Online Supplementary Material

Materials and Methods

Study subjects. Case ascertainment has been described previously[2]. In brief, cases that were subjected to the GWAS and used in this study were collected from eight locations in the arcOGEN consortium (Edinburgh, London, Nottingham, Newcastle, Oxford, Sheffield, Southampton and Wansbeck (Northumbria NHS Foundation Trust)). All cases were collected in the UK, were unrelated and of European origin. The phenotype was determined by two criteria; radiographic evidence of disease and clinical evidence of disease to a level requiring joint replacement. Each investigator defined radiographic disease as a Kellgren-Lawrence (KL)[18] grade of ≥2. We used 5122 publicly available population-based UK controls from the Wellcome Trust Case Control Consortium 2 (WTCC2) study: the 1958 Birth Cohort (WTCCC-58C) and the UK Blood Service control group (WTCCC-NBS) forming part of the Wellcome Trust Case Control Consortium study and genotyped in WTCCC2.

mtDNA Haplogroup determination. The hierarchical relationship amongst mtDNA variants is represented at www.phylotree.org. Each array variant (n=36, post QC), in each subject (n=12515, post QC), was compared to the rCRS and used to identify haplogroup specific motifs. Assignment of haplogroup was performed according to published criteria (Torroni 1996), for example haplogroup J is defined by variants m.11251 *and* [m.295+m.489+m.10398] (Supplementary Table 1). If a no-call was detected in a major-haplogroup defining SNP, then clade specific sub-type variants were used to identify mtDNA haplogroup. Based on available genotyping data 98.48% of subjects were assigned to a European haplogroup.

Table S1. European haplogroup definitions for Illumina array genotyping data. Table showing the major European haplogroups (H, V, J, T, U, K, W, X, I,) and corresponding sub-haplogroups. Shown are the non-rCRS (thus, non-haplogroup-H) branch SNPs, array specific 'super-haplogroup' SNPs (i.e. JT=11251), and array specific haplogroup defining SNPs (i.e. J=295+489+10398).

Major European haplogroups	***rCRS Branch SNPs***	***'Super-haplogroup' SNPs***	***Array haplogroup SNPs***
H	-	-	-
V	750, 1438, 2706, 4769	15904	15904
J	750, 1438, 2706, 4769, 14766	11251	295, 489, 10398
T	750, 1438, 2706, 4769, 14766	11251	4917, 10463, 15928
U	750, 1438, 2706, 4769, 14766	-	11467, 12308, 12372
K (aka – U8b)	750, 1438, 2706, 4769, 14766	11467,12308, 12372, 9698, 3480	10550, 14798
W	750, 1438, 2706, 4769, 14766, 12705	5046, 12414	5460
X	750, 1438, 2706, 4769, 14766, 12705	-	6221, 16278
I	750, 1438, 2706, 4769, 14766, 12705	1719, 10238, 13780, 10398, 15043, 250, 15294	10034, 16129, 16391

European sub-haplogroups	***rCRS Branch SNPs***	***'Super-haplogroup' SNPs***	***Array haplogroup SNPs***
I1	750, 1438, 2706, 4769, 14766, 12705	1719, 10238, 13780, 10398, 15043, 250, 15924, 10034, 16129, 16391	6734
I2	750, 1438, 2706, 4769, 14766, 12705	1719, 10238, 13780, 10398, 15043, 250, 15924, 10034, 16129, 16391	15758
I5	750, 1438, 2706, 4769, 14766, 12705	1719, 10238, 13780, 10398, 15043, 250, 15924, 10034, 16129, 16391	14233
X1	750, 1438, 2706, 4769, 14766, 12705	6221, 16278	16278
X2	750, 1438, 2706, 4769, 14766, 12705	6221, 16278	1719
J2	750, 1438, 2706, 4769, 14766	11251, 295, 489, 10398	15257
T1	750, 1438, 2706, 4769, 14766	11251, 4917, 10463, 15928	16163
T2	750, 1438, 2706, 4769, 14766	11251, 4917, 10463, 15928	14233
U5	750, 1438, 2706, 4769, 14766	11467, 12308, 12372	16270

U6	750, 1438, 2706, 4769, 14766	11467, 12308, 12372	3348
K1	750, 1438, 2706, 4769, 14766	11467, 12308, 12372, 9698, 3480, 10550, 14798	10398
K2	750, 1438, 2706, 4769, 14766	11467, 12308, 12372, 9698, 3480, 10550, 14798	9716
V1	750, 1438, 2706, 4769	15904	8869
V2	750, 1438, 2706, 4769	15904	13105
V6	750, 1438, 2706, 4769	15904	16162
H1	750, 4769, 1438	-	3010
H4	750, 4769, 1438	-	5004

Table S2. Comparison of mtDNA variant frequencies between cases and controls, stratified by gender, joint involvement, and method of ascertainment. Ascertainment groups: hip cases only = isolated hip OA on diagnosis; knee cases only = isolated knee OA on diagnosis; both cases only = both hip and knee OA on diagnosis; X-ray = diagnosis radiologically. Uncorrected chi-squared comparison of mtDNA variant frequencies in cohort 1 (*ARC1*, n = 3093 and *WTCCC-58C*, n = 2640) and cohort 2 (*ARC2*, n = 4300 and *WTCCC-NBS*, n = 2482), stratified by i) gender, ii) affected joint type (hip, knee and both) and iii) diagnosis ascertainment (arthro=arthroplasty and X-ray). The number of association tests reaching a nominal significance level are shown below the number of cases and controls contributing to each specific stratification. Uncorrected = uncorrected P-value; corrected (x48) = corrected for 48 different SNPs; and corrected (x336) = corrected for 99 different SNPs and each one of the seven phenotypic groups in two cohorts. n.a.= not available.

		Cohort 1							***Cohort 2***						
		Males v Males	*Females v Females*	*Hip cases only*	*Knee cases only*	*Both cases only*	*Arthro cases only*	*X-ray cases only*	*Males v Males*	*Females v Females*	*Hip cases only*	*Knee cases only*	*Both cases only*	*Arthro cases only*	*X-ray cases only*
	Cases n=	1136	1936	1503	1398	192	676	1270	1793	2507	1782	2071	447	3969	331
	Controls n=	1363	1277	2640	2640	2640	2640	2640	1228	1254	2482	2482	2482	2482	2482
Uncorrected	*P=<0.05*	1	7	3	3	1	3	2	2	4	4	6	4	8	1
Corrected (x48)	*P=<0.001*	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Corrected (x336)	*P=<0.0001*	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Array ID	***rCRS***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***	***P***
MitoC295T	295	0.600	0.724	0.393	0.922	0.512	0.586	0.701	0.112	0.790	0.117	0.265	0.597	0.260	0.160
MitoT491C	489	0.854	0.322	0.771	0.268	0.606	0.468	0.461	0.315	0.611	0.375	0.825	0.285	0.851	0.356
MitoG752A	750	0.311	0.710	0.039	0.846	0.644	0.306	0.610	0.338	0.688	0.328	0.925	0.836	0.707	0.509
MitoG1440A	1438	0.220	0.938	0.072	0.400	0.324	0.123	0.568	0.513	0.639	0.539	0.511	0.672	0.387	0.791
MitoG1721A	1719	0.842	0.217	0.579	0.487	0.914	0.585	0.535	0.451	0.337	0.825	0.894	0.848	0.750	0.687
MitoT2160C	2158	0.954	0.088	0.345	0.391	0.228	0.310	0.274	0.427	0.705	0.149	0.851	0.809	0.565	0.224
MitoG2708A	2706	0.728	0.986	0.211	0.297	0.315	0.507	0.383	0.991	0.789	0.527	0.889	0.079	0.814	0.625
MitoG3012A	3010	0.563	0.399	0.773	0.199	0.198	0.495	0.207	0.319	0.463	0.278	0.511	0.830	0.951	0.326

MitoA3349G	3348	0.063	0.064	0.068	0.040	0.046	0.026	0.060	0.086	0.064	0.041	0.026	0.048	0.070	0.526
MitoT3395C	3394	0.622	0.451	0.442	0.892	0.273	0.893	0.825	0.503	0.864	0.348	0.933	0.375	0.724	0.893
MitoA3481G	3480	0.812	0.629	0.596	0.545	0.904	0.412	0.246	0.380	0.230	0.491	0.254	0.736	0.621	0.583
MitoT4337C	4336	0.326	0.765	0.859	0.864	0.127	0.439	0.152	0.047	0.253	*n.a.*	0.944	0.253	0.032	0.490
MitoT4562C	4561	0.322	0.387	0.542	0.820	0.763	0.421	0.602	0.069	0.140	0.070	0.130	0.335	0.017	0.659
MitoA4918G	4917	0.699	0.583	0.420	0.400	0.773	0.771	0.662	0.269	0.162	0.259	0.243	0.010	0.500	0.657
MitoT5005C	5004	0.433	0.523	0.273	0.348	0.428	0.473	0.308	0.688	0.377	0.809	0.235	0.367	0.240	0.372
MitoG5047A	5046	0.089	0.235	0.801	0.931	0.744	0.688	0.824	0.212	0.455	0.951	0.827	0.831	0.616	0.286
MitoG5461A	5460	0.168	0.931	0.769	0.159	0.964	0.542	0.279	0.219	0.216	0.898	0.573	0.866	0.933	0.307
MitoA5657G	5656	0.923	0.224	0.516	0.462	0.689	0.820	0.068	0.236	0.834	0.319	0.669	0.106	0.417	0.409
MitoT6153C	6152	0.607	0.420	0.478	0.660	0.784	0.761	0.430	0.156	0.501	0.830	0.576	0.378	0.730	0.709
MitoT6222C	6221	0.975	0.370	0.386	0.945	0.920	0.345	0.742	0.949	0.483	0.603	0.487	0.085	0.544	0.801
MitoG6261A	6260	0.970	0.093	0.602	0.274	0.248	0.250	0.499	0.212	0.111	0.189	0.930	0.200	0.026	0.634
MitoG6735A	6734	0.931	0.143	0.636	0.392	0.379	0.451	0.436	0.611	0.032	0.054	0.387	1.000	0.171	0.658
MitoA7769G	7768	0.623	0.166	0.381	0.930	0.929	0.676	0.561	0.428	0.627	0.704	0.887	0.333	0.893	0.215
MitoA8870G	8869	0.038	0.014	0.010	0.060	0.550	0.010	0.130	0.117	0.064	0.120	0.020	0.394	0.012	0.018
MitoA9668G	9667	0.240	0.302	0.582	0.902	0.592	0.392	0.560	0.866	0.261	0.693	0.179	0.479	0.497	0.232
MitoT9699C	9698	0.376	0.053	0.331	0.026	0.379	0.158	0.053	0.867	0.764	0.698	0.256	*n.a.*	*n.a.*	0.260
MitoT9717C	9716	0.656	0.063	0.151	0.569	0.869	0.065	0.686	0.128	0.315	0.016	0.431	0.650	0.056	0.756
MitoT9900C	9899	0.070	0.116	0.687	0.813	0.181	0.810	0.585	0.656	0.319	0.305	0.312	0.751	0.641	*n.a.*
MitoT10035C	10034	0.987	0.016	0.151	0.097	0.995	0.101	0.202	0.323	0.733	0.293	0.280	0.355	0.892	0.136
MitoT10239C	10238	0.846	0.031	0.237	0.171	0.928	0.253	0.178	0.397	0.727	0.420	0.400	0.360	0.874	0.587
MitoG10399A	10398	0.928	0.020	0.173	0.011	0.391	0.083	0.022	0.132	*n.a.*	0.463	0.365	*n.a.*	*n.a.*	0.165
MitoT10464C	10463	0.667	0.537	0.481	0.509	0.469	0.818	0.667	0.497	0.183	0.428	0.307	0.030	0.096	0.441
MitoA10551G	10550	0.761	0.624	0.571	0.569	0.916	0.390	0.260	0.393	0.319	0.374	0.262	0.795	0.715	0.535
MitoA11252G	11251	0.724	0.467	0.793	0.083	0.451	0.569	0.294	0.739	0.173	0.886	0.358	*n.a.*	0.147	0.382

MitoA11468G	11467	0.882	0.049	0.079	0.368	0.821	0.111	0.332	0.950	0.356	0.948	0.381	0.482	0.396	0.538
MitoA12309G	12308	0.943	0.083	0.103	0.369	0.975	0.159	0.600	0.358	0.039	0.167	0.038	0.183	0.017	0.843
MitoG12373A	12372	0.421	0.169	0.010	0.118	0.657	0.012	0.137	0.208	0.014	0.075	0.013	0.083	0.040	0.982
MitoA13106G	13105	0.119	0.267	0.158	0.417	0.845	0.091	0.118	0.786	0.892	0.015	0.042	0.235	0.020	0.837
MitoA13781G	13780	0.699	0.011	0.073	0.078	0.638	0.059	0.103	0.204	0.690	0.460	0.280	0.351	0.796	0.349
MitoA14234G	14233	0.677	0.949	0.368	0.345	0.920	0.828	0.784	0.037	0.033	0.049	0.025	*n.a.*	0.010	0.933
MitoG15044A	15043	0.679	0.186	0.208	0.416	0.947	0.489	0.158	0.225	0.943	0.897	0.394	0.479	0.593	0.705
MitoG15258A	15257	0.834	0.139	0.644	0.130	0.556	0.226	0.440	0.754	0.638	0.735	0.290	0.669	0.753	0.162
MitoA15759G	15758	0.868	0.820	0.703	0.689	0.497	0.937	0.603	0.469	0.211	0.509	0.236	0.177	0.294	0.067
MitoC15905T	15904	0.089	0.526	0.624	0.424	0.662	0.319	0.977	0.271	0.944	0.058	0.828	0.881	0.274	0.340
MitoA15925G	15924	0.680	0.010	0.154	0.108	0.319	0.217	0.038	0.714	0.943	0.485	0.741	0.630	0.633	0.978
MitoG15929A	15928	0.768	0.617	0.374	0.326	0.606	0.764	0.562	0.460	0.234	0.451	0.379	0.019	0.125	0.653
MitoG16130A	16129	0.943	0.055	0.234	0.213	0.860	0.159	0.249	0.526	0.437	0.172	0.439	0.774	0.723	0.502
MitoA16163G	16162	0.990	0.659	0.302	0.896	0.211	0.402	0.834	0.619	0.684	0.522	0.981	0.127	0.975	0.894

Table S3. Comparison of mtDNA haplogroup frequencies between cases and controls, stratified by gender, joint involvement, and method of ascertainment Uncorrected chi-squared comparison of haplogroup frequencies in cohort 1 (*ARC1*, n = 3093 and *WTCCC-58C*, n = 4300) and cohort 2 (*ARC2*, n = 2640 and *WTCCC-NBS*, n = 2482), stratified by; a) gender, b) affected joint type and c) diagnosis ascertainment.

a) Stratified by gender

	Cohort 1		Cohort 2	
Haplogroup	*Male*	*Female*	*Male*	*Female*
H	9.09E-01	6.13E-01	8.37E-01	7.53E-01
V	1.24E-01	5.67E-01	2.73E-01	9.46E-01
J	7.82E-01	2.45E-01	9.23E-01	2.90E-01
T	6.41E-01	5.21E-01	2.71E-01	1.79E-01
U	9.81E-01	7.00E-03	7.10E-02	1.76E-01
K	7.75E-01	5.77E-01	3.46E-01	2.49E-01
W	9.60E-02	2.87E-01	2.43E-01	1.45E-01
X	9.86E-01	5.17E-01	9.87E-01	1.24E-01
I	9.06E-01	1.70E-02	4.46E-01	8.99E-01
O	3.36E-01	8.70E-01	1.03E-01	8.72E-01

b) Stratified by joint type

	Cohort 1			Cohort 2		
Haplogroup	*Hip*	*Knee*	*Both*	*Hip*	*Knee*	*Both*
H	4.20E-01	1.53E-01	2.21E-01	3.25E-01	6.60E-01	1.17E-01
V	6.14E-01	4.90E-01	6.59E-01	5.90E-02	8.24E-01	8.78E-01
J	6.33E-01	2.19E-01	6.43E-01	9.56E-01	4.98E-01	1.04E-01
T	4.12E-01	3.71E-01	7.57E-01	2.75E-01	2.57E-01	1.00E-02
U	8.30E-02	1.81E-01	8.80E-01	3.70E-02	1.41E-01	2.07E-01
K	6.04E-01	5.39E-01	9.00E-01	4.51E-01	2.83E-01	7.65E-01
W	7.66E-01	9.66E-01	7.28E-01	8.14E-01	7.96E-01	9.99E-01
X	5.06E-01	9.02E-01	8.54E-01	7.84E-01	1.83E-01	2.40E-02
I	1.07E-01	1.47E-01	6.59E-01	4.67E-01	4.18E-01	2.70E-01
O	6.46E-01	6.43E-01	1.46E-01	3.60E-01	2.52E-01	5.21E-01

c) Stratified by diagnosis ascertainment

	Cohort 1		Cohort 2	
Haplogroup	Arthroplasy	X-ray	Arthroplasy	X-ray
H	8.56E-01	2.17E-01	7.47E-01	5.28E-01
V	3.61E-01	9.81E-01	2.77E-01	3.43E-01
J	3.91E-01	3.54E-01	3.99E-01	6.28E-01
T	7.72E-01	6.29E-01	5.50E-02	6.49E-01
U	2.19E-01	6.40E-02	2.00E-02	8.88E-01
K	4.20E-01	2.43E-01	6.78E-01	5.59E-01
W	6.53E-01	8.58E-01	9.56E-01	2.23E-01
X	4.17E-01	7.28E-01	2.42E-01	8.99E-01
I	1.07E-01	1.50E-01	8.14E-01	6.31E-01
O	5.53E-01	4.60E-01	1.94E-01	9.75E-01

Table S4. Chi-squared tests of association between groups of principal component analysis (PCA) clusters and disease in cohort 1 (ARC1 versus WTCCC 58C), cohort 2 (ARC2 versus WTCCC-NBS) and combined cases and controls. Uncorrected chi-squared comparison of PCA-cluster frequencies in cohort 1 (*ARC1*, n = 3099 and *WTCCC-58C*, n = 2618), cohort 2 (*ARC2*, n = 4311 and *WTCCC-NBS*, n = 2434), and combined cases (*ARC1+ARC2*, *n=7410*) versus combined controls (WTCCC-58c+-NBS, n=5052).

	Cohort 1			***Cohort 2***			***Combined***		
PCA Cluster	***F ARC1***	***F WTCCC-58C***	***P***	***F ARC2***	***WTCCCC-NBS***	***P***	***F Cases***	***F Con.***	***P***
1	400	300	1.0E-01	509	330	4.0E-02	909	630	7.6E-01
2	55	57	3.2E-01	77	51	4.2E-01	132	108	2.0E-01
3	85	96	5.6E-02	122	70	9.7E-01	207	166	1.3E-01
4	534	410	1.2E-01	701	389	7.9E-01	1235	799	2.5E-01
5	1071	926	5.4E-01	1543	850	4.9E-01	2614	1776	9.0E-01
6	330	294	5.1E-01	514	290	9.9E-01	844	584	7.9E-01
7	221	201	4.6E-01	291	178	4.1E-01	512	379	2.2E-01
8	40	32	9.0E-01	40	28	4.5E-01	80	60	6.3E-01
9	59	39	2.7E-01	70	28	1.5E-01	129	67	8.0E-02
10	304	263	8.0E-01	444	220	1.0E-01	748	483	3.4E-01
	3099	2618		4311	2434		7410	5052	