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Genetic susceptibility to anterior cruciate ligament rupture in athletes: a genome-wide association case–control study

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Abstract

Objectives

Anterior cruciate ligament (ACL) rupture is a common and severe injury in athletes, influenced by both environmental and intrinsic factors. Genetic susceptibility has been suggested, but robust associations remain limited. We performed an exploratory genome-wide association study (GWAS) to identify genetic variants associated with ACL rupture in a well-characterised athlete cohort.

Study design

Case–control study.

Methods

A total of 607 participants of European ancestry were included: 401 patients with ACL rupture (293 unilateral, 108 bilateral) and 206 screened athlete controls with no history of ACL injury. Genotyping was performed using the Illumina Global Screening Array, and association analyses were conducted using logistic regression under an additive model, adjusting for population stratification.

Results

Several loci showed suggestive associations ($p < 5\times10^{-5}$), including variants in or near GALNT11, ITGAM, C10orf82, OR7E47P, HSPA12A, OPRD1, and NEK10. These genes are implicated in diverse biological processes, including inflammatory regulation, cellular stress responses, and ciliary function. No variants reached genome-wide significance ($p < 5\times10^{-8}$).

Conclusions

No genome-wide significant associations with ACL rupture were identified. However, several loci showed suggestive associations that highlight biological pathways related to inflammation, cellular stress responses, and ciliary function. These findings should be considered hypothesis-generating and require replication in larger independent cohorts before firm conclusions regarding their role in ACL injury susceptibility can be drawn.

BACKGROUND

Anterior cruciate ligament (ACL) injury is common among athletes and is associated with prolonged rehabilitation and delay in return to sport [1]. Although trauma is required for injury occurrence, most commonly through a non-contact valgus mechanism, both external (surface type, temperature, weather conditions) and internal factors (neuromuscular control, anatomy, sex, age, and prior knee injuries, dynamic Q-angle symmetry) influence injury risk [2–11]. Among internal factors, the role of genetic variants remains of particular interest, although no definitive associations have yet been established [12–13].

Previous genetic studies of ACL injury have primarily focused on candidate gene approaches: genes related to connective tissue structure, extracellular matrix (ECM) maturation and degradation, and the

inflammatory response following injury. Given that the ACL consists predominantly of collagen, mainly type I and, to a lesser extent, type III, early research primarily targeted collagen-related genes, reporting significant associations in several studies [12–14]. Components of the ECM, including proteoglycans, and enzymes involved in ECM remodelling, such as matrix metalloproteinases, have also shown suggestive but inconsistent associations with ACL injury [15–18].

Inflammatory mediators, including IL-6, IL-8, IL-10, and interleukin-1 receptor antagonist, play an important role in the response to micro-injuries and tissue regeneration [19]. Elevated IL-6 levels have been linked to poorer functional outcomes, yet these findings do not establish a clear genetic predisposition [20].

Most published studies are based on candidate gene analyses, with only a couple of genome-wide association studies (GWAS) [21–22]. Among the candidate gene variants, only a polymorphism in the COL3A1 gene has shown nominally significant association in GWAS analyses, while other reported loci have been more challenging to interpret functionally or have shown borderline statistical significance. In addition, existing studies are often constrained by limitations in phenotypic characterization within available databases.

The aim of this study was to perform a hypothesis-free genome-wide analysis to identify genetic variants associated with ACL rupture in a well-characterised athletic cohort. We hypothesized that polymorphisms in genes not traditionally implicated in ligament biology may contribute to ACL vulnerability and lead to rupture.

METHODS

Study design:

This case–control study was conducted between 2019 and 2024 at the National Institute of Sport Medicine (NISM), Hungarian University of Sports Science and the Pasamed Clinic in Budapest, Hungary.

Participants were divided into three groups: patients undergoing arthroscopic unilateral ACL reconstruction (ACL1), those undergoing bilateral ACL reconstruction (ACL2), and a screened control group (CON). Controls were active athletes aged ≥19 years with no history of ACL injury. ACL1 and ACL2 samples were collected during hospitalisation for surgery at NISM, while control samples were obtained from students of the Hungarian University of Sports Science and athlete patients attending the Pasamed Clinic. In cases where two ACL reconstructions were performed on the same knee, patients were classified into the unilateral group. Other procedures (eg, meniscal or cartilage interventions) were not considered.

The primary outcome was ACL rupture, confirmed by arthroscopic evaluation. The main exposures of interest were genetic variants assessed in a hypothesis-free genome-wide association framework. Additional variables included demographic factors such as age and prior knee injury history. All

participants were of Hungarian origin, and analyses were restricted to individuals of European ancestry to minimise population stratification, although recruitment from multiple institutions may still introduce some heterogeneity. Diagnostic criteria for ACL rupture and re-rupture were standardised across sites using clinical examination, MRI findings and surgical reports.

To minimise selection bias, participants were consecutively recruited using uniform inclusion criteria across all sites. Measurement bias was reduced by applying standardised diagnostic protocols, and genetic analyses were performed blinded to clinical outcomes.

Age was treated as a quantitative variable. A minimum age of 19 years was required for controls to ensure comparability with patient groups. Sample size considerations were based on previous studies and the hypothesis that bilateral ACL injury may reflect a stronger genetic predisposition; therefore, at least 100 bilateral cases, 300 unilateral cases and 200 controls were included to optimise statistical power.

DNA was collected from buccal epithelial cells using duplicate swabs and stored at −20 °C until processing. DNA purification was performed at the Department of Molecular Biology, Semmelweis University, initiated with an overnight incubation of the samples at 56 °C in 0.2 mg/ml proteinase K cell lysis buffer. This was followed by denaturing the proteins with a saturated NaCl solution. Finally, the DNA was precipitated using isopropanol, followed by 70% ethanol. The DNA pellet was then resuspended in 100 µL of 0.5× TE buffer (0.005 M Tris-HCl, pH 8.0, and 0.5 mM EDTA). The concentration and quality of the DNA samples were assessed using a NanoDrop One spectrophotometer to measure the A260/280 and A260/230 ratios. All samples had a minimum DNA concentration of 50 ng/µL. The purified DNA samples were stored at −20 °C until subsequent analysis. Genotyping was performed using the Illumina Global Screening Array (GSA) MD v3.0.

Genetic data analysis and statistical methods

Raw intensity data (.idat files) were converted to genotype calls using bcftools plugins (+idat2g tc and +gtc2vcf) with manufacturer-provided cluster and manifest files (GSA-24v3-0_A1). Genotypes were aligned to the GRCh37/hg19 human reference genome and annotated using dbSNP rsIDs.

Quality control was performed using PLINK v1.9. SNPs and individuals with call rates below 80% were excluded, followed by a stricter 98% threshold. Individuals were further removed based on sex discrepancies, excess heterozygosity, or cryptic relatedness (PI_HAT > 0.2), retaining the individual with lower missingness within each related pair. Variants with a minor allele frequency (MAF) <1% or significant deviation from Hardy–Weinberg equilibrium ($p < 1\times10^{-6}$ in controls, $p < 1\times10^{-10}$ globally) were removed.

Only autosomal SNPs were retained. To identify heterozygosity outliers and related individuals, SNPs in long-range linkage disequilibrium regions were excluded, and LD pruning was applied to the remaining variants (50-SNP window, step size 5, $r^2 < 0.2$). The dataset was merged with the 1000 Genomes Project

Phase 1 reference panel (20100804 release), strand-aligned, and filtered for mismatched SNPs. Multidimensional scaling (MDS) was performed using pruned SNPs, and the top 10 MDS components were used to infer genetic ancestry. Only individuals clustering with the European (EUR) reference group were retained. Genome-wide association analyses were conducted using logistic regression in PLINK, assuming an additive genetic model and adjusting for the top 10 MDS components as covariates.

SNPs with missing or invalid test statistics were excluded from downstream analysis. A suggestive significance threshold of $p < 5\times10^{-5}$ was applied to identify candidate loci.

Equity, diversity, and inclusion statement

The authors sought to minimise bias in study design, data collection, and analysis, and no participants were excluded on the basis of sex, gender, ethnicity or other protected characteristics unless scientifically justified.

RESULTS

Study population demographics

A total of 647 individuals were initially recruited, of whom 607 were included in the final analysis after quality control. All individuals who were invited to participate in the study agreed to enroll, reflecting a high participation rate. All participants have signed written informed consent. Only one participant withdrew consent during the study without providing a specific reason.

During DNA extraction, our sample size decreased by 17. In some cases, the samples were taken from closely related individuals. Due to the higher genetic similarity of these participants, 22 individuals were excluded from the analysisFollowing quality control procedures, 607 samples were retained for analysis. Figure 1.

The ACL1 group included 293 patients, the ACL2 group 108, and the control group 206; the sex distribution of the groups is shown in Table 1.

No significant differences were observed between the groups in sex distribution. (χ^2 test, P = 0.5789). However, analysis of variance (ANOVA) demonstrated significant between-group differences in patient age and Tegner activity score (Age: P=0.00432; Tegner score: P=0.0124)

Table 1. Sample demographics

Groups	Sex (Male/Female)	Mean Age (Years ± SD)	Mean Tegner Score ± SD
Control (CON)	112:94 (54% : 46%)	33.3 ± 12.1	7.84 ± 1.6
Unilateral ACL rupture (ACL1)	173:120 (59% : 41%)	30.2 ± 11.4	7.42 ± 1.7
Bilateral ACL rupture (ACL2)	61:47 (56% : 44%)	33.9 ± 11.2	7.4 ± 1.8

Legend: SD: standard deviation; No significant differences were observed in sex distribution, while age was significantly lower in the ACL1 group compared with controls, and Tegner scores were significantly lower in both ACL groups compared with controls.

Results of Genetic Associations Clustering of variants was observed in GALNT11 and ITGAM (ACL–CON), HSPA12A (ACL1–CON), OPRD1 (ACL2–CON), and NEK10 (ACL1–ACL2), while no genome-wide significant associations were identified.

The statistical analysis did not reveal any genome-wide significant association ($P<5\times10^{-8}$). For polymorphisms with p-values exceeding 5×10^{-3}, the observed significance values ranged between 5×10^{-5} and 5×10^{-7}. The results are shown in the Table 2.

Table 2. Genes containing multiple suggestively associated SNPs identified in the genome-wide association analyses

Comparison	Main genes/loci	Number of suggestive SNPs	Lowest p-value
ACL–CON	GALNT11	5	$2.46\text{x}10^{-5}$
	ITGAM	3	$4.52\text{x}10^{-5}$
	C10orf82	2	$1.39\text{x}10^{-5}$
	OR7E47P	2	$1.3\text{x}10^{-5}$
ACL1–CON	HSPA12A	2	$4.83\text{x}10^{-5}$
	OR7E47P	2	$3.72\text{x}10^{-5}$
ACL2–CON	OPRD1	4	$4.07\text{x}10^{-5}$
ACL1–ACL2	NEK10	4	$4.89\text{x}10^{-5}$

Legend: Top loci and suggestive SNP associations identified across comparison groups (ACL–CON, ACL1–CON, ACL2–CON, ACL1–ACL2). For each locus, the number of suggestive SNPs and the lowest p-

value are shown. Results represent suggestive (non–genome-wide significant) associations ($p < 5\times10^{-8}$), highlighting potential genetic signals differentiating ACL subgroups and controls.

ACL vs. CON

When comparing the whole ACL rupture group to controls the most robust finding was the GALNT11 gene, around which 5 SNPs were identified. We found 3 SNPs associated with the ITGAM gene, 2 SNPs each for the C10orf82 and OR7E47P genes, and 1-1 SNP for the DIPK1B, NAV3, and C16orf87 genes.

ACL1 vs. CON

When comparing the unilateral ACL rupture group to controls, 2 SNPs each were identified in the HSPA12A and OR7E47P genes. Additionally, 1 SNP was detected in each of the following genes: ANTXR1, NPAS2, DOCK4, DIPK1B, ITGAM, and C16orf87. The significance levels in these cases also ranged between 5×10^{-5} and 10^{-6}.

ACL2 vs. CON

In this group, 4 SNPs were identified in a single gene, OPRD1. In all other cases, 1 SNP each was detected in the TNNI3K, VAV3, ALK, CPNE4, LINC, SEMA4B, and CIB1 genes. All significance values were in the order of 10^{-5}.

ACL1 vs. ACL2

In this group, 4 SNPs were identified around a single gene, NEK10. The remaining findings involved only 1 SNP each for the LRRN1, CPE, ADAMTS19, ENTPD1, and CADM1 genes, with significance values in the range 10^{-5}.

The significance levels of the results were visualized using Manhattan plots (see Figure 2).

Due to its size, the table containing all the results is published as additional files.

DISCUSSION

ACL injury is common among athletes and often results in prolonged rehabilitation and substantial time loss in return to sport. Injury risk is influenced by multiple external and internal factors, including neuromuscular, anatomical and potentially genetic determinants. This study investigated the association between ACL rupture and genetic variants using a hypothesis-free genome-wide approach in our cohort. Our findings suggest that polymorphisms in less studied regulatory genes may contribute to ligament vulnerability.

The present exploratory GWAS identified several loci showing suggestive associations with ACL rupture, including variants in or near GALNT11, ITGAM, C10orf82, OR7E47P, HSPA12A, OPRD1, and NEK10. To

our knowledge, these genes have not previously been implicated in ACL rupture and therefore represent potential targets for future investigation.

Furthermore, this GWAS was conducted in our own well-characterised cohort, allowing accurate verification of the knee status of all included athletes. Another strength is that the screened control group consisted of active athletes with no history of ACL rupture, rather than unscreened members of the general population.

Notably, we did not find genome-wide significant associations with ACL injury using $p = 5 \times 10^{-8}$ as a cut-off, however, strong associations with significance levels below 5×10^{-5}.When comparing all ACL rupture cases to controls (ACL–CON), our findings highlight several genes that may be involved in ligament vulnerability. Given that the ACL is primarily composed of type I and III collagen fibres, alterations in collagen remodelling may influence ligament tensile properties [13]. In the present study, the strongest association was observed with polymorphisms in the ITGAM gene. ITGAM encodes the integrin αM (CD11b) subunit, which is involved in immune regulation and inflammatory responses, particularly through leukocyte adhesion and migration [23]. Variants of ITGAM have previously been linked to systemic inflammatory conditions, including systemic lupus erythematosus [24], and to knee osteoarthritis, supporting its potential relevance in joint tissue pathology [25].

While several intrinsic and extrinsic factors contribute to ACL injury risk [3, 5–10], ligament rupture occurs when mechanical loading exceeds tensile capacity [26]. During athletic activity, repetitive submaximal loading is common and may result in cumulative micro-injuries rather than immediate rupture [27]. Imaging studies have demonstrated transient, load-related changes in ACL structure, suggesting adaptive remodelling processes following micro-damage [28]. However, repeated microtrauma may impair tissue integrity, reduce tensile strength, and increase rupture susceptibility [28–32]. Experimental data indicate that increased loading frequency and reduced ligament thickness accelerate failure, which may partially explain the higher incidence of ACL injuries observed in female athletes [33, 34].

Although the role of ITGAM in ACL injury susceptibility remains unclear, its involvement in inflammatory pathways raises the possibility that variants in this gene may influence tissue remodelling processes following repetitive microinjury. However, the biological relevance of this observation requires further investigation.

The GALNT11 gene encodes an enzyme involved in mucin-type O-glycosylation and regulates key signalling pathways, including Notch signalling, with additional roles in cilia-related processes and left–right body asymmetry [35]. It also influences receptor function, such as megalin (LRP2), and normal renal physiology [36]. Although GALNT11 has not previously been linked to ligament pathology, its involvement in signalling pathways and ciliary processes suggests potential mechanisms that merit further study. [37]

Two SNPs were identified in the C10orf82 gene, which is thought to encode a microtubule-associated protein involved in ciliary and flagellar structure and stability; however, its precise biological function remains unclear [38]. To date, no association between C10orf82 and ACL injury has been reported.

OR7E47P is a pseudogene that does not encode a functional olfactory receptor and has no known direct role in olfaction [39].

Focusing specifically on unilateral ACL ruptures compared with controls (ACL1–CON), additional gene associations were identified that may reflect mechanisms related to single-ligament injury. In the ACL1 group, we also identified two genes with two proximal SNPs One of the genes is the previously mentioned OR7E47P, while the other is HSPA12A. This gene is an atypical member of the heat shock protein family. It plays a role in adaptation to metabolic and mechanical stress, and several of its functions are known. In their study, Mao and colleagues reported that in the heart it inhibits fibroblast activation, thereby preventing the development of fibrosis [40]. It enhances angiogenesis and endothelial cell responses both in vitro and in vivo [41]. Yu and colleagues emphasize in their study that it is essential for maintaining aerobic glycolysis and protein lactylation, which may also influence cellular stress responses and regenerative processes [42]. No previous studies have examined the role of HSPA12A in ACL injury. Given its known functions in cellular stress responses and tissue homeostasis, the observed association may warrant further investigation, although functional relevance remains speculative.

In the comparison of bilateral ACL ruptures and controls (ACL2–CON), a distinct pattern of genetic associations emerged, suggesting potentially different underlying biological mechanisms. Within this group, we observed enrichment of four SNPs at two distinct loci. One locus is located in an uncharacterized genomic region, while the other corresponds to the OPRD1 gene, which encodes a delta opioid receptor. Variants of OPRD1 have been linked to opioid dependence, modulate opioid-mediated signalling pathways, and influence pain perception [43]. To date, no studies have investigated the possible involvement of OPRD1 in ACL injury susceptibility, and the biological significance of this finding remains uncertain.

Finally, when comparing unilateral and bilateral ACL rupture cases (ACL1–ACL2), further differences in genetic variants were observed, which may indicate factors contributing to increased susceptibility to repeated injury. We also identified an enrichment of four SNPs around the NEK10 gene. NEK10 is a versatile kinase involved in multiple critical biological processes, ranging from cell cycle regulation and DNA damage responses to mitochondrial homeostasis and ciliogenesis. Clinically, it has been associated with ciliopathies and potentially with cancer, and it may also influence cellular stress signaling and energy metabolism [44, 45].

Several genes identified in the present study (GALNT11, C10orf82 and NEK10) are involved in ciliary structure or function. No established relationship between ciliary biology and ACL integrity has been reported to date; therefore, it remains uncertain whether this observation represents a biologically

meaningful pattern or merely reflects chance findings. Confirmation in independent cohorts will be required.

Clinical Implications

Although no genome-wide significant associations were identified, these findings highlight potential biological pathways, particularly those related to inflammation, cellular stress responses, and ciliary function, that may contribute to ligament vulnerability. While not yet applicable in clinical practice, the results may inform future multifactorial risk models integrating genetic, biomechanical, and environmental factors to support more individualised injury prevention strategies in athletes, pending validation in larger independent cohorts.

Summary

To date, most studies have focused on a limited number of SNPs within candidate genes. Our sample is less heterogeneous, has a more detailed phenotype, we used a "super-negative" control group instead of a general population. This is the first study to investigate genetic polymorphisms associated with ACL rupture in a cohort of patients with a clearly defined and reliably verified phenotypic diagnosis. We did not find any variant with a genome-wide significant association; however, we were able to demonstrate a suggestive associations between polymorphisms in the GALNT11, ITGAM, C10orf82, OR7E47P, HSPA12A, OPRD1 and NEK10 genes and ACL tears. These findings support the hypothesis that genetic susceptibility to ACL rupture may extend beyond traditionally studied candidate genes. However, the exploratory nature of the study and the absence of genome-wide significant associations necessitate replication in larger independent cohorts before firm conclusions can be drawn.

Limitations

This study has several limitations that should be considered when interpreting the findings. First, the sample size, although larger than most previous candidate gene studies, remains modest for a genome-wide association study and may have limited statistical power to detect variants reaching genome-wide significance. Second, the study population consisted exclusively of individuals of Hungarian origin and European ancestry, which may limit the applicability of the findings to other populations.

In addition, although population stratification was addressed using multidimensional scaling components, residual confounding cannot be entirely excluded. The cross-sectional design precludes causal inference, and environmental and biomechanical risk factors—such as neuromuscular control, training load, or playing surface—were not comprehensively assessed. Finally, functional validation of the identified loci was not performed, and therefore the biological relevance of these associations remains to be established.

Abbreviations

ACL Anterior cruciate ligament

GWAS Genome-Wide Association Study

NISM National Institute of Sport Medicine

ACL1 Unilateral ACL reconstruction

ACL2 Bilateral ACL reconstruction

CON Control group

MDS Multidimensional Scaling

ANOVA Analysis Of Variance

Declarations

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Conflicts of Interest

The authors declare no competing interests.

Authors' Contributions

EP, AnP, AP, CB and MT was responsible for recruiting the participants into the study. AF performed the statistical analysis. CB and ZR conceived the study and performed the isolation and genotyping analysis of the samples. MT was a major contributor to the writing of the manuscript. AP was the study coordinator and played a significant role in patient recruitment. HV played a role in organising the grant application required to secure funding for the study. AT and TH provided expert advice during the research. All the authors read and approved the final manuscript.

Ethical approval

The study was conducted in accordance with the Declaration of Helsinki and was approved by the National Public Health Center, Directorate of Health Administration (approval No. 800-6/2019).

Informed consent

Informed consent was obtained from all individual participants included in the study.

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Some findings of this study was previously presented as a conference presentation at the Australian Knee Society SatelliteMeeting, Stockholm, 13 June 2025, and at the Hungarian Arthroscopy and Sports Surgery Society Symposium, 7 November 2025.

Use of Artificial Intelligence

Artificial intelligence tools were used solely to assist with language editing and to optimize text length. No AI was used to generate scientific content, interpret data, or draw conclusions.

Data Availability

The datasets generated and/or analysed during the current study are publicly available in the Zenodo repository at: https://zenodo.org/records/19639900

Patient consent

All participants provided written informed consent prior to inclusion in the study.

Patient and public involvement:

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

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Figures

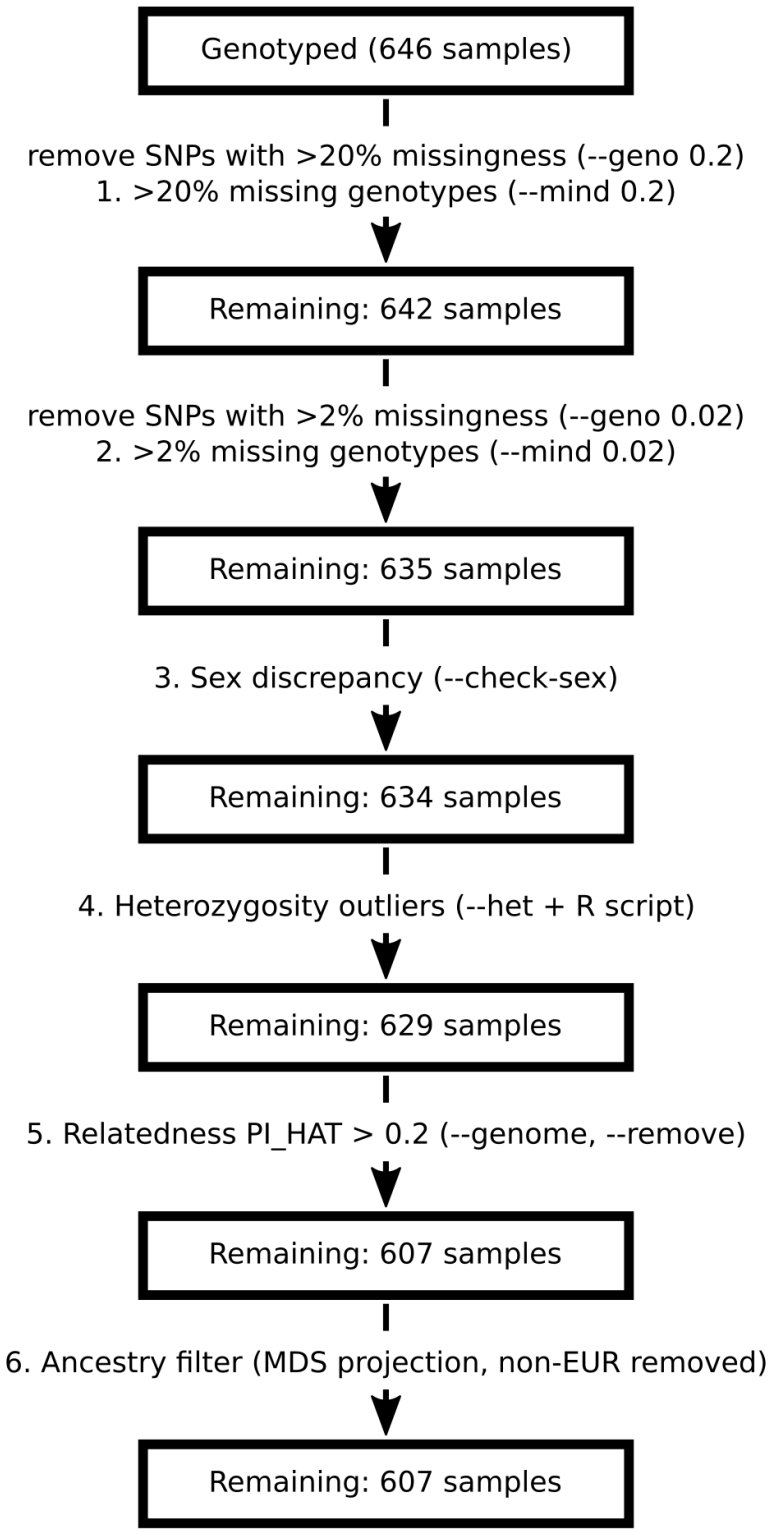


Figure 1

Flowchart of patient exclusions during analysis

Legend: A total of 607 samples remained for analysis after filtering for genotype missingness, sex discrepancies, heterozygosity outliers, relatedness, and non-European ancestry.

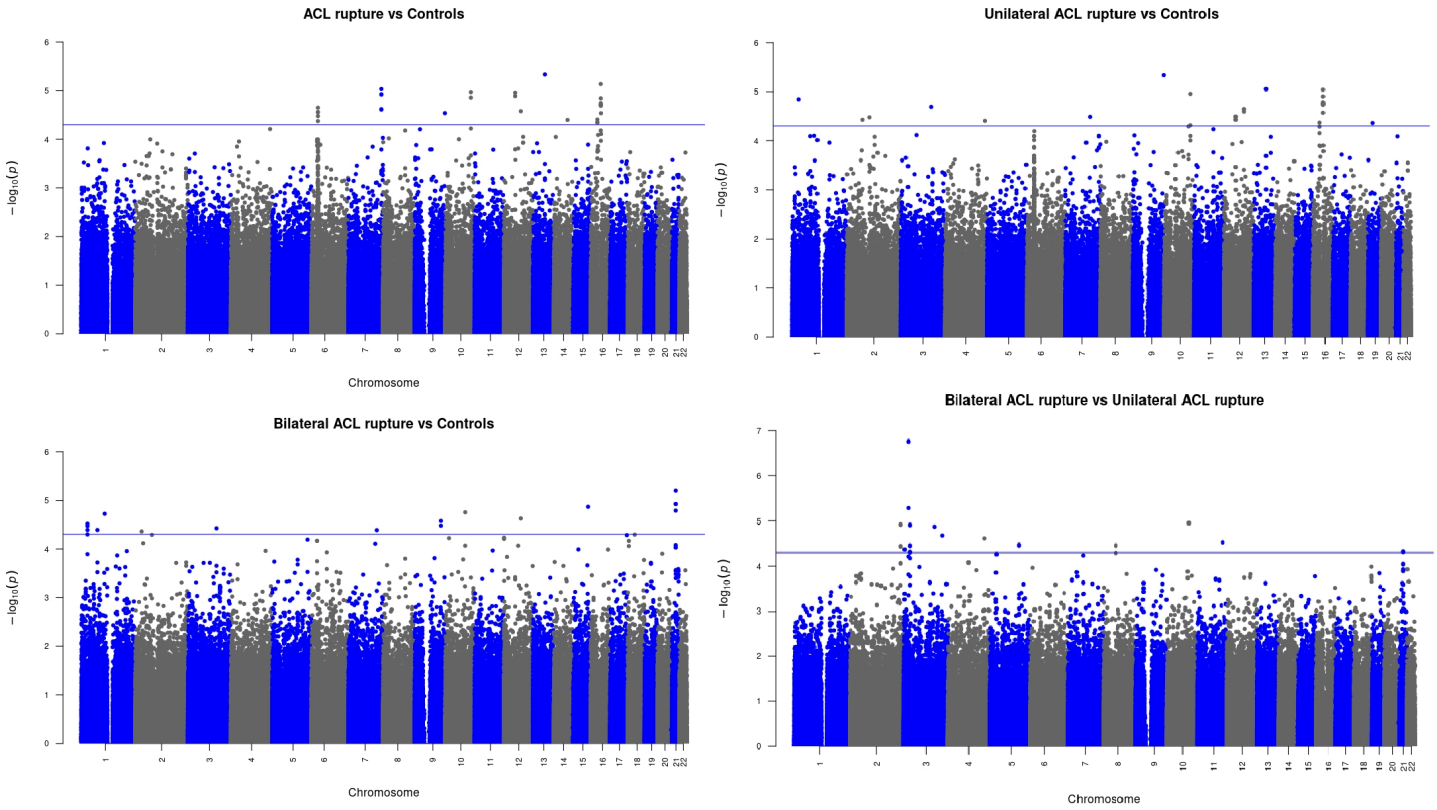


Figure 2

Manhattan plots

Legend: Manhattan plots for the investigated ACL rupture phenotypes, with the strongest association signal observed in the comparison of ACL1 vs. ACL2 cases.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- fullGenomicResults.xlsx