Human Heat Shock Protein Variants and Aging
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Heat Shock Protein Variants

Gene	Polymorphism	Function	SNP
HSPA1A (HSP70-1)	c-27g	Promoter	rs1043618
HSPA1B (HSP70-2)	c-1136t	Promoter	rs2763979
HSPA2 (HSP70-3)	a-4563g	Promoter	rs12432891
	a-3677c	Promoter	rs7151976
	a-6359g	Promoter	rs7160634
	c3838t	Intron	rs10143906
	c2792g	Intron	rs11848114
HSPA1L (HSP70-HOM)	Glu602Lys	Exon	rs2075800
HSPA5 (GRP78)	c-619t	Promoter	rs391957
	g-199t*	Promoter	rs7871419
	a6102g	Intron	rs12009
	a6926g	Intron	rs418496
HSPB1 (HSP27-1)	c-1271g	Promoter	rs2868371
	g1682t	Intron	rs2070804
	c2610g	Intron	rs7459185
HSPB2 (HSP27-2)	c-454t	Promoter	rs762550
	c-857g	Promoter	rs14133
	c1369t	Intron	rs4252591

* SNP in African Americans only

CHS Outcomes

Outcome	Measure	Analysis
Lifespan		
	Years of life	Regression
	Years of healthy life	Regression
	≥95 years	Logistic regression
Frailty		
	Average grip dominant hand (kg)	Regression
	15 FT Walk Time (sec.)	Regression
	Physical activity (kcals)	Regression
Stress response		
	Fibrinogen (mg/dl)	Regression
	CRP (mg/L)	Regression
	Factor VII (%)	Regression
	Factor VIII (%)	Regression
Disease		
	Cancer diagnosis	Logistic regression
	Incident cardio-, cerebro-vascular disease	Hazard ratio
Mortality		
	Cause of death	Logistic regression
	atherosclerotic CHD	
	cerebrovascular disease	
	other atherosclerotic disease	
	other cardiovascular	
	non-cardiovascular	
	Incident mortality	Hazard ratio

Heat Shock Protein Variant Associations

Gene	Polymorphism	Summary of Significant Associations
HSPA1A (HSP70-1)	c-27g	Cancer Diagnosis
HSPA1B (HSP70-2)	c-1136t	Cancer Diagnosis, Lived ≥95 years
HSPA2 (HSP70-3)	a-4563g	
	a-3677c	
	a-6359g	Years of Life
	c3838t	
	c2792g	
HSPA1L (HSP70-HOM)	Glu602Lys	Factor VIII
HSPA5 (GRP78)	c-619t	Fibrinogen
	g-199t*	CRP (AA)
	a6102g	Fibrinogen
	a6926g	
HSPB1 (HSP27-1)	c-1271g	Years of Life (AA), KCAL activity
	g1682t	
	c2610g	
HSPB2 (HSP27-2)	c-454t	Grip Strength
	c-857g	
	c1369t	Cancer Diagnosis, Grip Strength, Ath-CHD Death

* SNP in African Americans only

Lifespan

Lived ≥95 years

Caucasians

HSPA1B (HSP70-2) **c-1136t promoter**

genotype	≤75 + dead	≥95	OR
	n (%)	n (%)	
CC	112 (48)	46 (38)	1.0
CT	106 (45)	57 (48)	1.3 (0.82 - 2.1)
TT	19 (8)	17 (14)	2.2 (1.0 - 4.6)

Adjusted for sex and clinic site

Lifespan

Years of life after baseline

African Americans

HSPA2 (HSP70-3)	a-6359g promoter			*p-trend*
genotype	GG	AG	AA	
n (%)	559 (71)	201 (25)	30 (4)	
Years of life	9.6	9.0	8.8	*0.02*

HSPB1 (HSP27-1)	c-1271g promoter			
genotype	CC	CG	GG	
n (%)	617 (78)	161 (20)	11 (1)	
Years of life	9.3	9.9	10.5	*0.02*

Adjusted for age, sex and clinic site

Frailty

Leisure Physical Activity

HSPB1 (HSP27-1)	c-1271g promoter			*p-trend*
genotype	CC	CG	GG	
n (%)	3089 (60)	1801 (35)	251 (5)	
kcal/week	1271	1278	1878	*0.05*

Adjusted for age, sex, race, weight, health status and clinic site

Frailty

Grip Strength

HSPB2 (HSP27-2)	c-454t promoter			*p-trend*
genotype	CC	CT	TT	
n (%)	2311 (45)	2265 (44)	565 (11)	
Dominant hand grip strength (kg)	28.7	28.4	27.9	*0.01*

HSPB2 (HSP27-2)	c1369t intron			
genotype	CC	CT	TT	
n (%)	2512 (49)	2080 (41)	546 (10)	
Dominant hand grip strength (kg)	28.0	28.9	29.0	*0.0005*

Adjusted for age, sex, race, weight, health status and clinic site

Stress

C-reactive Protein

African Americans

HSPA5 (GRP78)	g-199t promoter			*p-trend*
genotype	GG	GT	TT	
n (%)	597 (76)	181 (23)	12 (2)	
CRP (μg/ml)	6.5	5.0	4.9	*0.02*

Adjusted for age, sex and clinic site

Stress
Fibrinogen

HSPA5 (GRP78)	c-619t promoter			*p-trend*
genotype	CC	CT	TT	
n (%)	1422 (28)	2470 (48)	1248 (24)	0.0004
Fibrinogen (mg/dl)	326	322	318	

HSPA5 (GRP78)	a6926g intron			
genotype	GG	AG	AA	
n (%)	2179 (42)	2227 (43)	734 (14)	0.003
Fibrinogen (mg/dl)	328	322	319	

Adjusted for age, sex, race and clinic site

Stress

Factor VIII

HSPA1L (HSP70-HOM)	Glu602Lys exon			*p-trend*
genotype	Glu/Glu	Glu/Lys	Lys/Lys	
n (%)	2488 (48)	2035 (40)	619 (12)	
Factor VIII (% of normal)	124	121	119	0.0004

Adjusted for age, sex, race and clinic site

Disease

Cancer Diagnosis

	No	Yes	
	n (%)	n (%)	OR
HSPA1A (HSP70-1)	**c-27g promoter**		
CC	1569 (36)	247 (34)	1.0
CG	1974 (45)	330 (45)	1.1 (0.92 - 1.3)
GG	850 (19)	160 (22)	1.6 (1.2 - 2.0)
HSPA1B (HSP70-2)	**c-1136t promoter**		
CC	1765 (40)	302 (41)	1.0
CT	1921 (44)	305 (41)	0.97 (0.81 - 1.2)
TT	697 (16)	129 (18)	1.3 (1.0 - 1.7)
HSPB2 (HSP27-2)	**c1369t intron**		
CC	2189 (50)	318 (43)	1.0
CT	1756 (40)	320 (44)	1.2 (0.98 – 1.4)
TT	441 (10)	98 (13)	1.4 (1.1 – 1.8)

Adjusted for age, sex, race and clinic site

Mortality

Atherosclerotic CHD Death

HSPA1A (HSP70-1)	c-27g promoter		
	No	Yes	OR
	n (%)	n (%)	
CC	2144 (49)	368 (51)	1.0
CG	1788 (40)	292 (41)	0.93 (0.78 - 1.1)
GG	490 (11)	56 (8)	0.64 (0.47 - 0.86)

Adjusted for age, sex, race and clinic site

Heat Shock Protein Variant Associations

Gene	Polymorphism	Summary of Significant Associations
HSPA1A (HSP70-1)	c-27g	Cancer Diagnosis
HSPA1B (HSP70-2)	c-1136t	Cancer Diagnosis, Lived ≥95 years
HSPA2 (HSP70-3)	a-4563g	
	a-3677c	
	a-6359g	Years of Life
	c3838t	
	c2792g	
HSPA1L (HSP70-HOM)	Glu602Lys	Factor VIII
HSPA5 (GRP78)	c-619t	Fibrinogen
	g-199t*	CRP (AA)
	a6102g	Fibrinogen
	a6926g	
HSPB1 (HSP27-1)	c-1271g	Years of Life (AA), KCAL activity
	g1682t	
	c2610g	
HSPB2 (HSP27-2)	c-454t	Grip Strength
	c-857g	
	c1369t	Cancer Diagnosis, Grip Strength, Ath-CHD Death

* SNP in African Americans only

Sirtuin Variants

Gene	Polymorphism	Function	SNP
SIRT1	a1604g	Intron	rs10823108
	c1106t	Intron	rs10997860
	a1471g	Intron	rs10997866
	c35344t	Intron	rs10997875
	a7586g	Intron	rs12413112
	c30847g	Intron	rs1966188
	332 L/L	Exon	rs2273773
	c20401t	Intron	rs7096385
SIRT3	a8996g	Intron	rs1023430
	c11805t	Intron	rs11246007
	c-543t	Promoter	rs2272563
	c10270t	Intron	rs3782116
	c16249t	Intron	rs3825075
	a4875c	Intron	rs4758629
	a14749g	Intron	rs535716
SIRT6	a(IV+25)g	Intron boundary	rs350844
	c1700t	Intron	rs352493
	a-1976g	Promoter	rs3760908
	g(VI-29)t	Intron boundary	rs7246235
	g(II+89)t	Intron boundary	rs7260071

Sirtuin Outcomes

Outcome	Measure	Analysis
Lifespan		
	Years of life	Regression
	Years of healthy life	Regression
	>=95 years	Logistic regression
Metabolism		
	Glucose	Regression
	Insulin	Regression
	HDL LDL	Regression
	Triglycerides	Regression
Frailty		
	Average grip dominant hand (kg)	Regression
	15 FT Walk Time (sec.)	Regression
	Physical activity (kcals)	Regression
	Blocks walked last week	Regression
Mortality		
	Cause of death	Logistic regression
	atherosclerotic CHD	
	cerebrovascular disease	
	other atherosclerotic disease	
	other cardiovascular	
	non-cardiovascular	
	Incident mortality	Hazard ratio

Lifespan

Lived ≥95 years

Caucasians

SIRT3 **c16249t intron**

genotype	<=75 + dead	>=95	OR
	n (%)	n (%)	
CC	121 (0.51)	51 (0.42)	1.0
CT	102 (0.43)	55 (0.46)	1.3 (0.80 - 2.0)
TT	15 (0.06)	15 (0.12)	2.4 (1.1 - 5.2)

Adjusted for sex and clinic site

Lifespan

Lived ≥95 years

Caucasians

		<=75 + dead	>=95	OR
SIRT1		c1106t intron		
		n (%)	n (%)	
	CC	106 (0.45)	65 (0.54)	1.0
	CT	102 (0.43)	49 (0.41)	0.80 (0.50 - 1.3)
	TT	30 (0.13)	7 (0.06)	0.38 (0.16 - 0.91)
SIRT1		a1471g intron		
		n (%)	n (%)	
	AA	98 (0.41)	63 (0.52)	1.0
	AG	108 (0.45)	50 (0.41)	0.73 (0.46 - 1.2)
	GG	32 (0.13)	8 (0.07)	0.38 (0.17 - 0.89)
SIRT1		c35344t intron		
		n (%)	n (%)	
	CC	106 (0.45)	66 (0.55)	1.0
	CT	102 (0.43)	48 (0.40)	0.77 (0.49 - 1.2)
	TT	30 (0.13)	7 (0.06)	0.37 (0.15 - 0.89)

Adjusted for sex and clinic site