Supplementary Information of:

MtDNA meta-analysis reveals both phenotype specificity and allele heterogeneity: a model for differential association

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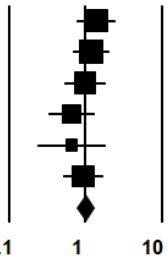
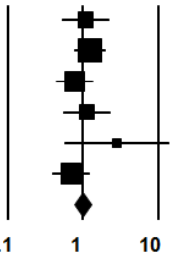
A AD - Haplogroup T

Study name	Odds ratio	Lower limit	Upper limit	p-Value
AD-1	1.379	0.767	2.482	0.283
AD-2	1.189	0.679	2.081	0.545
AD-9	0.977	0.523	1.826	0.942
AD-10	0.661	0.328	1.332	0.247
AD-13	0.658	0.230	1.881	0.435
AD-14	0.938	0.512	1.717	0.834
Fixed	1.002	0.769	1.305	0.989



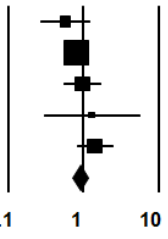
B AD - Haplogroup J

Study name	Odds ratio	Lower limit	Upper limit	p-Value
AD-1	1.088	0.525	2.254	0.821
AD-2	1.248	0.762	2.044	0.380
AD-9	0.781	0.439	1.389	0.400
AD-10	1.119	0.536	2.337	0.764
AD-13	2.806	0.570	13.814	0.205
AD-14	0.692	0.391	1.226	0.207
Fixed	0.987	0.757	1.285	0.920

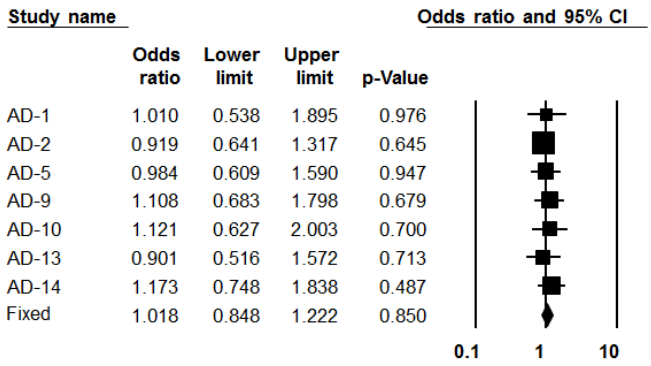


C AD - Haplogroup K

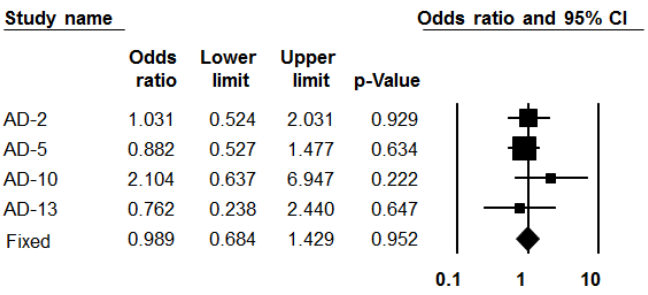
Study name	Odds ratio	Lower limit	Upper limit	p-Value
AD-1	0.569	0.264	1.226	0.150
AD-5	0.803	0.565	1.141	0.221
AD-9	0.966	0.551	1.691	0.902
AD-13	1.301	0.303	5.579	0.723
AD-14	1.419	0.806	2.497	0.225
Fixed	0.906	0.709	1.159	0.433



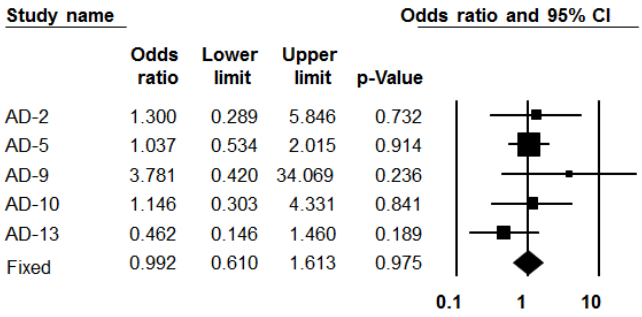
D AD - Haplogroup U



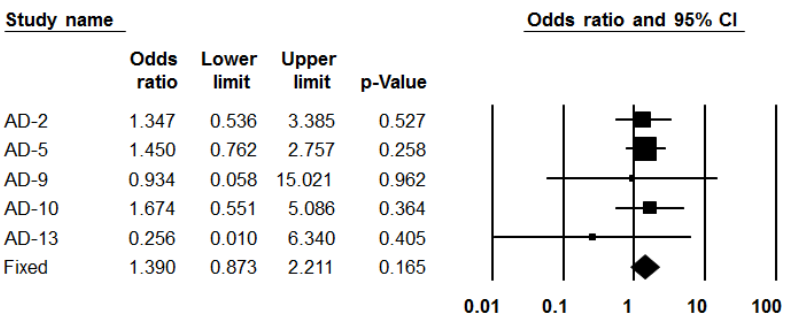
E AD - Haplogroup V



F AD - Haplogroup W

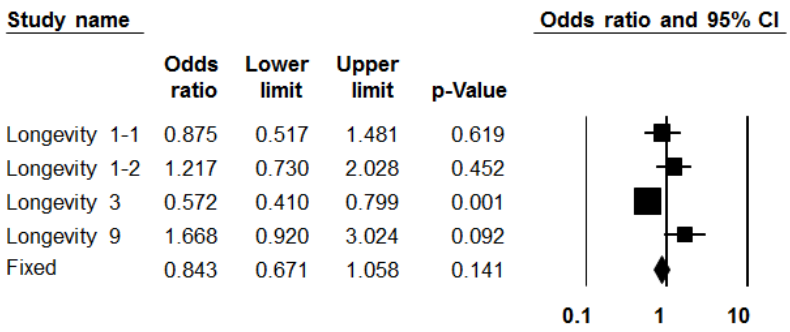


G AD - Haplogroup X

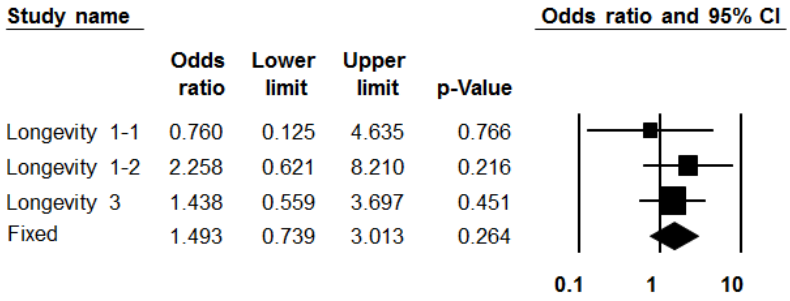


Supplementary Figure S1. Meta-analysis of previously reported AD and mtDNA haplogroup associations. A. Haplogroup T analysis. B. Haplogroup J analysis. C. Haplogroup K analysis. D. Haplogroup U analysis. E. Haplogroup V analysis. F. Haplogroup W analysis. G. Haplogroup X analysis.

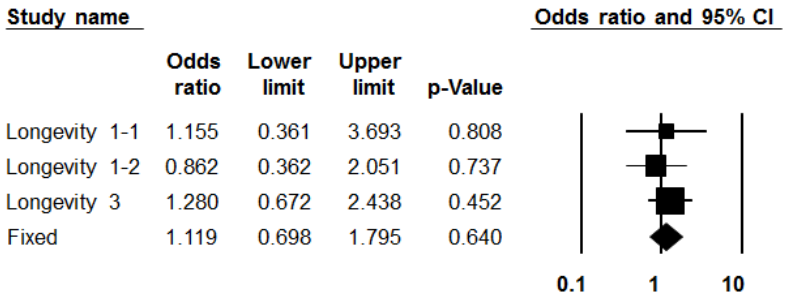
A Longevity - Haplogroup H



B Longevity - Haplogroup I

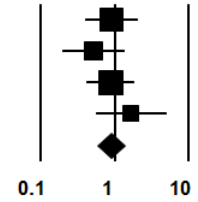


C Longevity - Haplogroup K



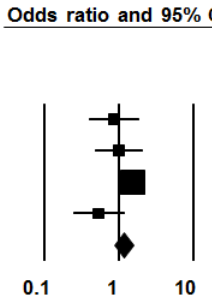
D Longevity - Haplogroup T

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Longevity 1-1	0.907	0.405	2.033	0.813
Longevity 1-2	0.518	0.196	1.372	0.186
Longevity 3	0.883	0.420	1.857	0.743
Longevity 9	1.653	0.549	4.976	0.372
Fixed	0.882	0.570	1.366	0.575



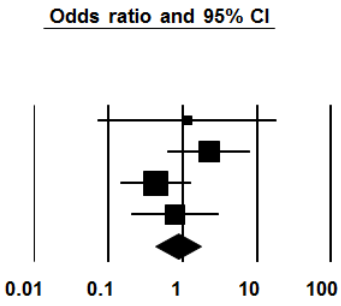
E Longevity - Haplogroup U

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Longevity 1-1	0.860	0.397	1.863	0.703
Longevity 1-2	0.996	0.468	2.118	0.992
Longevity 3	1.542	1.056	2.250	0.025
Longevity 9	0.532	0.237	1.193	0.126
Fixed	1.163	0.871	1.552	0.307



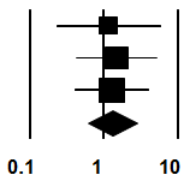
F Longevity - Haplogroup V

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Longevity 1-1	1.148	0.071	18.577	0.923
Longevity 1-2	2.258	0.621	8.210	0.216
Longevity 3	0.434	0.143	1.316	0.140
Longevity 9	0.786	0.202	3.066	0.729
Fixed	0.865	0.433	1.729	0.681

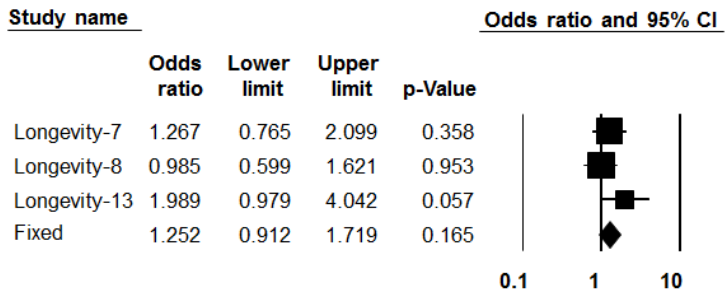


G Longevity - Haplogroup X

Study name	Odds ratio	Lower limit	Upper limit	p-Value
Longevity 1-1	1.151	0.227	5.824	0.865
Longevity 1-2	1.480	0.417	5.247	0.544
Longevity 3	1.276	0.400	4.068	0.680
Fixed	1.315	0.617	2.802	0.477

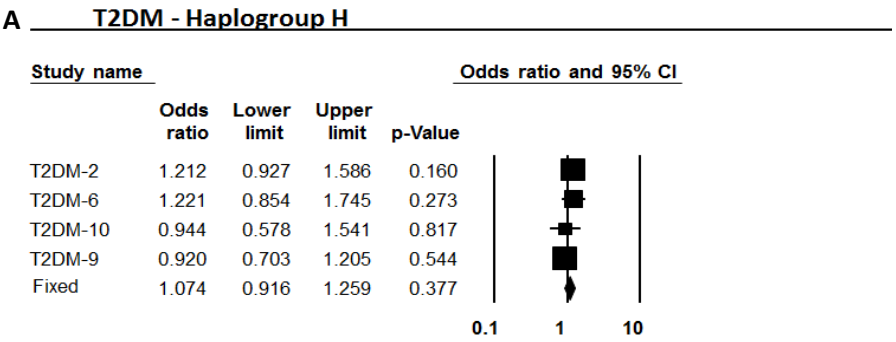


H Longevity – Asian - Haplogroup D

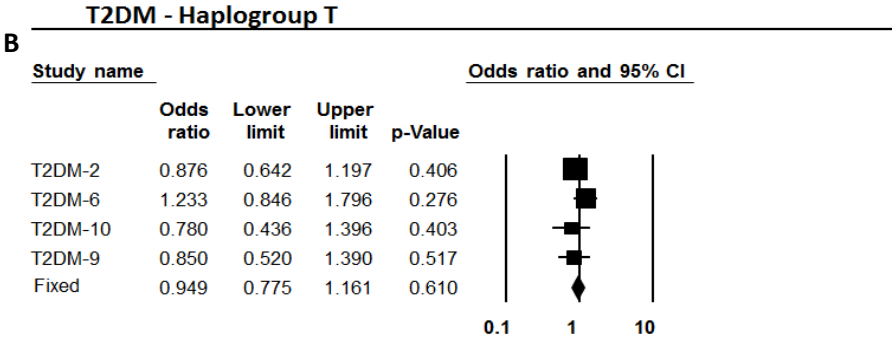


Supplementary Figure S2. Meta-analysis of previously reported Longevity mtDNA haplogroup associations. A. Haplogroup H analysis. B. Haplogroup I analysis. C. Haplogroup K analysis. D. Haplogroup T analysis. E. Haplogroup U analysis. F. Haplogroup V analysis. G. Haplogroup X analysis. H. Haplogroup D analysis.

A



B



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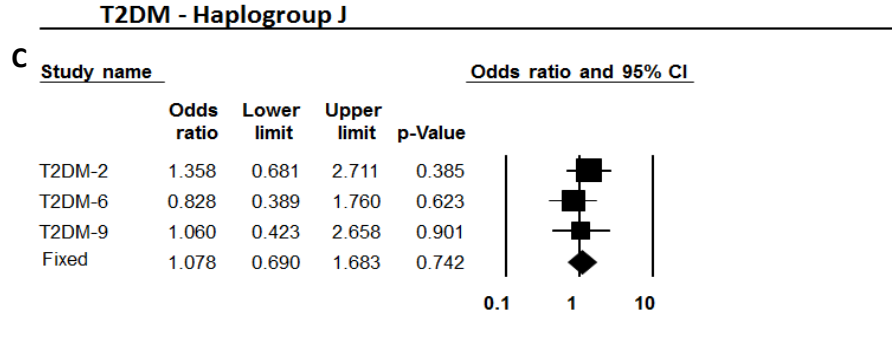

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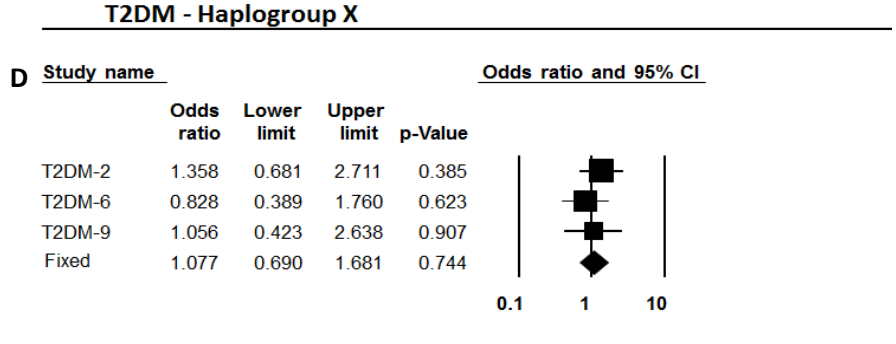
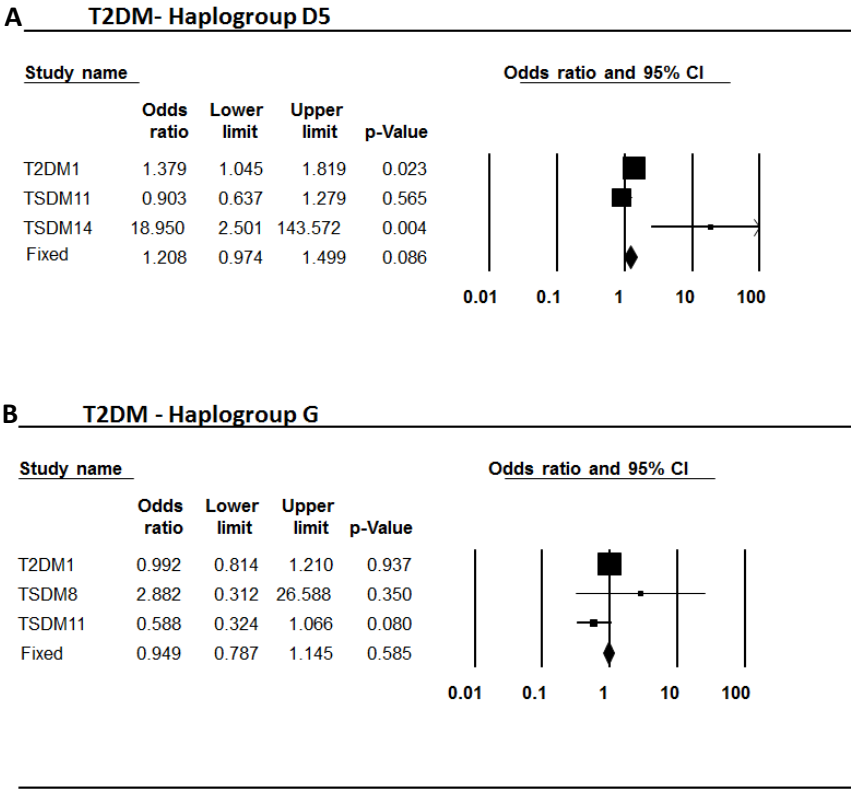
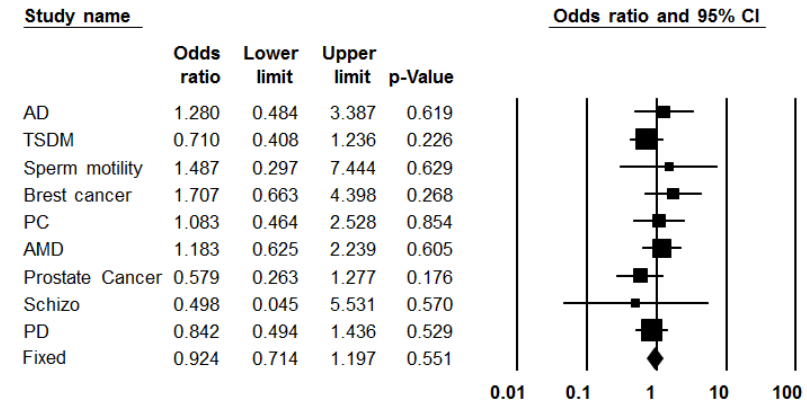


Supplementary Figure S3. Meta-analysis of previously reported T2DM in Caucasian population and mtDNA haplogroup associations. A. Haplogroup H analysis. B. Haplogroup T analysis. C. Haplogroup J analysis. D. Haplogroup X analysis.

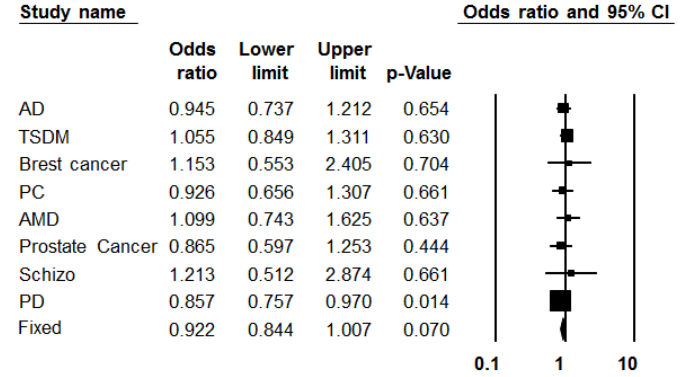


Supplementary Figure S4. Meta-analysis of previously reported T2DM in Asian population and mtDNA haplogroup associations. A. Haplogroup D5 analysis. B. Haplogroup G analysis.

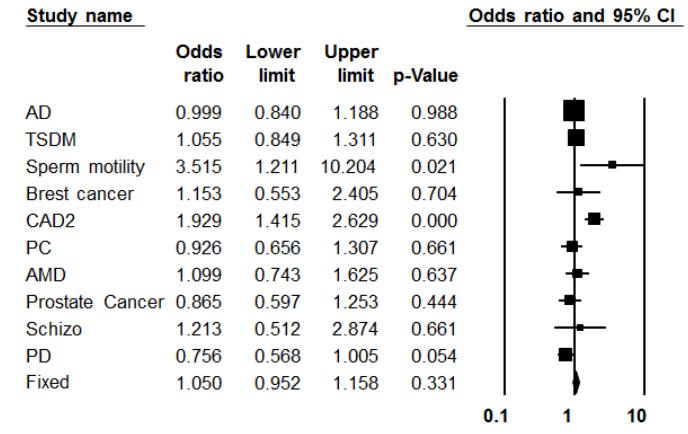
A Haplogroup I



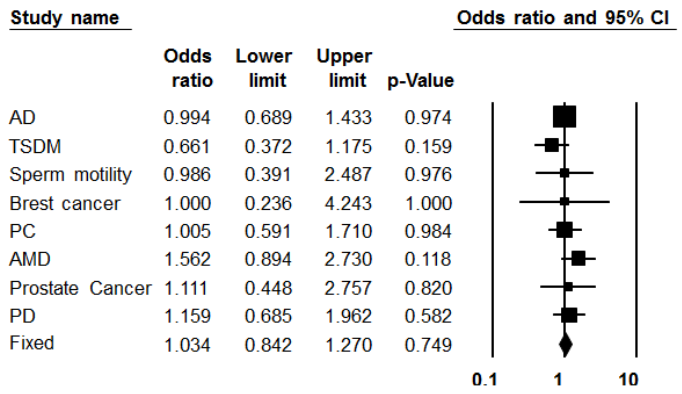
B Haplogroup T



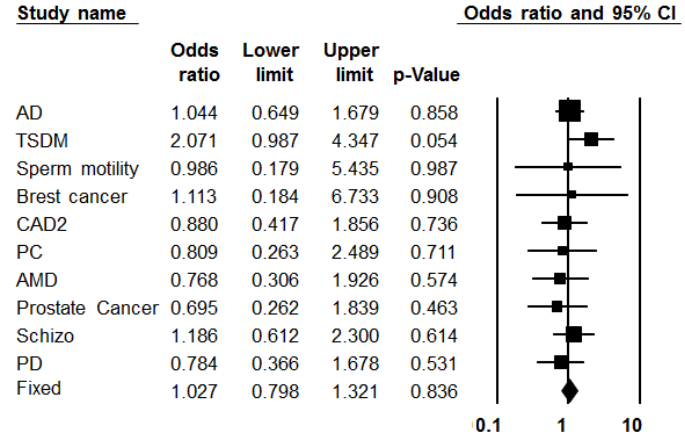
C Haplogroup U



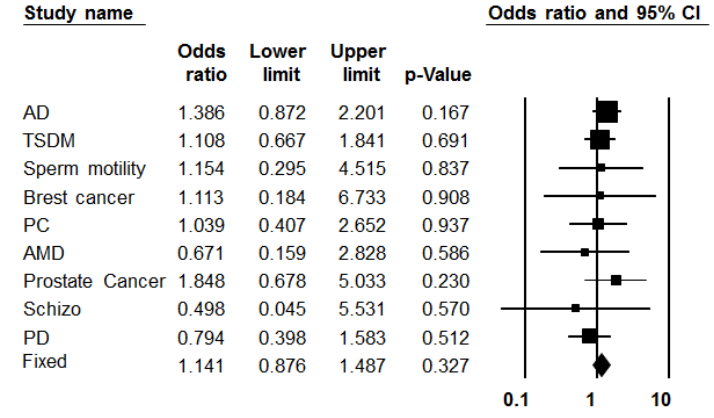
D Haplogroup V



E Haplogroup W



F Haplogroup X



Supplementary Figure S5. MtDNA haplogroup association with grouped phenotypes. Forest plot for the analysis of the different phenotype. AD - Alzheimer's

disease, T2DM-type 2 diabetes mellitus, PC- prostate cancer, AMD - Age-related macular degeneration, Schizo – Schizophrenia, PD- Parkinson's disease. A. Haplogroup I analysis. B. Haplogroup T analysis. C. Haplogroup U analysis. D. Haplogroup V analysis. E. Haplogroup W analysis. F. Haplogroup X analysis.

Supplementary Table S1. Search strategies

Search 1: PubMed, Scholar search through February 30, 2016 (" mitochondrial DNA association studies", "mitochondrial DNA haplogroup association studies", "mitochondrial DNA polymorphism")

Search 2 – per phenotype: PubMed, Scholar search through February 30, 2016

Alzheimer disease: "mitochondrial DNA association with Alzheimer disease", "mitochondrial DNA haplogroup association with Alzheimer disease"

Parkinson disease: "mitochondrial DNA association with Parkinson disease", "mitochondrial DNA haplogroup association with Parkinson disease"

Type 2 diabetes mellitus: "mitochondrial DNA association with T2DM", "mitochondrial DNA haplogroup association with T2DM ", " mitochondrial DNA association with Type 2 diabetes mellitus", "mitochondrial DNA haplogroup association with diabetes mellitus"

Schizophrenia: "mitochondrial DNA association with Schizophrenia", "mitochondrial DNA haplogroup association with Schizophrenia"

Longevity: " mitochondrial DNA association with Longevity", "mitochondrial DNA haplogroup association with Longevity"," mitochondrial DNA association with extreme longevity", "mitochondrial DNA haplogroup association with extreme longevity"

Age related macular degeneration (AMD): "mitochondrial DNA association with AMD", "mitochondrial DNA haplogroup association with AMD", "mitochondrial DNA association with Age related macular degeneration ", "mitochondrial DNA haplogroup association with Age related macular degeneration"

Sperm motility: "mitochondrial DNA association with sperm motility", "mitochondrial DNA haplogroup association with Sperm motility"

Cancer: "mitochondrial DNA association with cancer", "mitochondrial DNA haplogroup association with cancer"," mitochondrial DNA association with Breast cancer", "mitochondrial DNA haplogroup association with Breast cancer","mitochondrial DNA association with Prostate cancer motility", "mitochondrial DNA haplogroup association with Prostate cancer"

Supplementary Table S2. References for forest plot "study name". A. AD - Alzheimer's disease; B. PD- Parkinson's disease; C. T2DM-type 2 diabetes mellitus; D. Longevity; E. Breast Cancer; F. AMD - Age-related macular degeneration, MS - multiple sclerosis, MI - myocardial infarction, CAD - coronary artery disease and schizophrenia.

A.

Study name	Reference
AD 1	1
AD 2	2
AD 3	3
AD 4	4
AD 5	5
AD 6	6
AD 7	7
AD 8	8
AD 9	9
AD 10	10
AD 11	11
AD 12	12
AD 13	13
AD 14	14

B.

Study name	Reference
PD 1	15
PD 2	16
PD 3	14
PD 4	17
PD 5	18
PD 6	19
PD 7	20
PD 8	21
PD 9	22
PD 10	23
PD 11	24
PD 12	25
PD 3-1-1	26
PD 3-1-2	26

C.

Study name	Reference
T2DM 1	27
T2DM 2	28
T2DM 3	29
T2DM 4	30
T2DM 5	31
T2DM 6	32
T2DM 7	33
T2DM 8	34
T2DM 9	35
T2DM 10	36
T2DM 11	37
T2DM 12	38
T2DM 13	39
T2DM 14	40
T2DM 15	41

D.

Study name	Reference
Longevity 1	42
Longevity 2	43
Longevity 3	44
Longevity 4	45
Longevity 5	46
Longevity 6	47
Longevity 7	48
Longevity 8	49
Longevity 9	50
Longevity 10	51
Longevity 11	52
Longevity 12	53
Longevity 13	54
Longevity 14	55

E.

Study name	Reference
Breast cancer 1	56
Breast cancer 2	57
Breast cancer 3	58
Breast cancer 4	59
Breast cancer 5	60
Breast cancer 6	61
Breast cancer 7	62
Breast cancer 8	63
Breast cancer 9	64
Breast cancer 10	65
Breast cancer 11	66
Breast cancer 12	67
Breast cancer 13	68

F.

Study name	Reference
MS1	69
MS2	70
MS3	71
MS4	72
MI1	73
MI2	74
MI3	75
CAD1	76
CAD2	77
PC1	78
PC2	79
AMD1	80
AMD2	81
AMD3	82
AMD4	83
Schizophrenia1	84
Schizophrenia2	85
Sperm motility1	86
Sperm motility2	87
Sperm motility3	88
Sperm motility4	89
Prostate cancer1	90
Prostate cancer2	91
Prostate cancer3	92
Prostate cancer4	93
Prostate cancer5	94
Prostate cancer6	95

Supplementary Table S3. References for forest plot "study name". mtDNA haplogroup H association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease.

Study name	Reference
AD	2,5,10,13,14,32
T2DM	28,32,35
Breast cancer	56
Sperm motility	86
PC	78,79
AMD	83
CAD	77
Prostate cancer	91,93
PD	14,15,24

Supplementary Table S4. References for forest plot "study name". mtDNA haplogroup K association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	2,5,10,13,14,32
T2DM	28
Breast cancer	56
Sperm motility	86
PC	78,79
AMD	83
CAD	77
Schizo	84
Prostate cancer	91,93
PD	14,15,17,18,21-24,26

Supplementary Table S5. References for forest plot "study name". mtDNA haplogroup J association with grouped phenotypes. AD - Alzheimer's disease, T2DM- type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	1,2,4,9,10,13,14
T2DM	28,32,35
Breast cancer	56
Sperm motility	86
PC	78,79
AMD	83
CAD	77
Schizo	84
Prostate cancer	91,93
PD	14-18,21-24,26

Supplementary Table S6. References for forest plot "study name". mtDNA haplogroup I association with grouped phenotypes. AD - Alzheimer's disease, T2DM- type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	9,10,13
T2DM	32,36
Sperm motility	86
Breast cancer	56
PC	78
AMD	83
Prostate cancer	91-93
Schizo	84
PD	15,24

Supplementary Table S7. References for forest plot "study name". mtDNA haplogroup T association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	2,4,9,10,13,14,96
T2DM	28,32,35
Sperm motility	86
Breast cancer	56
PC	78,79
AMD	83
Prostate cancer	91,93
Schizo	84
PD	14,15,17,18,22-24,26

Supplementary Table S8. References for forest plot "study name". mtDNA haplogroup U association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	2,4,9,10,13,14,96
T2DM	28,32,35
Breast cancer	56
Sperm motility	86
PC	78,79
AMD	83
CAD	77
Prostate cancer	91,93
Schizo	84
PD	14,15,21,22,24

Supplementary Table S9. References for forest plot "study name". mtDNA haplogroup V association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease.

Study name	Reference
AD	2,5,10,13
T2DM	28
Breast cancer	56
Sperm motility	86
PC	78,79
AMD	83
Prostate cancer	91,93
PD	15,24

Supplementary Table S10. References for forest plot "study name". mtDNA haplogroup W association with grouped phenotypes. AD - Alzheimer's disease, T2DM-type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	2,5,9,10,13
T2DM	28,32,36
Breast cancer	56
Sperm motility	86
PC	79
AMD	83
CAD	77
Prostate cancer	91,93
Schizo	84
PD	15,24

Supplementary Table S11. References for forest plot "study name". mtDNA haplogroup X association with grouped phenotypes. AD - Alzheimer's disease, T2DM- type 2 diabetes mellitus, PD- Parkinson's disease, PC - Pancreatic cancer, AMD - Age-related macular degeneration, CAD - coronary artery disease. Schizo – Schizophrenia.

Study name	Reference
AD	2,5,9,10,13
T2DM	28,32
Breast cancer	56
Sperm motility	86
PC	79
AMD	83
Prostate cancer	91,93
Schizo	84
PD	24,97

Supplementary Table S12. Example Data Extraction for Longevity (Longevity 3)

	Longevity			Non Longevity (controls)		
Hap	Haplogroup sample size	Others sample size	Total	Haplogroup sample size	Others sample size	Total
H	84	141	225	204	196	400
I	8	217	225	10	390	400
J	19	206	225	25	375	400
K	17	208	225	24	376	400
M	1	224	225	4	396	400
T	11	214	225	22	378	400
U	64	161	225	82	318	400
V	4	221	225	16	384	400
W	8	217	225	5	395	400
X	5	220	225	7	393	400

Supplementary Table S13. Longevity merged data and classification to haplogroups

	Haplogroup	Longevity			Non Longevity (Control)		
		Haplogroup sample size	Others sample size	Total	Haplogroup sample size	Others sample size	Total
Longevity 1-1	H	41	68	109	51	74	125
Longevity 1-2	H	44	59	103	57	93	150
Longevity 3	H	84	141	225	204	196	400
Longevity 9	H	37	28	65	61	77	138
Longevity 1-1	I	2	107	109	3	122	125
Longevity 1-2	I	6	97	103	4	146	150
Longevity 3	I	8	217	225	10	390	400
Longevity 1-1	J	17	92	109	6	119	125
Longevity 1-2	J	6	97	103	7	143	150
Longevity 3	J	19	206	225	25	375	400
Longevity 9	J	2	63	65	15	123	138
Longevity 1-1	K	6	103	109	6	119	125
Longevity 1-2	K	9	94	103	15	135	150
Longevity 3	K	17	208	225	24	376	400
Longevity 1-1	T	12	97	109	15	110	125
Longevity 1-2	T	6	97	103	16	134	150
Longevity 3	T	11	214	225	22	378	400
Longevity 9	T	6	59	65	8	130	138
Longevity 1-1	U	13	96	109	17	108	125
Longevity 1-2	U	13	90	103	19	131	150
Longevity 3	U	64	161	225	82	318	400
Longevity 9	U	9	56	65	32	106	138
Longevity 1-1	V	1	108	109	1	124	125
Longevity 1-2	V	6	97	103	4	146	150
Longevity 3	V	4	221	225	16	384	400
Longevity 9	V	3	62	65	8	130	138
Longevity 1-1	W	2	107	109	4	121	125

Longevity 1-2	W	1	102	103	6	144	150
Longevity 3	W	8	217	225	5	395	400
Longevity 1-1	X	3	106	109	3	122	125
Longevity 1-2	X	5	98	103	5	145	150
Longevity 3	X	5	220	225	7	393	400
Longevity 4	J2	8	38	46	3	54	57
Longevity 3	M	1	224	225	4	396	400
Longevity 9	O	1	64	65	14	124	138
Longevity 4	T2	1	45	46	4	53	57
Longevity 4	U5	34	12	46	48	9	57

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