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Genetic variation in *SIRT1* is associated with lipid profiles but not with longevity in Ashkenazi Jews

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Human SIRT1 is an NAD-dependent protein deacetylase with homologs reported to extend lifespan in yeast, worms, fruit flies, and mice.¹ In particular, studies in mice have indicated that SIRT1 plays a key role in regulating metabolism and mitochondrial function in different tissues through targets that include PPAR γ , PGC-1 α , and AMP kinase.² Based on these studies in model organisms, there has been much interest in determining the role of SIRT1 functions in healthy aging in humans. To date, polymorphisms in *SIRT1* have been associated with several disease-related phenotypes, including diabetes, BMI, obesity, cholesterol metabolism, energy expenditure, glucose tolerance, and cardiovascular disease.³

To further investigate the role of SIRT1 in healthy aging, we searched for *SIRT1* polymorphisms associated with either longevity or lipid profiles in an Ashkenazi Jewish (AJ) population. We began by performing comprehensive resequencing analysis of *SIRT1* to identify variants in the exons, exon-intron junctions, and 3.1kb proximal promoter region of 16 centenarians and 16 controls. A total of 36 sequence variants in the *SIRT1* gene were identified, among which 5 had not been previously reported (Table I).

We next selected 19 common *SIRT1* SNPs with total minor allele frequency (MAF) greater than 0.05 in the initial 32 individuals (indicated as **bold** in Table I) and genotyped them in 213 AJ centenarians and 169 AJ controls. A centenarian is defined as a healthy individual living independently at 95 years of age or older and a control is defined as an individual without a family history of unusual longevity; parents of controls survived to the age of 85 years or less. The association analysis of *SIRT1* with longevity was performed using SNP & Variation suite version 7.6.11 (Golden helix). Basic allelic test, genotypic test, additive model test, dominant model test, and recessive model test were performed and statistical

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differences among groups were assessed by the Fisher's exact test. No association was found between *SIRT1* SNPs and longevity (Table I).

We further performed association analysis between *SIRT1* genotype and lipid profiles in the same 382 individuals. Since 5 tagSNPs (rs10997854, rs142194353, rs12778366, rs35706870, and rs932658) could capture all the SNPs with MAF greater than 0.05 across the *SIRT1* gene region ($r^2 = 0.9$), association analysis with lipid profiles was performed with those tagSNPs.

The test was performed using the JMP genomics program (version 6, Cary, NC) and numeric variables were expressed as mean $\pm$ SD (Table II). To assess the effect of each genotype within the SNP and continuous variables of lipid parameters, logistic regression with adjustment for age and gender for additive model was carried out. The results revealed that two *SIRT1* tagSNPs were associated with three lipid parameters (Table II). The C allele of rs10997854, which served as a tag for 8 SNPs across the *SIRT1* gene region, showed association with large LDL and large HDL by an additive model after multiple testing correction ($p = 0.0365$ and $p = 0.0412$, respectively). In addition, the CT genotype of rs142194353 showed association with large LDL and HDL size by an additive model after multiple testing correction ($p = 0.0035$ and $p = 0.0033$, respectively). Other lipid parameters showed no significant correlation with these *SIRT1* SNPs.

Taken together, our data suggest that common variants in *SIRT1* are associated with lipid profile but not longevity in this AJ cohort. Prior association studies examining the relationship between *SIRT1* variants and longevity have been mixed, with only three out of more than nine independent studies detecting a significant link. This suggests that the role of *SIRT1* common variants in human longevity is minor or population specific. Interestingly, our resequencing analysis of *SIRT1* from 32 individuals identified 5 novel SNPs which were rare in frequency (Table I). Four of these SNPs were only found in centenarians, suggesting a potential role of rare *SIRT1* variant in longevity. Further studies will be required to address this possibility.

In our study, lipid profiles have been determined by NMR-based subfractioned lipoprotein particle size. It is now well recognized that the cholesterol values from LDL-cholesterol or HDL-cholesterol do not accurately reflect the number of circulating LDL or HDL particles or metabolic syndrome risk associated with them.⁴ Our study is the first to report the positive associations of subfractioned lipoprotein particle sizes with *SIRT1* variants, suggesting a role of *SIRT1* in modulating risk of metabolic syndrome in the AJ population.

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Table I

Discovery, genotyping, and association analysis of *SIRT1* gene region with longevity.

SNP ID	Position *	region	Maj > Min	control MAF ^a	centenarian MAF ^a	control MAF ^b	centenarian MAF ^b	P-Value ^b
rs10997854	Chr10: 69641369	upstream	C>A	0.34	0.25	0.39	0.40	0.865
rs10997855	Chr10: 69641401	upstream	G>A	0.34	0.25	0.39	0.40	0.865
rs142194353	Chr10: 69641539	upstream	C>T	0.06	0.06	0.06	0.06	0.967
rs10823100	Chr10: 69641693	upstream	G>C	0.09	0.03	0.05	0.04	0.501
rs10997856	Chr10: 69641706	upstream	C>T	0.34	0.25	0.39	0.40	0.865
rs10823101	Chr10: 69641711	upstream	T>A	0.09	0.03	0.05	0.04	0.501
rs10997857	Chr10: 69641715	upstream	T>A	0.09	0.03	0.05	0.04	0.501
rs10823102	Chr10: 69641833	upstream	T>A	0.34	0.25	0.39	0.40	0.833
rs12250285	Chr10: 69641954	upstream	c>T	0.37	0.25	0.43	0.42	0.840
rs148743102	Chr10: 69642058	upstream	ins T	0.09	0.09	0.10	0.12	0.527
novel	Chr10: 69642546	upstream	ins T	0	0.03	n.a.	n.a.	n.a.
rs10740280	Chr10: 69642668	upstream	T>A	0	0	n.a.	n.a.	n.a.
novel	Chr10: 69642675	upstream	del T	0.06	0	n.a.	n.a.	n.a.
novel	Chr10: 69642766	upstream	C>T	0	0.06	n.a.	n.a.	n.a.
rs12778366	Chr10: 69643079	upstream	T>C	0.16	0.13	0.15	0.15	0.960
rs3758391	Chr10: 69643342	upstream	T>C	0.34	0.25	0.39	0.40	0.905
novel	Chr10: 69643586	upstream	T>A	0	0.03	n.a.	n.a.	n.a.
rs35706870	Chr10: 69643617	upstream	A>C	0.09	0.09	0.10	0.13	0.362
rs3740051	Chr10: 69643959	upstream	A>G	0.09	0.03	0.05	0.03	0.227
rs932658	Chr10: 69644217	upstream	A>C	0.34	0.25	0.42	0.46	0.561
rs3740053	Chr10: 69644335	upstream	A>G	0.09	0.03	0.05	0.03	0.406
rs2394443	Chr10: 69644341	upstream	G>C	0.41	0.25	0.45	0.42	0.739
novel	Chr10: 69647182	Exon 2	del TCT	0	0.03	n.a.	n.a.	n.a.
rs932657	Chr10: 69647332	intron	G>T	0.06	0	n.a.	n.a.	n.a.
rs7896005	Chr10: 69651125	intron	A>G	0.37	0.25	0.38	0.39	0.909
rs36107781	Chr10: 69651319	intron	T>C	0.03	0	n.a.	n.a.	n.a.
rs2273773	Chr10: 69666598	Exon 5	T>C	0.09	0.03	0.05	0.04	0.613
rs149313098	Chr10: 69672556	Exon 8	G>A	0.03	0	n.a.	n.a.	n.a.
rs61666042 [†]	Chr10: 69676547	3UTR	ins T	0.5	0.47	n.a.	n.a.	n.a.
rs2394445 [†]	Chr10: 69676560	3UTR	T>A	0.13	0.13	n.a.	n.a.	n.a.
rs35461348 [†]	Chr10: 69676610	3UTR	del CTTT	0.37	0.28	n.a.	n.a.	n.a.
rs752578	Chr10: 69677060	3UTR	C>T	0	0	n.a.	n.a.	n.a.
rs34934649	Chr10: 69677458	3UTR	del C	0.03	0	n.a.	n.a.	n.a.
rs200236450	Chr10: 69677699	3UTR	C>T	0.03	0	n.a.	n.a.	n.a.
rs199731267	Chr10: 69677758	3UTR	G>A	0.03	0	n.a.	n.a.	n.a.
rs2234975	Chr10: 69678078	3UTR	C>T	0.06	0.03	n.a.	n.a.	n.a.

Bold SNPs indicate common SNPs that have total MAF>0.05 that were chosen for genotyping.

n.a. indicates SNPs that were not genotyped and thus non-applicable.

* Position is based on NCBI human genome build 37 coordinates.

[†] These were not chosen for further genotyping due to the unclear sequence reads caused by multiple deletions in the region.

^a MAF from sequencing analysis for *SIRT1* gene region in 16 AJ centenarians and 16 AJ controls.

^b MAF and p-value from genotyping and association analysis of SIRT1 in 213 AJ centenarians and 169 AJ controls.

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Table II

Association of SIRT1 tagSNPs with lipid profiles in 283 AJ individuals.

SNP Genotype	rs10997854			rs142194353			* _p adjust			rs12778366			* _p adjust			rs35706870			* _p adjust			rs932658			* _p adjust		
	AA	CA	CC	CC	CT	TT	TT	TC	CC	CC	AA	CA	CC	CC	GG	GT	TT	TT	GG	GT	TT	GG	GT	TT	GG	GT	TT
n	195	158	29	341	41	0	290	85	7	7	303	76	2	179	170	32	32	179	170	32	179	170	32	179	170	32	
Large LDL (%)	72 ± 3.6	85.8 ± 4.5	109 ± 14	<u>0.0365</u>	77.5 ± 3	98.2 ± 8.9	0.0816	75.9 ± 3.1	94.5 ± 6.6	92.5 ± 27.9	0.0816	79.4 ± 3	81.1 ± 7.9	172	0.0816	73.3 ± 3.7	84.9 ± 4.5	98.5 ± 14	0.0816	73.3 ± 3.7	84.9 ± 4.5	98.5 ± 14	0.0816	73.3 ± 3.7	84.9 ± 4.5	98.5 ± 14	
Large HDL (%)	30.3 ± 1.6	36.4 ± 2.1	44.1 ± 5.2	<u>0.0412</u>	32.2 ± 1.3	46.1 ± 4.1	0.0035	32.1 ± 1.4	39.1 ± 2.9	44.5 ± 15.8	0.1314	34 ± 1.5	32.6 ± 2.5	80.4	0.0554	31.5 ± 1.8	35.6 ± 2	40.5 ± 4.4	0.0554	31.5 ± 1.8	35.6 ± 2	40.5 ± 4.4	0.0554	31.5 ± 1.8	35.6 ± 2	40.5 ± 4.4	
HDL Size (nm)	9.4 ± 0.1	9.4 ± 0.1	9.6 ± 0.1	0.5753	9.4 ± 0	9.8 ± 0.1	0.0033	9.4 ± 0	9.5 ± 0.1	9.6 ± 0.2	0.3446	9.4 ± 0	9.4 ± 0.1	10.1	0.5753	9.4 ± 0.1	9.4 ± 0.1	9.6 ± 0.1	0.5753	9.4 ± 0.1	9.4 ± 0.1	9.6 ± 0.1	0.5753	9.4 ± 0.1	9.4 ± 0.1	9.6 ± 0.1	

Cholesterol (mg/dL), Triglycerides (mg/dL), HDL-C (mg/dL), LDL-C (mg/dL), Large LDL (%), Medium LDL (%), Small LDL (%), Large HDL (%), Medium HDL (%), Small HDL (%), LDL particles, LDL size (nm), HDL size (nm), VLDL (mg/dL) were measured for association analysis with each SNP but only the parameters that were significant (p_{adjust} value < 0.05) are shown in this table.

Bold indicates significant associations (p < 0.05).

* p_{adjust}, Multiple corrections by FDR has been implemented.