Mitochondrial DNA haplogroups Associated with MRI-Detected Structural Damage in Early Knee Osteoarthritis

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RUNNING HEADLINE

mtDNA and Structural Features in Knee OA

ABSTRACT

Objective: MRI-detected structural features are associated with increased risk of radiographic osteoarthritis (ROA). Specific mitochondrial DNA (mtDNA) haplogroups have been associated with incident ROA. Our objective was to compare the presence of MRI-detected structural features across mtDNA haplogroups among knees that developed incident ROA.

Design: Knees from the Osteoarthritis Initiative that developed incident ROA during 48 months follow-up were identified from Caucasian participants. mtDNA haplogroups were assigned based on a single base extension assay. MRIs were obtained annually between baseline and 4-year follow-up and scored using the MRI Osteoarthritis Knee Score (MOAKS). The association between mtDNA haplogroups and MRI-detected structural features was estimated using log-binomial regression. Participants who carried haplogroup H served as the reference group.

Results: The sample included 255 participants contributing 277 knees that developed ROA. Haplogroups included H (116, 45%), J (17, 7%), T (26, 10%), Uk (61, 24%), and the remaining less common haplogroups ("others") (35, 14%). Knees of participants with haplogroup J had significantly lower risk of medium/large BMLs in the medial compartment [3.2%, RR=0.17; 95%CI: 0.05, 0.64;p=0.009] compared to knees of participants who carried haplogroup H [16.3%], as did knees from participants within the "others" group [2.8%, RR=0.20; 95%CI: 0.08, 0.55;p=0.002], over the four year follow-up period.

Conclusions: mtDNA haplogroup J was associated with lower risk of BMLs in the medial compartment among knees that developed ROA. Our results offer a potential hypothesis to explain the mechanism underlying the previously reported protective association between haplogroup J and ROA.

Keywords

Mitochondrial DNA, haplogroups, knee osteoarthritis, MRI, bone marrow lesions, meniscus

INTRODUCTION

Knee Osteoarthritis (OA) is a chronic condition that affects an estimated 250 million adults worldwide[1].The initial steps of disease manifestation involve molecular derangements followed by structural tissue damage that involves cartilage degradation, as well as synovial inflammation, subchondral sclerosis and damage to other joint structures such as menisci and ligaments, eventually resulting in loss of articular function and pain[2].Despite high prevalence, available therapies to treat OA are limited in terms of efficacy and safety, and existing treatments are only palliative. Prevention efforts and development of disease-modifying treatments require identification of modifiable targets, ideally with insights underlying the mechanisms involved.

Multi-feature assessment of joint structure in knee OA has been accomplished through the use of semi-quantitative scoring of magnetic resonance imaging (MRI)[3]. Articular tissues commonly assessed include cartilage damage, subchondral bone marrow lesions (BMLs) and cysts, osteophytes, bone attrition, synovitis/effusion, periarticular cysts/bursitis, anterior and posterior cruciate ligaments, the collateral ligaments, the menisci, and intra-articular loose bodies.

Mitochondria contain their own genetic material, mitochondrial DNA (mtDNA), which codes for 13 essential peptides of the mitochondrial respiratory chain, as well as for 22 transferent RNAs (tRNAs) and 2 ribosomal RNAs (rRNAs). As a consequence of the high mutation rate of mtDNA, there are distinct haplogroups, defined by the presence of a particular set of single nucleotide polymorphisms (SNPs) in the mtDNA sequence. These mtDNA haplogroups are the result of maternally inherited mutations in the mtDNA acquired throughout human history and shaped by climate selection when humans migrated into colder climates[4]. Specific polymorphisms that are characteristic of the different mitochondrial haplogroups influence the behavior of the mitochondria and interact with the nuclear genome modulating critical processes such as complement activation, inflammation or apoptosis[5], and therefore they have been associated with degenerative disorders[6], metabolic

alterations[7] and longevity[8]. The role of mitochondria in the pathogenesis of OA has been previously described[9], and mtDNA haplogroups have been associated with the prevalence[10], incidence, and progression of radiographic knee OA (ROA) in different cohorts worldwide[11-14].

Knee structural pathologies have been associated with the development of ROA[15], radiographic progression[16] and incident knee pain[17]. Whether genetic variability influences the underlying pathology of OA is largely unknown, however. Notably, mtDNA haplogroup J has been associated with a lower rate of incident ROA[14]. Our objective was to compare the presence of MRI-detected structural features across mtDNA haplogroups among knees that developed incident ROA over 48 months.

METHODS

Study Design/Setting/Participants

The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational study of knee osteoarthritis. Study overview, objectives, protocol, and data are available online (https://oai.epi-ucsf.org/datarelease/About.asp). Briefly, 4,796 men and women with or at risk for knee osteoarthritis aged 45-79 enrolled between February 2004 and May 2006 from the following sites: Ohio State University (Columbus, OH), University of Maryland School of Medicine and Johns Hopkins University School of Medicine (Baltimore, MD), University of Pittsburgh School of Medicine (Pittsburgh, PA), Brown University School of Medicine and Memorial Hospital of Rhode Island (Pawtucket, RI). The study was approved by the Institutional Review Board (IRB) of the OAI Coordinating Center at the University of California, San Francisco and the IRBs of each site.

Knees that developed incident ROA within four years of OAI baseline were selected for annual MRI readings in a substudy, Pivotal Osteoarthritis Initiative MRI Analyses (POMA), including 355 knees from 323 participants[15]. Briefly, annual bilateral posteroanterior fixed-flexion weight-bearing radiographic views were obtained using a

SynaFlexer™ frame (Synarc, San Francisco, CA, USA) according to standardized procedures (https://oai.epi-ucsf.org/datarelease/operationsManuals/RadiographicManual.pdf). Radiographs were centrally read and scored with Kellgren-Lawrence (KL) grades to ascertain the development of incident ROA (i.e., KL grade ≥2)[18].

Because our study aims to compare the presence of MRI-detected structural features across European mtDNA haplogroups, we restricted the POMA sample to self-identified Caucasian participants, to avoid confounding by population stratification. The available sample for analysis included 255 Caucasian participants contributing 277 knees, with an average of 3.9 annual MRIs (4% with 2 MRIs; 35% with 3 MRIs; 27% with 4; 34% with 5 MRIs).

Mitochondrial DNA haplogroup assignment

The most common Caucasian mtDNA haplogroups were assigned to participants using a previously described assay[10]. Briefly, a multiplex polymerase chain reaction was performed to amplify the six mtDNA fragments that contain the diagnostic SNPs that enable the identification of the most common Caucasian mtDNA haplogroups. Resulting PCR fragments were then purified with ExoSap-IT (ThermoFisher Scientific, Waltham, MA, United States) and analyzed by the Single Base Extension (SBE) assay using the SNaPshot multiplex Kit (ThermoFisher Scientific, Waltham, MA, United States). Once purified with SAP (ThermoFisher Scientific, Waltham, MA, United States), resulting products were loaded into an ABI 3130XL genetic analyzer (ThermoFisher Scientific, Waltham, MA, United States) and informative SNPs were visualized with GeneMapper software v5.0. Haplogroups with a frequency below 5% were pooled into the "Others" group.

Knee MRI Acquisition and Assessment

Annual MRIs were obtained on identical 3T systems (Siemens Trio, Erlangen, Germany) and acquired with a dedicated quadrature transmit/receive knee coil using a coronal intermediate-weighted 2-dimensional turbo spin-echo sequence, a sagittal 3-dimensional dual-echo steady-state sequence and coronal and axial

reformations, and a sagittal intermediate-weighted fat-suppressed turbo spin-echo sequence. The complete pulse sequence protocol and sequence parameters have been described previously[19].

Outcomes

MRI-detected structural features of knee OA were assessed by two expert readers with extensive experience in MRI assessment of OA (FWR, AG) using the MRI Osteoarthritis Knee Score (MOAKS), a semi-quantitative scoring instrument[20]. Outcomes of interest included damage thought to be of greatest clinical significance, including medium/large effusion-synovitis, moderate/severe Hoffa-synovitis, BMLs scored as ≥33% of the subregional volume (grade 2 and 3 , i.e. moderate and large BMLs), meniscal tear/maceration, and meniscal extrusions ≥3mm. Cartilage damage was defined as loss ≥10% of the surface area and/or ≥10% full-thickness loss.

Statistical Methods

Baseline characteristics of the sample were summarized, including participant age, sex, body mass index (BMI), and self-reported history of knee injury or knee surgery. The proportion of each mtDNA haplogroup with the outcome of interest (MRI-detected structural damage) was estimated and compared using log-binomial regression to estimate relative risks (RR) and 95% confidence intervals (CI), and Poisson regression with robust variance as a planned alternative when the log-binomial model failed to converge[21]. Participants who carried haplogroup H served as the reference group for comparisons since haplogroup H is the most common in the Caucasian population. Generalized estimating equations were used to account for repeated annual MRI observations of knees between baseline and four-year follow-up, and potentially two knees contributed per participant. All estimates were reported unadjusted, as well as adjusted for age, sex, and BMI. BMLs, cartilage damage, meniscal damage, and extrusions were examined at the compartment level, as well as at the knee level.

RESULTS

The sample of 255 Caucasian participants contributing knees that developed incident ROA within four years of baseline had a mean age of 61 years (sd 8.7), was predominately female (64%) and overweight (43%) or obese (36%). Haplogroups included H (116, 45%), J (17, 7%), T (26, 10%), Uk (61, 24%), and less common (<5%) haplogroups ("others") (35, 14%).

Modest imbalances in baseline characteristics existed between haplogroups; participants carrying haplogroup T were older, while participants carrying haplogroup J were more frequently male than other groups, and less often obese (Table 1). Since these characteristics have the potential to confound associations between mtDNA haplogroup and MRI-detected structural features in our sample, we interpreted results from the adjusted analyses.

Knees of participants with haplogroup J had significantly lower risk of large BMLs in the medial compartment [3.2%, RR=0.17; 95%CI: 0.05, 0.64; p=0.009] compared to knees of participants who carried haplogroup H [16.3%], as did knees from participants within the "others" group [2.8%, RR=0.20; 95%CI: 0.08, 0.55; p=0.002]. While 4.7% of haplogroup H carriers had large BMLs detected in the lateral compartment, haplogroup J carriers had none, potentially suggesting a protective effect of haplogroup J for tibiofemoral BMLs overall [3.2% in J vs 18.8% in H; RR=0.15; 95%CI: 0.04, 0.57; p=0.005]. No evidence of an association between haplogroups and BMLs in the patello-femoral joint (PFJ) was observed (Table 2).

Hoffa´s synovitis (moderate/severe) and effusion-synovitis (medium/large) were less common among participants carrying haplogroup J compared to H, though the differences were not statistically significant [1.7% vs 10.1%, RR=0.16; 95%CI: 0.02, 1.16; p=0.070 and 9.5% vs 17.3%, RR=0.55; 95%CI: 0.20, 1.52; p=0.248, respectively] (Table 2).

Higher risk of meniscal tear/maceration in the lateral compartment was seen among participants carrying haplogroups J [31.8%, RR=3.35; 95%CI: 1.30, 8.61; p=0.012], T [28.3%, RR=3.06; 95%CI: 1.47, 6.39; p=0.003], and Uk [25.0%, RR=2.73; 95%CI: 1.45, 5.13; p=0.002], compared to haplogroup H [9.1%]. Similarly, carriers of haplogroup T experienced a higher risk of meniscal extrusion ≥3mm in the lateral compartment [11.5%, RR=11.7; 95%CI: 2.90, 47.22; p=0.001], compared to haplogroup H [0.8%]. No remarkable effect sizes or significant differences in cartilage damage were observed between haplogroups (Table 3).

DISCUSSION

In our longitudinal observational study of participants who developed radiographic incident knee OA, those who carried mtDNA haplogroup J were significantly less likely to have large tibiofemoral BMLs compared to participants who carried the more common haplogroup H.

Severe early changes in different articular features, especially BMLs and meniscal pathology, have been associated with symptomatic progression and radiographic worsening over a 24-month period[22], including increased risk of joint replacement and increased cartilage loss[23]. Specifically, BMLs have emerged as a central component of a wide variety of inflammatory and non-inflammatory rheumatologic conditions, and therefore they are not only potential sources of pain, but may also reflect disease activity[24]. BMLs have been consistently identified by MRI in patients with knee OA[25-27] related to mechanical loading, as well as increased subchondral stress. BMLs are characterized by high bone turnover as well as an increased vascularization induced by angiogenic factors and pro-inflammatory cytokines, which could explain the elevated bone marker levels in patients with severe, progressive OA as a consequence of the severe disruption of subchondral bone architecture[24, 28].

Participants harboring the haplogroup J had a lower rate of large BMLs when compared with participants with haplogroup H. We hypothesize that both metabolic activity and inflammation that takes place in BMLs[29] could be behind this association.

Haplogroups J and H are substantially different with respect to nucleotide composition: haplogroup J comprises a set of uncoupling mitochondrial polymorphisms, preferentially non-synonymous, acquired during evolutionary history[4, 30], while haplogroup H has higher levels of conserved amino acids[4]. Thus, these haplogroups are biochemically different in terms of oxidative phosphorylation system (OXPHOS) coupling efficiency, adenosine triphosphate (ATP) levels and reactive oxygen species (ROS) production[31, 32], leading to different expression patterns of genes affecting several signalling pathways such as complement, inflammation or apoptosis[5, 33]. Further, cells harboring haplogroup J show lower ATP levels accompanied by decreased ROS production, while haplogroup H associates with higher ATP levels, increased ROS production and lower ability to cope with oxidative stress[14, 34, 35]. These characteristics make haplogroup J less efficient and metabolically active compared to H[31, 35], however, haplogroup J also shows a decreased expression of genes affecting inflammation and apoptosis[5].

Metabolic differences between haplogroups H and J have additional consequences. Mitochondria-derived ROS also leads to an upregulation of metalloproteinases (MMPs)[36, 37], as well as an overproduction of pro-inflammatory cytokines[38]. Thus, MMP-13 is highly expressed in subchondral bone affected by BMLs[29], and increased levels of IL-6 and C-reactive protein have been detected in the serum of patients with large-BMLs[39, 40]. In addition, knee effusion-synovitis has been positively associated with BMLs[41]. We found that Hoffa's synovitis and effusion-synovitis were less common in participants with the haplogroup J, although not statistically significant. Interestingly, mtDNA haplogroups have been associated with serum levels of type-2 collagen

biomarkers and MMPs, where those participants with haplogroup J had lower serum levels of catabolic type-2 collagen biomarkers and MMP-13 than those harboring the haplogroup H[42, 43].

Fernández-Moreno *et al*, in a meta-analysis of mtDNA haplogroups in 3214 subjects from OAI and CHECK cohorts, concluded that participants who carried haplogroup J had a lower risk of developing incident ROA over 96 months of follow-up [ref 14]. Our study was restricted to OAI participants who developed incident ROA, and evaluated the association of mtDNA haplogroups with MRI-detected structural abnormalities not visible on radiographs, in the years leading up to ROA. We found a lower frequency of large BMLs, potentially as a consequence of differences in genetically-driven metabolic activity and inflammation at the cellular level. Soto-Hermida *et al* reported that among OAI participants with prevalent disease at baseline (i.e., the progression subcohort of the OAI, defined as having frequent knee symptoms and ROA at baseline) carriers of haplogroup T had a lower rate of cartilage deterioration [ref 44]. In our sample of early OA knees, there was no evidence of an association between mtDNA haplogroups and cartilage damage. This is not entirely surprising given that incident ROA is defined by radiographic detection of an osteophyte, often prior to evidence of joint space narrowing, while disease progression following ROA is characterized by more profound cartilage loss. Our findings, together with the earlier studies [references 14 and 44], highlight the relevance of the mitochondrial genome in the development and progression of knee OA, and offer a hypothesis for the potential mechanism underlying the protective effect of haplogroup J in the development of incident radiographic knee OA and haplogroup T in the progression of prevalent knee OA.

Significant associations between mtDNA haplogroups and meniscal damage and extrusions were also found. Meniscal tears are categorized as traumatic or non-traumatic (degenerative). Traumatic tears are usually caused by a serious injury, often during sports participation; degenerative tears are more common in the medial compartment and often accompanied by knee OA, with increased prevalence as joint space narrowing becomes

more severe[45]. Participants with haplogroup H had a significantly lower prevalence of meniscal tears in the lateral compartment. We do not have a definitive explanation for this finding, though we speculate that since these differences were detected in the lateral compartment, which is less commonly associated with degenerative tears, the association could be related to traumatic episodes or even to knee alignment.

Our findings should be interpreted in context of the limitations. Our study had a limited sample of 255 Caucasian participants contributing 277 knees, and we examined multiple outcomes, yet this is a well-characterized cohort of participants, evaluated by objective methods at annual visits with detailed imaging assessments of OA pathology. In addition, this work examined the forms of joint damage with the greatest potential clinical relevance. Due to the multiple comparisons, the study findings could be considered hypothesis-generating, and replication should be attempted in an independent sample.

In summary, participants carrying the mtDNA haplogroup J had a lower risk of large BMLs in the tibio-femoral medial compartment compared to participants carrying the common haplogroup H among knees from the OAI that developed ROA during 48 months follow-up. Our results offer a potential hypothesis to explain the mechanism underlying the protective effect of haplogroup J for ROA that has been previously reported[14].

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CONTRIBUTIONS

All persons designated as authors have made substantial contributions to all three of sections 1, 2, and 3 below:

1) Conception and design of the study (CKK, IRP, FJB, FWR), or acquisition of data (CKK, DJH, AG, FWR, FJB, IRP, MJH), or analysis (DR, ELA) and interpretation of data (all authors)

2) Drafting of the article (IRP, ELA, FJB, CKK) or revising it critically for important intellectual content (all authors)

3) Final approval of the version to be submitted (all authors).

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DISCLOSURES

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Table 1. Baseline characteristics by mtDNA haplogroup

	Haplotype					
	H	**J**	**T**	**Uk**	**Others***	**All**
			Participant-level			
	n=116	**n=17**	**n=26**	**n=61**	**n=35**	**n=255**
Age, years, mean(sd)	60.7 (9.0)	60.4 (7.6)	63.6 (8.4)	62.2 (8.3)	59.9 (9.1)	61.3 (8.7)
Sex, Male (%)	45 (38.8)	8 (47.1)	8 (30.8)	24 (39.3)	7 (20.0)	92 (36.1)
BMI (Kg/m^2), mean(sd)	28.7 (4.6)	27.1 (3.8)	28.3 (4.8)	28.5 (4.3)	29.2 (3.9)	28.6 (4.4)
Normal (18.5-24.9 kg) (%)	23 (19.8)	7 (41.2)	6 (23.1)	13 (21.3)	6 (17.1)	55 (21.6)
Overweight (25-29.9 kg) (%)	54 (46.6)	6 (35.3)	11 (42.3)	25 (41.0)	13 (37.1)	109 (42.7)
Obese (≥30 kg) (%)	39 (33.6)	4 (23.5)	9 (34.6)	23 (37.7)	16 (45.7)	91 (35.7)
			Knee-level			
	n=126	**n=17**	**n=29**	**n=67**	**n=38**	**n=277**
History of knee injury (%)	44 (35.2)	6 (35.3)	3 (10.3)	14 (21.5)	5 (13.2)	72 (26.3)
History of knee surgery or arthroscopy (%)	10 (8.0)	2 (11.8)	0 (0.0)	4 (6.0)	0 (0.0)	16 (5.8)

Abbreviations: BMI, Body Mass Index; sd, standard deviation

*Others includes mtDNA haplogroups with a frequency < 5%.

Table 2. Mitochondrial DNA haplogroups and association with synovitis and bone marrow lesions

Haplogroup	MRI-detected Structural Features						
	Feature Present[a] (%)	RR	(95%CI)	P-value	Adjusted[b] RR	(95%CI)	P-value
Effusion-Synovitis and Hoffa-synovitis							
	Hoffa's synovitis, Moderate/Severe						
H	49 (10.1)	1.00	(reference)		1.00	(reference)	
J	1 (1.7)	0.16	(0.02, 1.19)	0.074	0.16	(0.02, 1.16)	0.070
T	11 (9.7)	0.96	(0.37, 2.51)	0.939	0.96	(0.37, 2.52)	0.938
Uk	26 (9.4)	0.93	(0.46, 1.90)	0.847	0.91	(0.45, 1.85)	0.800
Others	5 (3.5)	0.34	(0.10, 1.15)	0.083	0.40	(0.12, 1.36)	0.142
	Effusion synovitis, Medium/Large						
H	84 (17.3)	1.00	(reference)		1.00	(reference)	
J	6 (9.5)	0.55	(0.20, 1.51)	0.246	0.55	(0.20, 1.52)	0.248
T	24 (21.2)	1.23	(0.69, 2.17)	0.485	1.25	(0.70, 2.23)	0.443
Uk	36 (13.0)	0.75	(0.47, 1.22)	0.246	0.75	(0.46, 1.22)	0.248
Others	15 (10.3)	0.60	(0.29, 1.22)	0.156	0.61	(0.30, 1.24)	0.168
	Hoffa's synovitis (Moderate/Severe) or Effusion-synovitis (Medium/Large)						
H	113 (23.3)	1.00	(reference)		1.00	(reference)	
J	7 (11.1)	0.48	(0.20, 1.15)	0.099	0.46	(0.19, 1.12)	0.086
T	32 (28.3)	1.22	(0.75, 1.97)	0.428	1.25	(0.77, 2.02)	0.373
Uk	53 (19.2)	0.82	(0.55, 1.25)	0.359	0.82	(0.54, 1.24)	0.349
Others	20 (13.8)	0.59	(0.33, 1.06)	0.079	0.62	(0.35, 1.11)	0.111
Bone Marrow Lesions (≥33% subregional volume)							
	Whole knee						
H	208 (42.9)	1.00	(reference)		1.00	(reference)	
J	23 (36.5)	0.85	(0.51, 1.43)	0.540	0.80	(0.46, 1.38)	0.424
T	49 (43.4)	1.01	(0.67, 1.53)	0.958	0.99	(0.66, 1.48)	0.946
Uk	100 (36.2)	0.84	(0.62, 1.15)	0.282	0.83	(0.61, 1.12)	0.219
Others	52 (35.9)	0.84	(0.57, 1.23)	0.359	0.87	(0.59, 1.28)	0.475
	Whole knee (no PFJ)						
H	91 (18.8)	1.00	(reference)		1.00	(reference)	
J	2 (3.2)	0.17	(0.05, 0.64)	0.009	0.15	(0.04, 0.57)	0.005
T	17 (15.0)	0.80	(0.35, 1.82)	0.597	0.80	(0.36, 1.74)	0.568
Uk	45 (16.3)	0.87	(0.56, 1.36)	0.539	0.83	(0.54, 1.29)	0.417
Others	8 (5.5)	0.29	(0.14, 0.63)	0.002	0.34	(0.16, 0.73)	0.006
	Medial compartment						
H	79 (16.3)	1.00	(reference)		1.00	(reference)	
J	2 (3.2)	0.19	(0.05, 0.74)	0.016	0.17	(0.05, 0.64)	0.009
T	10 (8.9)	0.54	(0.19, 1.59)	0.266	0.55	(0.19, 1.56)	0.260
Uk	29 (10.5)	0.65	(0.37, 1.12)	0.118	0.62	(0.36, 1.07)	0.086
Others	4 (2.8)	0.17	(0.06, 0.46)	0.001	0.20	(0.08, 0.55)	0.002
	Lateral compartment						

H	23 (4.7)	1.00	(reference)		1.00	(reference)	
J	0 (0.0)	…	…	…	…	…	…
T	9 (8.0)	1.68	(0.53, 5.32)	0.378	1.64	(0.57, 4.74)	0.358
Uk	18 (6.5)	1.38	(0.56, 3.37)	0.487	1.34	(0.56, 3.23)	0.516
Others	5 (3.5)	0.73	(0.23, 2.37)	0.603	0.80	(0.23, 2.80)	0.730
PFJ							
H	140 (28.9)	1.00	(reference)		1.00	(reference)	
J	22 (34.9)	1.21	(0.67, 2.16)	0.527	1.21	(0.67, 2.19)	0.519
T	44 (38.9)	1.35	(0.83, 2.19)	0.230	1.30	(0.80, 2.10)	0.284
Uk	76 (27.5)	0.95	(0.62, 1.45)	0.819	0.93	(0.61, 1.42)	0.733
Others	46 (31.7)	1.10	(0.68, 1.76)	0.703	1.13	(0.70, 1.80)	0.622

Abbreviations: PFJ, Patello-Femoral Joint; RR, Relative Risk; CI, Confidence Interval

[a]Number of MRIs with feature present with at least moderate/medium severity/size, with repeated annual MRIs for each knee.

[b]Adjusted for sex, age, and BMI

Table 3. Mitochondrial DNA haplogroups and association with cartilage damage and meniscal damage

Haplogroup	MRI-detected Structural Features						
	Feature Present[a] (%)	RR	(95%CI)	P-value	Adjusted[b] RR	(95%CI)	P-value
Cartilage Damage							
	Whole knee						
H	446 (92.0)	1.00	(reference)		1.00	(reference)	
J	55 (87.3)	0.95	(0.80, 1.13)	0.551	0.97	(0.82, 1.13)	0.681
T	99 (87.6)	0.95	(0.83, 1.09)	0.489	0.93	(0.82, 1.06)	0.302
Uk	233 (84.4)	0.92	(0.82, 1.02)	0.119	0.91	(0.82, 1.01)	0.070
Others	128 (88.3)	0.96	(0.87, 1.06)	0.426	0.97	(0.88, 1.06)	0.468
	Whole knee (no PFJ)						
H	305 (62.9)	1.00	(reference)		1.00	(reference)	
J	42 (66.7)	1.06	(0.77, 1.46)	0.719	1.05	(0.77, 1.42)	0.772
T	72 (63.7)	1.01	(0.79, 1.30)	0.917	0.95	(0.73, 1.23)	0.695
Uk	159 (57.6)	0.92	(0.74, 1.13)	0.421	0.90	(0.74, 1.09)	0.290
Others	81 (55.9)	0.89	(0.68, 1.16)	0.380	0.92	(0.71, 1.20)	0.532
	Medial compartment						
H	229 (47.2)	1.00	(reference)		1.00	(reference)	
J	20 (31.8)	0.67	(0.36, 1.24)	0.206	0.72	(0.42, 1.25)	0.246
T	44 (38.9)	0.82	(0.55, 1.24)	0.351	0.81	(0.55, 1.20)	0.299
Uk	108 (39.1)	0.83	(0.61, 1.12)	0.221	0.83	(0.62, 1.10)	0.193
Others	61 (42.1)	0.89	(0.62, 1.29)	0.542	0.95	(0.64, 1.41)	0.792
	Lateral compartment						
H	159 (32.8)	1.00	(reference)		1.00	(reference)	
J	28 (44.4)	1.36	(0.75, 2.46)	0.318	1.35	(0.74, 2.47)	0.325
T	38 (33.6)	1.03	(0.60, 1.75)	0.926	1.02	(0.61, 1.73)	0.933
Uk	100 (36.2)	1.11	(0.76, 1.62)	0.606	1.10	(0.75, 1.61)	0.622
Others	47 (32.4)	0.99	(0.61, 1.60)	0.963	1.03	(0.64, 1.67)	0.894
	PFJ						
H	366 (75.5)	1.00	(reference)		1.00	(reference)	
J	49 (77.8)	1.03	(0.79, 1.34)	0.824	1.08	(0.85, 1.37)	0.543
T	90 (79.7)	1.06	(0.86, 1.30)	0.611	1.02	(0.83, 1.25)	0.855
Uk	206 (74.6)	0.99	(0.84, 1.17)	0.897	0.97	(0.82, 1.14)	0.728
Others	108 (74.5)	0.99	(0.79, 1.23)	0.906	0.98	(0.80, 1.20)	0.820
Meniscus Tear/Maceration							
	Whole knee						
H	263 (54.2)	1.00	(reference)		1.00	(reference)	
J	44 (69.8)	1.29	(0.94, 1.77)	0.116	1.11	(0.77, 1.61)	0.566
T	61 (54.0)	1.00	(0.72, 1.38)	0.978	1.06	(0.82, 1.37)	0.661
Uk	181 (65.6)	1.21	(0.98, 1.49)	0.071	1.14	(0.94, 1.37)	0.187
Others	51 (35.2)	0.65	(0.43, 0.97)	0.034	0.70	(0.47, 1.03)	0.070
	Medial compartment						

H	232 (47.8)	1.00	(reference)		1.00	(reference)	
J	29 (46.0)	0.96	(0.57, 1.63)	0.886	0.85	(0.53, 1.37)	0.509
T	40 (35.4)	0.74	(0.47, 1.16)	0.186	0.86	(0.61, 1.21)	0.374
Uk	136 (49.3)	1.03	(0.78, 1.35)	0.832	0.97	(0.77, 1.23)	0.799
Others	41 (28.3)	0.59	(0.36, 0.97)	0.037	0.63	(0.38, 1.05)	0.075
	Lateral compartment						
H	44 (9.1)	1.00	(reference)		1.00	(reference)	
J	20 (31.8)	3.50	(1.43, 8.54)	0.006	3.35	(1.30, 8.61)	0.012
T	32 (28.3)	3.12	(1.43, 6.82)	0.004	3.06	(1.47, 6.39)	0.003
Uk	69 (25.0)	2.76	(1.45, 5.24)	0.002	2.73	(1.45, 5.13)	0.002
Others	18 (12.4)	1.37	(0.53, 3.50)	0.513	1.51	(0.57, 3.96)	0.404
Meniscus Extrusion (≥3mm)							
	Whole knee						
H	95 (19.6)	1.00	(reference)		1.00	(reference)	
J	11 (17.5)	0.89	(0.32, 2.50)	0.827	0.91	(0.32, 2.59)	0.866
T	34 (30.1)	1.54	(0.92, 2.57)	0.101	1.40	(0.83, 2.35)	0.203
Uk	50 (18.1)	0.92	(0.59, 1.46)	0.736	0.88	(0.57, 1.37)	0.569
Others	19 (13.1)	0.67	(0.34, 1.30)	0.234	0.69	(0.36, 1.32)	0.263
	Medial compartment						
H	91 (18.8)	1.00	(reference)		1.00	(reference)	
J	8 (12.7)	0.68	(0.19, 2.38)	0.543	0.70	(0.20, 2.48)	0.583
T	21 (19.6)	0.99	(0.54, 1.81)	0.975	0.93	(0.51, 1.70)	0.824
Uk	42 (15.2)	0.81	(0.49, 1.35)	0.420	0.77	(0.47, 1.28)	0.315
Others	19 (13.1)	0.70	(0.36, 1.36)	0.292	0.73	(0.38, 1.43)	0.363
	Lateral compartment						
H	4 (0.8)	1.00	(reference)		1.00	(reference)	
J	3 (4.8)	5.77	(0.60, 55.70)	0.130	6.22	(0.66, 58.83)	0.111
T	13 (11.5)	13.95	(3.04, 64.09)	0.001	11.70	(2.90, 47.22)	0.001
Uk	8 (2.9)	3.51	(0.77, 16.07)	0.105	3.34	(0.72, 15.39)	0.123
Others	0 (0.0)	…	…	…	…	…	…

Abbreviations: PFJ, Patello-Femoral Joint; RR, Relative Risk; CI, Confidence Interval

[a]Number of MRIs with feature present with at least moderate/medium severity/size, with repeated annual MRIs for each knee.

[b]Adjusted for sex, age, and BMI

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