to fibril disruption and an inflammatory-mediated aberrant healing response (6,7). This leads to an increase in deposition of biomechanically inferior type III collagen at the expense of native type I collagen—the hallmark of chronic tendinopathy (8,9). Subsequent immune cell influx and increased vascularity within the tendon and tendon sheath likely contribute to the sensation of pain experienced by individuals with this condition (6,10). Even with proper treatment, symptoms can be prolonged and some athletes do not experience complete resolution of symptoms (11).

The reasons why some athletes develop patellar tendinopathy while others do not, even taking into account similar workloads and overuse activities, are unknown. An attractive hypothesis is that genetic differences partly account for individual differences in the susceptibility to patellar tendinopathy. A small body of work has investigated the genetics of patellar tendinopathy, finding a potential association with single nucleotide polymorphisms (SNP) in BMP4 (12) and FCRL3 (13), as well as epigenetic (methylation) status promoters for MMP-11, TIMP2, and ADAMTS4 (14,15). As is typical of candidate gene studies, these studies were extremely small in their sample size, which can lead to risk of false-negative results.

The purpose of this study was to perform a screen of the entire genome for polymorphisms associated with patellar tendinopathy using data from two large cohorts containing hundreds of thousands of participants. The advantages of a genome-wide association (GWA) screen are that it reports the strongest signals from across the entire genome, and the criteria for statistical significance are well developed, which aids in reproducibility in validation studies. The main disadvantage of GWA studies—that large cohorts are required to achieve statistical significance ($P < 5 \times 10^{-8}$) to account for the large number of tested polymorphisms (multiple hypothesis correction)—can be overcome with large sample size. In this study, we used individual genotype data and diagnosis-related

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TABLE 1. Phenotype definitions.

Code	Description	Cases
KPRB		
ICD-9		
726.64	Patellar tendinopathy	1340
727.66	Nontraumatic rupture of patellar tendon	87
ICD-10		
M76.51	Patellar tendinopathy, right knee	80
M76.52	Patellar tendinopathy, left knee	71
	Total unique cases	1201
	Total unique controls	82,213
UK Biobank		
Read V2		
N2164	Patellar tendinopathy	139
Read v3		
N2164	Patellar tendinopathy	454
	Total Unique Cases	469
	Total unique controls	211,653

ICD-9, International Classification of Disease, Ninth Revision; *ICD-10, International Classification of Disease, Tenth Revision*)

codes from the Kaiser Permanente Research Board (KPRB) and the UK Biobank to search for genetic associations of patellar tendinopathy. We also utilized our existing data set to attempt to validate candidate gene associated with patellar tendinopathy previously reported in the literature.

METHODS

Genome-wide association analyses (GWAS) for patellar tendinopathy were performed using data from the KPRB (with which the Kaiser Permanente, Northern California Research Program in Genes, Environment and Health is affiliated) and from the v3 release of UK Biobank. This study analyzed stored data from KPRB and UK Biobank participants who consented to genomic testing and use of their genomic data, as well as health data from the KPNC and UK Biobank electronic health records. The health and genotype data for the participants were deidentified. All study procedures were approved by the institutional review board of the Kaiser Foundation Research Institute.

KPRB cohort. KPRB is an integrated health care delivery organization, which has an active membership of 3.5 million people (16). Comparisons with the general population have shown that the membership is a representative of the population of Northern California, with the exception of extremes of the socioeconomic spectrum. In 1995, KPRB instituted a comprehensive electronic health system, which records physician diagnoses, prescriptions, and laboratory results from all Kaiser inpatient and outpatient encounters. KPRB has high membership retention, with over 90% of those older than 65 yr and 66% of all active members as of June 2012, having five or more years of retrospective membership.

Our analysis cohort includes 83,414 individuals of European ancestry who were genotyped at 670,572 SNPs using Affymetrix Axiom genome-wide arrays. Genotypes were prephased with Shape-IT v2.r644 (accessed February 2, 2016) and then imputed to a cosmopolitan reference panel consisting of all individuals from the 1000 Genomes Project (March 2012 release) using IMPUTE2 v2.2.2 (accessed February 2, 2016) and standard procedures with a cutoff of $R^2 > 0.3$. The final number of SNPs following imputation was 12,510,553. The quality of the imputed data was previously validated (16).

UK Biobank cohort. The UK Biobank consists of approximately 500,000 participants with a wide variety of phenotypic and genotypic information (17). Ethics approval for the UK Biobank study was obtained from the North West Centre for Research Ethics Committee (11/NW/0382) (17). Genotype data were obtained from the v3 release of UK Biobank (17). The UK Biobank electronic health care records were available for 212,122 individuals of European ancestry and included data until June 2019. Genotype data were imputed centrally by UK Biobank with IMPUTE2 using the Haplotype Reference Consortium and the UK10k + 1000GP3 reference panels (18). Metrics for quality control were established and then used to filter DNA variants by UK Biobank (17). Imputed SNPs were excluded if they had an IMPUTE2 info score <0.4.

Database quality control. For both the KPRB and UK Biobank cohorts, individuals were excluded if they were outliers based on genotyping missingness rate or heterogeneity, whose sex inferred from the genotypes did not match their self-reported sex, who withdrew from participation or who were not of European ancestry. The purpose of restricting individuals to those with European ancestry is to reduce population stratification in the study; for example, if the risk of patellar tendinopathy among individuals with African ancestry is higher than that for European individuals, then any SNP with an allele frequency that is different between African and European ancestries would seem to be associated with patellar tendinopathy. Overall, these filters resulted in excluding 18.9% and 3.1% of individuals (mostly due to the ancestry filter) in the KPRB and UK Biobank cohorts, respectively. Genetic variants that failed quality control procedures in any of the genotyping batches were excluded, which showed a

TABLE 2. Study demographics.

	Case	Control	*P*
KPRB			
Female, *n* (%)	691 (1.4)	47,529	
Height, mean (SD), inches	64.9 (2.7)	64.5 (2.7)	0.003
Weight, mean (SD), lb	162.7 (38.2)	157.8 (36.1)	0.0004
BMI, mean (SD), kg·m^{-2}	27.1 (6.2)	26.5 (5.9)	0.008
Obese, n (%)	181 (27.1)	10,082 (22.1)	
Male, *n* (%)	510 (1.4)	34,684	NS[a]
Height, mean (SD), inches	70.6 (2.8)	70.3 (2.8)	0.02
Weight, mean (SD), lb	196.5 (36.6)	191.3 (34.3)	0.0007
BMI, mean (SD), kg·m^{-2}	27.7 (4.6)	27.1 (4.5)	0.01
Obese, *n* (%)	125 (24.9)	6982 (20.7)	
UK Biobank			
Female, *n* (%)	174 (0.15)	115,854	
Height, mean SD), inches	64.0 (2.42)	63.9 (2.46)	NS
Weight, mean (SD), lb	158.3 (30.2)	157.8 (30.8)	NS
BMI, mean (SD), kg·m^{-2}	27.0 (6.2)	26.9 (5.9)	NS
Obese, *n* (%)	51 (29.3)	26,680 (23.0)	
Male, *n* ((%)	296 (0.31)	96,175	<0.0001[a]
Height, mean SD), inches	68.3 (3.7)	67.6 (3.8)	0.002
Weight, mean (SD), lb	179.3 (34.9)	178.4 (34.3)	NS
BMI, mean (SD), kg·m^{-2}	27.9 (4.6)	27.3 (4.5)	0.02
Obese, *n* (%)	83 (28)	23,082 (24)	
Age of injury, mean (SD), yr	51.0 (11.1)	56.7 (8.0)	<0.0001

[a]Compared with females.
NS, not significant.

TABLE 3. Distribution for age of diagnosis for UK Biobank cases.

Age of Diagnosis, yr	Total	Male	Female
<21	4	1	3
21–30	11	9	2
31–40	66	50	16
41–50	142	91	51
51–60	148	82	66
61–70	88	56	88
>70	11	7	4

Mean (SD) age of diagnosis, 60.0 (11.1) yr; range, 13–76 yr.

TABLE 5. Genotype counts for patellar tendinitis.

KPRB					
rs149047058	A1	A2	A1/A1	A1/A2	A2/A2
Control	G	A	99788	740	3
Case	G	A	1464	21	0
Expected HW for 1485 cases			1473	12	0
rs142128304	A1	A2	A1/A1	A1/A2	A2/A2
Control	G	A	99721	879	5
Case	G	A	1464	24	0
Expected HW for 1488 cases			1474	14	0
UK Biobank					
rs149047058	A1	A2	A1/A1	A1/A2	A2/A2
Control	G	A	207497	3195	18
Case	G	A	442	25	0
Expected HW for 467 cases			463	5	0
rs142128304	A1	A2	A1/A1	A1/A2	A2/A2
Control	G	A	207436	3338	21
Case	G	A	442	26	0
Expected HW for 468 cases			463	5	0

departure from Hardy–Weinberg of $P < 10^{-50}$ or had a minor allele frequency <0.004.

Phenotype definitions. In the KPRB cohort, patellar tendinopathy cases were identified based on clinical diagnoses captured in the Kaiser Permanente Northern California electronic health record system from 1995 to July 22, 2015. *International Classification of Disease, Ninth Revision* or *International Classification of Disease, Tenth Revision* codes were used to identify cases of patellar tendinopathy. In the UK Biobank cohort, patellar tendinopathy cases were identified from primary care data (Read v2 or Read v3). Within the UK health care setting, individuals seeking advice or treatment for a health concern normally first meet with a family physician (known as a general practitioner) or a nurse (e.g., a nurse practitioner) at their local general practice. General practitioners can refer patients who require more specialized treatment (or further tests) to hospital or other community-based services. Read codes are a coded thesaurus of clinical terms used in primary care since 1985. There are two versions: version 2 (Read v2) and version 3 (CTV3 or Read v3). Both provide a standard vocabulary for clinicians to record patient findings and procedures.

Genome-wide association. GWA studies were conducted using PLINK v2.0a2. SNP associations with patellar tendinopathy were tested with a logistic regression model using allele counts for typed and imputed SNPs. The model was adjusted for genetic sex, height, weight, and race/ethnicity using 10 principal components. For the UK Biobank, the age of diagnosis was included as an adjustment as well. Covariates were ascertained centrally by either KPRB or UK Biobank. Determination of genetic ancestry was performed by principal component analysis computed centrally by either KPRB or UK Biobank, as previously described (17).

The final number of SNPs that were analyzed was 12,510,553 in the KPRB cohort and 17,136,336 in the UK Biobank cohort. To account for inflation due to population stratification, the genomic control parameter (λgc) was calculated (λgc = 0.991 for KPRB; λgc = 0.931 for UK Biobank). Subsequently, *P* values were adjusted for the genomic control in each population.

Results using odds ratios (OR) per allele from each cohort were combined by inverse-variance, fixed-effects meta-analysis using PLINK v2.0a2. Here, meta-analysis refers to a statistical method to combine data from GWAS performed on two independent cohorts. A total of 9,263,932 SNPs were present in both GWAS and used in the meta-analysis. A value of $P < 5 \times 10^{-8}$ was used as a threshold for genome-wide significance.

The results from the meta-analysis were used to test for replication of candidate genes previously reported to show an association with patellar tendinopathy. Power calculations were conducted using the Genetic Association Study Power Calculator (accessed September 11, 2020) (19). The assumptions in the power calculation were as follows: 1670 cases, 14% prevalence, 0.05 minor allele frequency, and a genotype relative risk of 1.25. These assumptions were made based on the number of cases and the prevalence for patellar tendinitis in the two cohorts, and the lower limits of minor allele frequency and genotype relative risk for success in GWAS studies.

Further bioinformatics investigations of the top genome-wide significant loci from the GWAS were conducted. QQ and Manhattan plots were created using the R package qqman.

TABLE 4. Summary statistics.

A. Meta-analysis							**Meta-analysis**	
Chr	**BP**	**SNP**	**Gene**	**EA**	**AF UKB**	**AF KPRB**	**OR (95% CI)**	***P***
7	43681639	rs149047058	*COA1*	A	0.0044	0.0088	2.75 (2.03–3.67)	2.00E–11
7	43708823	rs142128304	*COA1*	A	0.0053	0.0091	2.64 (1.98–3.50)	2.10E–11
B. KPRB and UKB GWAS					**UK Biobank GWAS**		**KPRB GWAS**	
		SNP	**Gene**	**EA**	**OR (95% CI)**	***P***	**OR (95% CI)**	***P***
		rs149047058	*COA1*	A	3.37 (2.25–5.04)	7.67E–10	2.16 (1.39–3.35)	5.40E–04
		rs142128304	*COA1*	A	3.35 (2.25–4.98)	5.25E–10	2.05 (1.36–3.09)	5.70E–04
C. Correlation (*R*) between rs149047058 and rs142128304								
R = 0.97								

AF KPRB, allele frequency in KPRB; AF UKB, allele frequency in UK Biobank; BP, base pair, GRCh37; EA, effect allele; 95% CI, confidence interval.

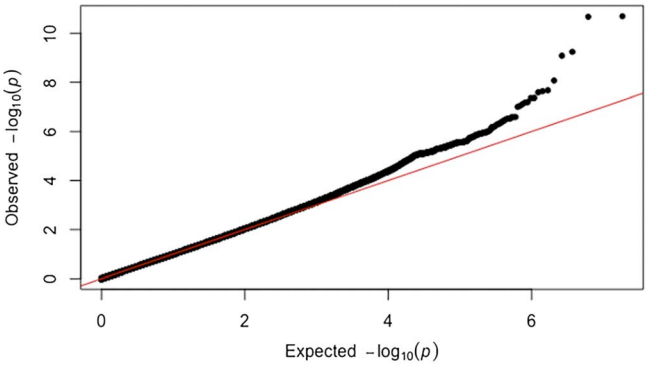

FIGURE 1—Quantile–quantile plot for patellar tendonitis. The expected versus observed log-transformed values for 9,263,932 *P* values from the meta-analysis of the KPRB and UK Biobank GWAS are graphed. The *y*-axis shows the observed *P* values, and the *x*-axis shows the *P* values expected by chance. The black dots represent the SNPs arranged by their observed *P* values, and the red line shows the expected trajectory if the SNPs had *P* values expected by chance.

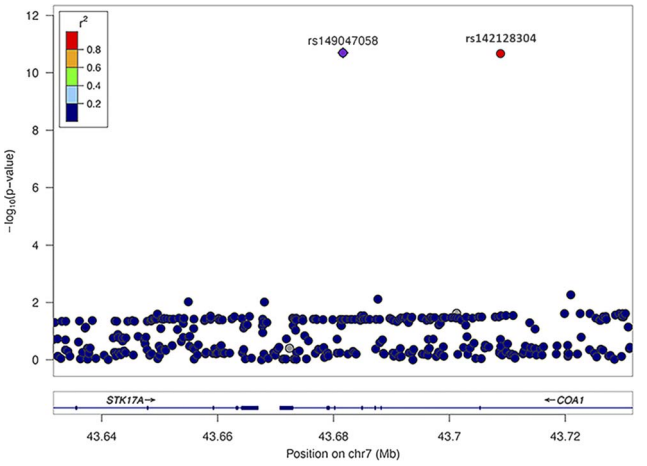

FIGURE 3—Regional-association plots COA1. Tested SNPs are arranged by genomic position around the lead SNP (purple diamond). The *y*-axis indicates $-\log_{10}$ *P* values for association with patellar tendinopathy for each SNP. The color of dots of the flanking SNPs indicates their linkage disequilibrium (R^2) with the lead SNP as indicated by the heat-map color key. The two SNPs are located within an intron of the *COA1* gene.

Regional association plots were generated for each locus with LocusZoom (accessed November 21, 2020) (20). The genomic context of each SNP was investigated using RegulomeDB (accessed November 21, 2020) (21) web tools. ChIP seq data from the ENCODE project were used to determine whether SNPs were located within transcription factor binding sites (22). Summary statistics for all SNPs from the GWAS and the meta-analysis will be available at the NHGRI-EBI Catalog of human GWA studies (https://www.ebi.ac.uk/gwas/) upon acceptance of this manuscript.

RESULTS

Identification of DNA variants associated with patellar tendinopathy. For KPRB, there were 1201 cases of patellar tendinopathy and 82,213 controls (Table 1). For UK Biobank, there were 469 cases and 211,653 controls (Table 1). The demographics for sex, height, weight, and age of diagnosis for the two cohorts are shown in Table 2. In KPRB, individuals who were taller and heavier had a slightly higher risk of patellar tendinopathy. In UK Biobank, increased risk was only observed for male height. Males were at higher risk compared with females in UK Biobank but not KPRB. In addition, the overall incidence of patellar tendinopathy was higher in KPRB than the UK Biobank. It is not clear what causes either the difference in sex or overall incidence between the KPRB and UK Biobank cohorts. One possibility is that this reflects a real difference in the underlying population between the Bay Area and the United Kingdom. Another possibility is that the difference reflects variability in how patellar diagnosis is coded between the health care systems in the Bay Area and the United Kingdom. As expected, the average age of controls was older than the age of individuals diagnosed with the injury. Table 3 shows the distribution of the age of diagnosis from the UK Biobank cohort.

GWA analyses for patellar tendinopathy were performed with the KPRB (83,414 individuals) and UK Biobank (212,122 individuals) cohorts using sex, weight, height, and age of diagnosis as adjustments (Table 4). Data from the two GWAS were combined in a meta-analysis (Table 5).

The observed *P* values were compared with the distribution of *P* values expected by chance in a Q-Q plot (Fig. 1). The black dots deviate from the red line for the lowest observed *P* values in the upper right-hand corner, indicating that the observed association signals are significantly stronger than the signals that would be expected by chance.

The *P* values from every SNP in the meta-analysis are shown in a Manhattan plot (Fig. 2). There were two SNPs (rs149047058 and rs142128304) with genome-wide significant associations with patellar tendinopathy (Fig. 3; Table 4). The genotype counts for cases and controls from each cohort are shown in Table 5. The two SNPs are located with ~27 kb of each on chromosome 7, and their genotypes are 97% correlated.

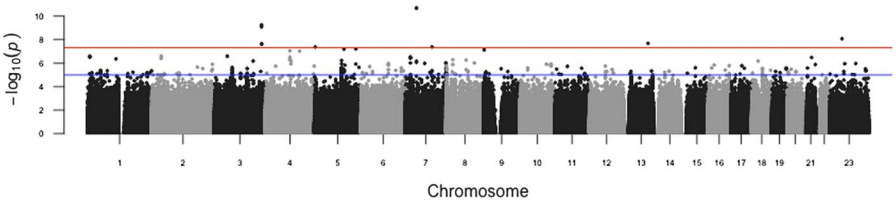

FIGURE 2—Manhattan plot for genome-wide association analysis of patellar tendinopathy. The −log10 *P* values for association with patellar tendinopathy for SNPs from the meta-analysis are plotted by genomic position with chromosome number listed across the bottom. Each dot represents 1 of the 9,263,932 SNPs from the meta-analysis. The red and blue lines indicate the thresholds for genome-wide significance ($P \times 10^{-8}$) and suggestive association ($P < 10^{-5}$).

TABLE 6. Patellar tendinitis validation.

SNP	Gene	OR (95% CI)	*P*	Ref
rs2761884	*BMP4*	1.05 (0.83–1.27)	0.20	(12)
rs7528684	*FCRL3*	1.01 (0.81–1.21)	0.70	(13)

95% CI, 95% confidence interval.

Attempted validation of previous candidate gene studies. Previous studies tested candidate genes for association with tendinopathy in patellar, Achilles, shoulder, and hip abductors tendons in volleyball players (12,13). In these prior investigations, significant associations of rs2761884 in BMP4 (OR, 2.39; $P = 0.03$) and rs7528684 in FCRL3 (OR, 1.44; $P = 0.04$) were reported. When these variants were tested in the meta-analysis with 1670 cases, no significant association was observed with patellar tendinopathy (Table 6). Power calculations indicate a 90% chance of obtaining a significant result assuming a genotype relative risk of 1.25.

DISCUSSION

This study provides new information about a possible genetic association with patellar tendinopathy risk. Two SNPs were associated with patellar tendinopathy in a meta-analysis from two GWAS performed in this study. The two SNPs are highly correlated and thus represent a single-linkage disequilibium group associated with patellar tendinopathy.

Individuals harboring risk alleles for these two SNPs have an increased risk for patellar tendinopathy. Although the risk alleles from the GWA studies are relatively rare (0.5%–0.9% allele frequency), they confer an increased risk of about 2.5-fold. Genetic testing could provide key information to uninjured individuals about their risk for patellar tendinopathy, allowing them to take extra precautions to avoid injury. The genetic information could also be used by medical professionals to make more informed decisions regarding patellar tendinopathy diagnosis, management, and return to play.

Both SNPs are located in the intron of the cytochrome *c* oxidase assembly factor 1 (*COA1*) gene. Cytochrome *c* oxidase assembly factor 1 is a housekeeping enzyme that functions to generate ATP within the mitochondria of all cells. As expected, the *COA1* gene is broadly expressed across all cell lines and tissues from data downloaded from the GTEX portal (Fig. 4).

Neither of the SNPs affect protein coding or are known to be associated with changes in expression of *COA1* or any other nearby gene. On the one hand, the two SNPs might target COA1, which is involved in generating energy from mitochondria via respiratory oxidation. The biological mechanism of how this mitochondrial protein might play a role in patellar tendonitis is unclear. On the other hand, it is possible that the two SNPs might target a nearby gene, rather than *COA1*. DNA polymorphisms often affect expression of genes located at a distance. Although current data from the GTEX consortium do not show an effect on expression on nearby genes, such an effect might have been missed because the relevant tissue or physiological condition has not yet been tested.

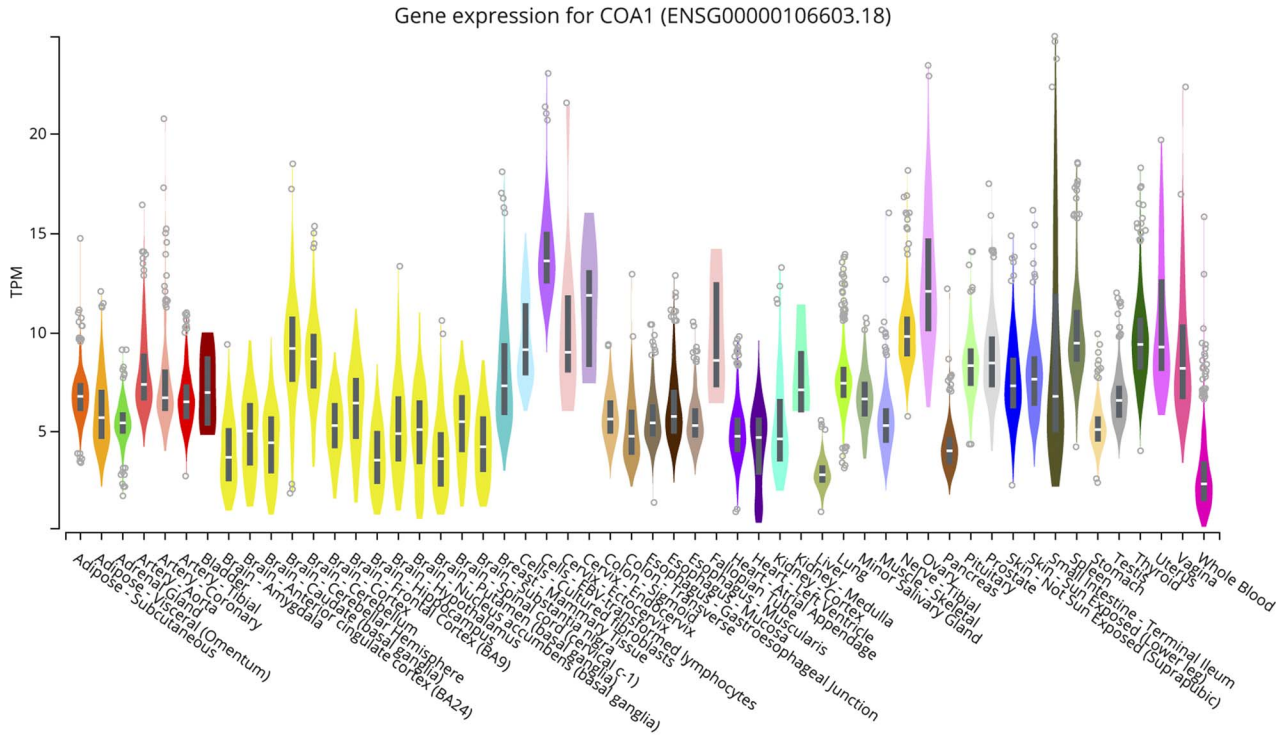

FIGURE 4—Expression of COA1. Shown are violin plots showing expression levels of *COA1* in cell lines and tissues. White bars indicate mean expression level, and black lines indicate quartile levels. *Y*-axis shows the transcripts per million reads (TPM) for *COA1* expression. The violin plot indicates the probability density of the data at different values, smoothed by a kernel density estimator. The dots indicate expression level in outlier samples. Data are downloaded from the GTEX portal.

In addition, two candidate genes were previously reported to be associated with tendinopathy, but these associations were not replicated in our meta-analysis data for patellar tendinopathy (12,13). The previous studies, both from the same group, considered tendinopathy from the patella, Achilles, shoulder, and hip abductors tendons in volleyball athletes, whereas this study evaluated patellar tendinopathy in the general civilian population. It is possible that genetic risk factors differ for tendinopathy of tendons from different anatomic locations, and the prior group's findings represent signal from anatomic locations other than the patella tendon. Furthermore, the articles by Salles et al. (12,13) included higher-level athletes from Brazil, a demographic that was not included in the current investigation.

Limitations. Our analysis found only one independent genome-wide significant signal, possibly because patellar tendinopathy may be poorly documented in these cohorts. This type of misclassification error would mostly tend to dilute the strength of any signals, if present. Alternatively, it could be that the heritability of patellar tendinopathy is low. Another limitation is that the phenotypes were defined from codes contained in electronic health records from the United States and the United Kingdom, and thus, we have no information regarding the clinical scenarios surrounding the event or if there are systematic differences in how patellar tendinitis is assigned codes between the two countries. In addition, the cohort included people regardless of whether or not they participated in a sport.

Lastly, this study only evaluated individuals from the European ancestry group, and the effect of either rs149047058 or rs142128304 on patellar tendinitis risk in other ethnicities is unknown. Furthermore, the frequency of the risk allele for rs149047058 or rs142128304 in the Asian or African ancestry groups is lower than in the European ancestry group.

Future studies. It will be important to replicate these results in independent cohorts, especially for athletes. Additional studies are warranted to illuminate the underlying biological mechanism for COA1 with patellar tendinopathy. These future studies may provide further evidence for using these genetic polymorphisms as diagnostic markers to help predict which athletes harbor a higher risk for incidence of patellar tendinopathy. Follow-up experiments could look at whether the genetic markers affect other aspects of patellar tendinopathy, such as bone/tendon anatomy, length of recovery time or response to different types of treatment.

This study is not funded. The results of the study are presented clearly, honestly, and without fabrication, falsification, or inappropriate data manipulation. The results of the present study do not constitute endorsement by the American College of Sports Medicine.

S. K. K. is President and Founder of AxGen Incorporated, a genetic testing company.

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