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A Genetic Marker Associated with De Quervain's Tenosynovitis

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ABSTRACT

De Quervain's tenosynovitis is a repetitive strain injury involving synovial inflammation of the tendons of the first extensor compartment of the wrist. It is relatively common in the general population, and is the most common radial-sided tendinopathy seen in athletes. Identifying a genetic marker associated with de Quervain's tenosynovitis could provide a useful tool to help identify those individuals with an increased risk for injury. A genome-wide association screen was performed using publically available data from the Research Program in Genes, Environment and Health (RPGEH) including 4,129 cases and 98,374 controls. rs35360670 on chromosome 8 showed an association with de Quervain's tenosynovitis at genome-wide significance ($p = 1.9 \times 10^{-8}$; OR = 1.46; 95 % CI = 1.38–1.59). This study is the first genome-wide screen for de Quervain's tenosynovitis and provides insights regarding its genetic etiology as well as a DNA marker with the potential to inform athletes and other high-risk individuals about their relative risk for injury.

Introduction

De Quervain's tenosynovitis is a common cause of radial-sided wrist pain and swelling in both the general and athletic population. Repetitive motion of the wrist leads to repeated gliding of the tendons within the first extensor compartment of the wrist (abductor pollicis longus and extensor pollicis brevis) through a fibro-osseous tunnel at the level of the radial styloid. Frictional mictrotrauma from repeated gliding may lead to tendon sheath inflammation and chronic thickening. Clinical symptoms are local tenderness, swelling and pain stemming from activities such as grasping, thumb abduction and ulnar deviation [17].

De Quervain's tenosynovitis is more common in women than men, in African Americans compared to Caucasians and those 30 to 50 years of age compared to older and younger age groups [36]. Within the general population, repetitive housework, industrial labor and child-rearing activities can trigger de Quervain's tenosynovitis [17]. Several anatomic variations such as increased compartment septation and presence of multiple tendon slips may have an effect on the underlying pathophysiology and predisposition for de Quervain's tenosynovitis [1, 2, 22, 23, 25, 32].

Hand and wrist injuries are common in the athletic population and are the site of 3–9 % of all sports injuries [28]. De Quervain's tenosynovitis is the most common radial-sided tendinopathy in athletes [5]. This injury occurs frequently in athletes participating in racquet sports, rowing, golf, volleyball and bowling [30, 31, 34, 37]. In racquet sports (e. g., tennis) and golf, de Quervain's tenosynovitis has been attributed to grasp and swing technique [34, 37]. In rowing, development of this condition has been attrib-

uted to tight grip and poor rowing technique [31]. In volleyball, the repetitive microtrauma from impact of the ball on the dorsal radial wrist region increases the risk of de Quervain's tenosynovitis [30, 34, 36, 37].

Little is known about genetic differences that might affect the inherent tendency for an individual to develop de Quervain's tenosynovitis. In this paper, we address this question by performing a genome-wide association analysis for de Quervain's tenosynovitis. Using a cohort containing 4,129 cases, we identified one marker showing an association with genome-wide significance.

Methods

A genome-wide association screen (GWAS) was performed for de Quervain's tenosynovitis using data from the genotyped Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort of the Research Program in Genes, Environment and Health (RPGEH). The data generation and data analysis pipeline have been previously described [29]. A complete description of the cohort and study design can be found in dbGaP (Study Accession: phs000674.v1.p1).

Our analysis cohort (n = 102,503) includes 59,479 females, 42,958 males, and 66 individuals of uncertain sex (▶ **Table 1**). Sex was determined previously based on heterozygosity of the X chromosome (dbGaP Study Accession: phs000674.v1.p1). Moreover, our analysis cohort is ethnically diverse, including 83,264 European-White (EUR); 8,560 Latino (LAT); 7,518 East Asian (EAS); and 3,161 African American (AFR) individuals based on ancestry principal components.

Participants were genotyped at over 650,000 SNPs on four race/ethnicity-specific Affymetrix Axiom genome-wide arrays optimized for individuals of EUR, LAT, EAS and AFR race/ethnicity [13]. Genotype quality control procedures for the GERA cohort were performed on an array-wise basis, as described previously [21]. The final number of SNPs that were directly genotyped was 670,572 for EUR; 802,186 for LAT; 708,373 for EAS arrays; and 878,176 for AFR arrays.

Genotypes were pre-phased with Shape-IT v2.r644 (https://mathgen.stats.ox.ac.uk/genetics_software/shapeit/shapeit.html; accessed Feb. 2, 2016) then imputed to a cosmopolitan reference panel consisting of all individuals from the 1000 Genomes Project (Mar 2012 release) using IMPUTE2 v2.2.2 (https://mathgen.stats.ox.ac.uk/impute/impute_v2.html; accessed Feb. 2, 2016) and standard procedures with a cutoff of $R^2 > 0.3$ [14–16]. The R^2 metric from IMPUTE2 estimates the correlation between the true and imputed genotype. SNPs were imputed if the R^2 metric was greater than 0.3 [24]. The final number of SNPs that were imputed was 9,207,988 for EUR, 10,380,912 for LAT, 8,355,578 for EAS, and 16,659,640 for AFR arrays. The quality of the imputed data was previously validated in Jorgenson et al., 2015 [19].

Determination of genetic ancestry was performed by principal component analysis (PCA), as previously described [3]. These ancestry principal components were used in the GWAS to adjust for genetic ancestry.

Phenotype Definition

De Quervain's tenosynovitis cases were identified in the GERA cohort based on clinical diagnoses and surgical procedures captured in the Kaiser Permanente Northern California (KPNC) electronic health record system. The electronic health record includes reported injuries over the entire lifetime of the patients, including those that occurred prior to enrollment in KPNC as well as those that occurred after the genotyping analysis was performed if reported by the patient and recorded by the physician. De Quervain's tenosynovitis cases were identified by International Classification of Disease, Ninth Revision (ICD-9 727.04), de Quervain syndrome/radial styloid tenosynovitis (3,981 cases); International Classification of Disease, Tenth Revision (ICD-10 M65.4), radial styloid tenosynovitis [de Quervain] (237 cases); and Common Procedural Terminology, Fourth Edition (CPT-4 25000), incision, extensor tendon sheath, wrist (e. g., de Quervain's disease) (154 cases).

Genome-wide association and meta-analysis

Genome-wide association analyses of the GERA cohort genomic data were conducted using PLINK v1.90 (b3.34) (https://www.cog-genomics.org/plink2, accessed Feb. 1, 2016) [10, 27]. SNP associations with de Quervain's tenosynovitis were tested with a logistic

▶ **Table 1** Demographic factors of the GERA study population used in genome-wide association analyses of de Quervain's tenosynovitis.

	Cases[a]	Controls	Overall
Subjects (%)	4,129 (4.0%)	98,374 (96.0%)	102,503
Sex (%)[b]			
Female	3,284 (5.2%)	56,195 (94.8%)	59,479
Male	845 (2.0%)	42,113 (98.0%)	42,958
Undetermined	0 (0%)	66 (100%)	66
Ancestry Group (%)[c]			
European	3,190 (3.8%)	80,074 (96.2%)	83,264
Latin American	418 (4.9%)	8,142 (95.1%)	8,560
East Asian	341 (4.5%)	7,177 (95.5%)	7,518
African American	180 (5.9)	2,981 (94.1)	3,161
Age[d]	61.3 (±12.5)	62.8 (±13.7)	62.8 (±13.7)

[a] Cases with de Quervain's tenosynovitis as defined by individuals with one or more qualifying ICD-9, ICD-10 or CPT-4 codes in their EHR. For details, see Methods; [b] Sex/gender as determined by an individual's genetic data, reported as the number and percentage of total; [c] Race/ethnic groups as determined by PCA on an individual's genetic data from the GERA cohort. Reported as the number and percentage of total for each respective group; [d] Age at subject enrollment in the GERA cohort, reported as mean age with standard deviation

regression model using allele counts for typed and imputed SNPs in an additive genetic model for each of the race/ethnic populations. The model was adjusted for genetic sex, age at enrollment into the RPGEH cohort, race/ethnicity using principal components, and variations in genotyping protocol. The variations in genotyping protocol include: chip type for all populations (refers to the Affymetrix chip version), genotyping package (refers to the set of chips that were processed together) and reagent kit (refers to A vs O reagent kit distributed by Affymetrix) when there was variation in the individuals of a specific population. We used 10 principal components for European (EUR), 6 for Latin American (LAT), 6 for East Asian (EAS) and 6 for African American (AFR). The final numbers of SNPs that were analyzed was 8,795,348 for EUR; 9,153,118 for LAT; 8,055,053 for EAS; and 14,989,676 for AFR populations. To account for inflation due to population stratification, the genomic control parameter (λgc) was calculated: EUR (1.007), LAT (1.014), EAS (1.013), AFR (1.027). λgc is defined as the median of the resulting chi-squared test statistics divided by the expected median of the chi-squared distribution [9]. Subsequently, p-values were adjusted for genomic control in each population. Results from each population were combined by inverse-variance, fixed-effects meta-analysis as previously described [29]. SNPs that did not contain data for EUR were removed because EUR comprises more than 80 % of the cohort. The final number of SNPs that was analyzed in the fixed-effects meta-analysis was 8,156,340. Power calculations were made using the software at http://csg.sph.umich.edu/abecasis/cats/gas_power_calculator/index.html; accessed Dec. 20, 2016 [33].

We examined the level of heterogeneity using two measures: 1) the I^2 statistic, which measures the percentage of variability across ancestry groups that is due to heterogeneity, where a lower value indicates more consistent results across races, and 2) Cochran's Q statistic, which measures whether observed differences in results between different ancestry groups are due to chance alone, where a low associated p-value indicates heterogeneity [6, 12]. The 95 % confidence interval for I^2 was calculated using the heterogi module for STATA.

Further bioinformatics investigation of the top genome-wide significant loci from the meta-analysis was conducted. QQ and Manhattan plots were created using qqman [35]. Regional association plots were generated for each locus with LocusZoom (http://locuszoom.sph.umich.edu/locuszoom/, accessed Dec. 18, 2016) [26]. The genomic context of each SNP was investigated using RegulomeDB (http://regulomedb.org/, accessed Dec. 18, 2016) [4] web tools. Whether each SNP is an expression quantitative trait locus (eQTL) was queried using the NCBI eQTL browser (http://www.ncbi.nlm.nih.gov/projects/gap/eqtl/index.cgi, accessed Dec. 18, 2016) and the Genotype-Tissue Expression (GTEx) portal (http://www.gtexportal.org/home/, accessed Dec. 18, 2016). ChIP-seq data from the ENCODE project was used to determine whether SNPs were located within transcription factor binding sites [7].

Ethical considerations

This study analyzed stored data from RPGEH subjects who consented to genomic testing and use of their genomic data as well as health data from the KPNC electronic health record for future research studies. The health and genotype data for the subjects were de-identified. All study procedures were approved by the Institutional Review Board of the Kaiser Foundation Research Institute. This paper conforms to the ethical standards established by this journal [11].

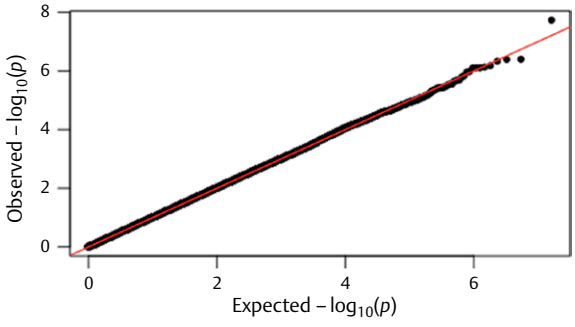
Results

Study population and genotype information

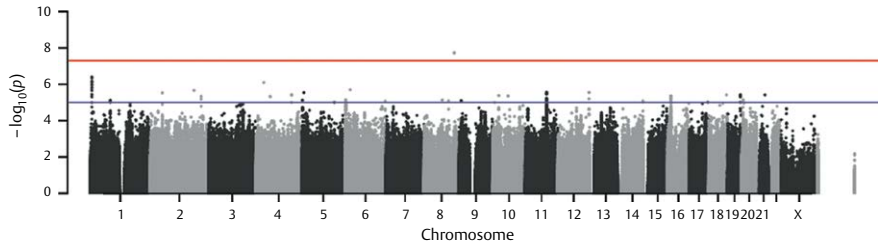
Patients with de Quervain's tenosynovitis were identified by ICD-9, ICD-10 and CPT codes referring to de Quervain's syndrome, radial styloid tenosynovitis and de Quervain's disease (see Methods). There were 4,129 cases and 98,374 controls in the GERA cohort, resulting in a period prevalence of 4.0 % (▶ **Table 1**). Participation in sports was not included in the electronic health record, and hence we were not able to determine the incidence rate for the subset of the population who were athletes. Men showed a lower incidence of de Quervain's tenosynovitis than women that was statistically significant ($p = 2.2 \times 10^{-16}$; OR = 0.34; 95 % CI = 0.32–0.37), consistent with previous results [36].

Genome-wide study for association with de Quervain's tenosynovitis

We compared the observed p-values to the distribution of p-values expected by chance in a Q-Q plot (▶ **Fig. 1**). The black dot in the upper right hand corner deviates from the red line. The p-value for every SNP from the meta-analysis is shown in a Manhattan plot in ▶ **Fig. 2**. rs35360670 on chromosome 8 showed a genome-wide significant association with de Quervain's tenosynovitis ($p = 1.9 \times 10^{-8}$, ▶ **Table 2**). rs35360670 was not directly genotyped on the Affymetrix chips, but rather its genotype data was imputed (▶ **Table 2**). The R^2 value for imputation of rs35360670 was 0.72, indicating that the genotype was only partially accurate using imputation and that care should be taken until true genotype data can be obtained (▶ **Fig. 3**).



▶ **Fig. 1** Quantile-quantile plot for genome-wide association analysis of De Quervain's tenosynovitis. The expected versus observed log transformed values for the 8,156,340 p-values from the meta-analysis 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.

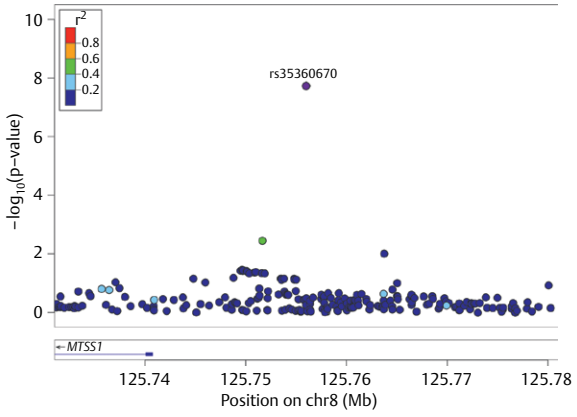


▶ **Fig. 2** Manhattan plot for genome-wide association analysis of De Quervain's tenosynovitis. The -log10 p-values for association with De Quervain's tenosynovitis for SNPs from the meta-analysis are plotted by genomic position with chromosome number listed across the bottom. The y-axis shows the -log10 p-value for association with De Quervain's tenosynovitis. The blue line represents suggestive genome-wide significance ($p < 5 \times 10^{-5}$) and the red line represents genome-wide significance ($p < 5 \times 10^{-8}$).

▶ **Table 2** Genome-wide association analyses for de Quervain's tenosynovitis.

Variant	Gene(s)	EA[a]	EAF[b]	P-value[c]	OR (95 % CI)[d]
rs35360670[e]	*MTSS1*	A	0.024	1.9×10^{-8}	1.46 (1.38–1.59)

[a] Effect allele (minor allele); [b] Effect allele frequency in the control population; [c] P-value from fixed-effects meta-analysis; [d] Adjusted allelic odds ratio with 95 % confidence interval; [e] Genotype for rs35360670 was imputed ($R^2 = 0.72$)



▶ **Fig. 3** Regional-association plot for rs35360670 with De Quervain's tenosynovitis. Tested SNPs are arranged by genomic position on chromosome 8 (x-axis) in a 50 kb window around the lead SNP rs35360670 (purple diamond). The y-axis indicates -log10 p-values for association with De Quervain's tenosynovitis for each SNP. rs35360670 is located in the upstream region of the MTSS1 gene. 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.

For rs35360670, individuals that carried one copy of the risk allele (genotype A/C) had a 1.38 fold increased risk of de Quervain's tenosynovitis compared to individuals with no risk alleles (genotype C/C) (▶ **Table 3**). The risk was even higher in people carrying two copies of the risk allele, but there were too few individuals homozygous for the risk allele to be statistically significant.

The GWAS results were analyzed to determine whether the association of rs35360670 with de Quervain's tenosynovitis was

▶ **Table 3** Genotype distributions for rs35360670.

rs35360670	A/A	A/C	C/C
Cases	4	237	3468
Controls	49	4,101	83,985
Overall	53	4,338	87,453
Risk for de Quervain's tenosynovitis	0.075	0.055	0.040
Relative risk for de Quervain's tenosynovitis[a]	1.90 (0.69–5.26)[b]	1.38 (1.20–1.58)	1.00

[a] Risk relative to individuals homozygous for the protective allele (95 % CI); [b] p-value = 0.21

stronger in some ancestry groups than in others, a phenomenon known as heterogeneity [18]. ▶ **Table 4** shows the p-values and odds ratios for this SNP for each ancestry group. As expected, the smallest p-value was observed for the European population because 82 % of the cohort was European. The p-values for the LAT and EAS ancestry groups were nominally significant, but the p-value for the AFR ancestry group was not significant. For the EUR, LAT and EAS ancestry groups, the odds ratios for each race were in the same direction and of similar magnitude. However, the odds ratio was reversed in the AFR ancestry group compared to the others. The I^2 estimate was 48 %, suggesting that there might be heterogeneity between the different ancestry groups. However, the 95 % confidence interval for I^2 was 0–90, indicating that the presence and extent of heterogeneity is not certain.

rs35360670 is located in the upstream region of the MTSS1 gene, about 15 kb from the transcription start site. MTSS1 encodes metastasis suppressor protein 1, which is a protein involved in actin scaffolding whose expression decreases in many cancer types [38]. rs35360670 does not change the protein sequence of MTSS1. To date, gene expression studies have not yet been able to show a link

▶ **Table 4** Association statistics for rs35360670 with de Quervain's tenosynovitis in individual ancestry groups.

Race	P-value[a]	OR (95 % CI)[b]	$I^{2,c}$	Q[d]
EUR	2.7×10^{-6}	1.42 (1.23–1.64)	48 (0–90)	0.12
LAT	4.3×10^{-3}	1.77 (1.19–2.61)		
EAS	2.4×10^{-2}	1.85 (1.08–3.16)		
AFR	0.14	0.34 (0.08–1.40)		

[a]P-value for rs35360670 adjusted for lambda genomic inflation factor from fixed-effect meta-analysis; [b]Allelic odds ratio with A as the effect allele (95 % confidence interval); [c]Percentage of variability between ancestry groups that is due to heterogeneity (95 % confidence interval); [d]Cochran's Q, p-value that the association is different between ancestry groups

between variation in rs35360670 and change in expression of MTSS1. There are no other SNPs linked to rs35360670 either in the genotype data from the GERA cohort or from the 1000 Genomes Project. In summary, the target gene for rs35360670 is not known and it is unclear how variation at rs35360670 might affect nearby gene activity to increase risk for de Quervain's tenosynovitis.

Discussion

De Quervain's tenosynovitis is a painful overuse injury involving the tendons within the first extensor compartment of the wrist. This condition is seen commonly in both the general population as well as athletes spanning a variety of sports including racquet sports, golf, volleyball and rowing [30, 31, 34, 37]. It is the most common radial-sided tendinopathy observed in athletes [5, 30, 34, 37]. Besides overuse, there may be other contributing factors such as inflammatory arthritis.

We identified the first genetic variant associated with de Quervain's tenosynovitis using large-scale genotype and phenotype data comprised of 4,129 cases of de Quervain's tenosynovitis and 98,374 controls. Power calculations indicate that a cohort of this size would have about a 90 % chance of detecting an SNP with an association with de Quervain's tenosynovitis at a genome-wide significance (assuming genotype relative risk of 1.4, minor allele frequency of 5 %).

rs35360670 on chromosome 8 showed an association with de Quervain's tenosynovitis that was significant genome-wide ($p = 1.9 \times 10^{-8}$). The imputed genotype was inferred with only 72 % accuracy, indicating that the association of rs35360670 with de Quervain's tenosynovitis should be viewed with some caution. rs35360670 is located about 15 kb 5' to the MTSS1 gene, which encodes an actin scaffolding protein involved in tumor metastasis [38]. However, it is unclear how changes in the function of the MTSS1 gene due to variation at rs35360670 leads to increased risk for de Quervain's tenosynovitis; this SNP changes neither the coding sequence of MTSS1 nor has it been found to alter expression of MTSS1 in cell lines and tissues that have been assayed [8].

Individuals that have one copy of the risk allele for rs35360670 (genotype A/C) have a 38 % increased risk of de Quervain's tenosynovitis compared to individuals lacking a risk allele in our cohort (genotype C/C). For the general population, a 38 % increased relative risk for de Quervain's tenosynovitis may not warrant preventative measures. For elite athletes participating in sports such as golf or tennis, however, this level of risk may warrant attention with regard to training regimen, because the consequences of injury can be substantial. Altering hand grip in tennis or establishing proper swing technique in golf are two training modifications that might possibly reduce the risk for de Quervain's tenosynovitis for individuals with the rs35360670 risk allele [34, 37].

As noted in previous analyses of this cohort, there are several limitations to this type of study [20, 29]. First, the phenotype was defined from codes contained in the electronic health records, which may be inaccurate. Intersection syndrome is a separate condition that clinically resembles de Quervain's tenosynovitis. Intersection syndrome lacks a specific ICD code, and thus it is possible that some cases of intersection syndrome were incorrectly assigned to the ICD code for de Quervain's tenosynovitis. Because cases were specified by attending physicians in Kaiser Permanente Northern California, we cannot be certain that we captured all relevant patients and excluded those that were not relevant. Second, the cohort included people regardless of whether or not they participated in a sport. We cannot document whether the statistical association of rs35360670 with de Quervain's tenosynovitis was derived predominantly from the subset of the population that were active in one or more sports. Third, the number of individuals of Latin American, East Asian or African American ancestry was relatively small, and hence the association results for these ancestry groups are weaker than those from the European ancestry group.

In the future, it will be important to replicate the gene association results with de Quervain's tenosynovitis in an independent cohort. It will also be interesting to perform the analysis on populations of athletes competing in sports with high rates of this condition, such as golf or tennis. The results from these studies may reveal whether certain genetic polymorphisms such as rs35360670 could be used as diagnostic markers to help predict which athletes harbor a higher risk for de Quervain's tenosynovitis and to inform the development of strategies to prevent it.

Conclusion

A genome-wide association screen revealed rs35360670 with a significant association for de Quervain's tenosynovitis. Our data indicate that rs35360670 could explain part of the variation in risk for this injury between individuals.

What are the findings?

- We performed a genome-wide association study for de Quervain's tenosynovitis using data from Kaiser Permanente Northern California consisting of 4,129 cases and 98,374 controls.
- We discovered rs35360670 to be associated with de Quervain's tenosynovitis at genome-wide significance ($p = 1.9 \times 10^{-8}$; OR = 1.46).

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Conflict of interest

The authors have no conflict of interest to declare.

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