

## An Integrative Genomic Strategy Identifies sRAGE as a Causal and Protective Biomarker of Lung Function

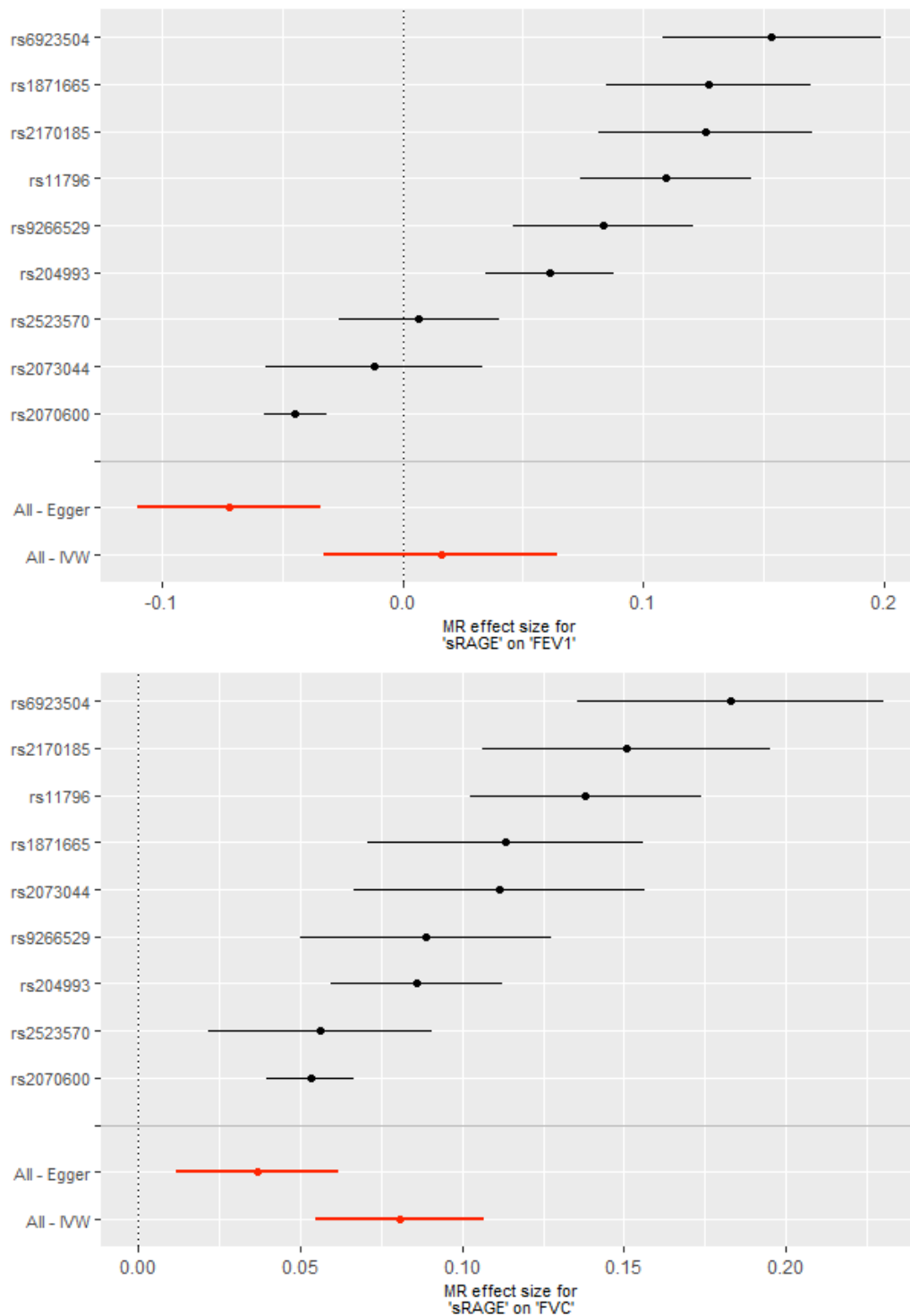
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**e-Figure 1.** Effect of individual SNPs included as instrumental variables in Mendelian randomization for FEV1 (top) and FVC (bottom).



**e-Table 1.** Genome-wide significant of SNPs associated with plasma sRAGE (*cis*-pQTLs) within 1 megabase pairs upstream and downstream from *AGER*

SNP rsID	Chr	Phys_location	N	iMAF	variMAF	h2q	beta	se	chisq	pval	effect allele	noneffect allele
rs9263853	6	31156573	6834	0.92	0.07	0.01	0.29	0.03	74.84	5.11E-18	C	A
rs9263867	6	31167113	6834	0.92	0.07	0.01	0.29	0.03	74.72	5.42E-18	G	A
rs6934570	6	31173422	6834	0.92	0.07	0.01	0.29	0.03	73.90	8.20E-18	A	G
rs28744242	6	31175374	6834	0.92	0.07	0.01	0.29	0.03	73.22	1.16E-17	A	G
rs28360992	6	31183135	6834	0.92	0.07	0.01	0.29	0.03	73.46	1.03E-17	C	T
rs28360993	6	31183431	6834	0.92	0.07	0.01	0.29	0.03	71.88	2.29E-17	G	A
rs28744275	6	31200557	6834	0.93	0.07	0.01	0.30	0.04	69.69	6.92E-17	G	A
rs28744276	6	31201206	6834	0.92	0.07	0.01	0.30	0.04	69.32	8.36E-17	G	A
rs28361022	6	31205812	6834	0.93	0.07	0.01	0.30	0.04	69.39	8.07E-17	T	C
rs28361024	6	31208733	6834	0.93	0.07	0.01	0.30	0.04	69.39	8.06E-17	G	A
rs28744282	6	31216818	6834	0.93	0.06	0.01	0.33	0.04	71.72	2.48E-17	T	A
rs28744283	6	31217622	6834	0.93	0.06	0.01	0.33	0.04	71.71	2.49E-17	G	A
rs1793892	6	31221351	6834	0.90	0.07	0.01	0.25	0.04	51.64	6.66E-13	T	C
rs9264419	6	31230137	6834	0.94	0.03	0.01	0.39	0.05	53.86	2.16E-13	G	A
rs9264757	6	31248170	6834	0.93	0.04	0.01	0.35	0.05	60.62	6.91E-15	G	A
rs9264769	6	31261961	6834	0.94	0.03	0.01	0.35	0.05	49.03	2.53E-12	C	A
rs9264954	6	31275395	6834	0.93	0.03	0.01	0.38	0.05	57.20	3.94E-14	G	A
rs9264955	6	31275583	6834	0.93	0.03	0.01	0.40	0.05	60.44	7.59E-15	C	T
rs9264967	6	31277740	6834	0.92	0.03	0.01	0.38	0.05	53.41	2.70E-13	A	G
rs9266380	6	31334477	6834	0.91	0.08	0.01	0.26	0.03	65.19	6.81E-16	G	A
rs9266391	6	31335351	6834	0.91	0.08	0.01	0.26	0.03	65.25	6.58E-16	C	T
rs112907408	6	31336402	6834	0.91	0.07	0.01	0.28	0.03	66.96	2.78E-16	G	A
rs9266433	6	31337633	6834	0.91	0.08	0.01	0.26	0.03	65.34	6.30E-16	C	T
rs9266462	6	31338768	6834	0.91	0.07	0.01	0.27	0.03	65.59	5.56E-16	A	G
rs9266504	6	31340767	6834	0.91	0.08	0.01	0.26	0.03	65.38	6.18E-16	T	C
rs9266644	6	31347213	6834	0.91	0.07	0.01	0.27	0.03	65.14	6.99E-16	C	T
rs9266651	6	31347458	6834	0.91	0.07	0.01	0.27	0.03	65.14	6.99E-16	A	G
rs9266731	6	31350505	6834	0.91	0.07	0.01	0.27	0.03	63.94	1.28E-15	T	C
rs9266773	6	31352348	6834	0.91	0.07	0.01	0.27	0.03	63.79	1.39E-15	T	C
rs9266778	6	31354387	6834	0.91	0.07	0.01	0.27	0.03	63.68	1.47E-15	C	T
rs9266853	6	31387725	6834	0.92	0.03	0.01	0.42	0.05	62.28	2.98E-15	C	G
rs112310209	6	31401225	6834	0.95	0.03	0.02	0.59	0.05	124.92	5.30E-29	A	C



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rs3893526	6	31413742	6834	0.91	0.08	0.01	0.27	0.03	63.81	1.37E-15	A	G
rs77349273	6	31428987	6834	0.92	0.07	0.01	0.29	0.03	72.36	1.79E-17	C	T
rs75640364	6	31433566	6834	0.92	0.07	0.01	0.29	0.03	70.21	5.32E-17	G	C
rs79501286	6	31442912	6834	0.92	0.07	0.01	0.26	0.03	61.22	5.11E-15	G	A
rs17200593	6	31445476	6834	0.92	0.08	0.01	0.26	0.03	62.07	3.32E-15	G	A
rs17206973	6	31445564	6834	0.92	0.08	0.01	0.26	0.03	61.59	4.22E-15	C	T
rs75303729	6	31447487	6834	0.92	0.08	0.01	0.26	0.03	61.46	4.53E-15	G	A
rs112417354	6	31450567	6834	0.92	0.08	0.01	0.26	0.03	61.71	3.98E-15	G	A
rs113551020	6	31456840	6834	0.92	0.07	0.01	0.28	0.03	66.35	3.78E-16	T	C
rs34451818	6	31583841	6834	0.96	0.04	0.02	0.63	0.05	173.20	1.48E-39	C	G
rs35502919	6	31604355	6834	0.96	0.04	0.02	0.63	0.05	174.62	7.24E-40	C	A
rs805284	6	31682029	6834	0.96	0.04	0.03	0.64	0.05	180.79	3.25E-41	G	A
rs2844456	6	31864674	6834	0.96	0.04	0.03	0.69	0.05	210.76	9.36E-48	T	C
rs2844454	6	31873292	6834	0.96	0.04	0.03	0.69	0.05	211.17	7.62E-48	C	T
rs34562262	6	32020961	6834	0.96	0.04	0.03	0.72	0.05	221.44	4.38E-50	G	C
rs137893789	6	32055486	6834	0.95	0.04	0.03	0.70	0.05	226.02	4.39E-51	G	A
rs10947233	6	32124424	6834	0.96	0.04	0.03	0.71	0.05	236.74	2.02E-53	G	T
rs41268924	6	32135137	6834	0.96	0.04	0.03	0.71	0.05	237.08	1.71E-53	G	A
rs41268928	6	32147157	6834	0.96	0.04	0.03	0.71	0.05	239.30	5.60E-54	G	C
rs9391855	6	32149801	6834	0.96	0.04	0.04	0.71	0.04	251.29	1.36E-56	C	T
rs2070600	6	32151443	6834	0.96	0.04	0.04	0.71	0.04	251.73	1.09E-56	C	T
rs41268932	6	32154711	6834	0.96	0.04	0.03	0.72	0.05	235.84	3.17E-53	A	G
rs2022059	6	32156489	6834	0.95	0.04	0.03	0.60	0.04	195.11	2.44E-44	G	C
rs2856437	6	32157364	6834	0.95	0.04	0.03	0.60	0.04	194.90	2.71E-44	G	A
rs8192575	6	32166384	6834	0.94	0.06	0.02	0.42	0.04	125.15	4.73E-29	C	G
rs9378121	6	32167513	6834	0.94	0.06	0.02	0.42	0.04	125.11	4.80E-29	C	T
rs8192574	6	32169145	6834	0.96	0.04	0.03	0.71	0.05	233.56	9.98E-53	G	A
rs2555457	6	32173800	6834	0.94	0.06	0.02	0.42	0.04	124.65	6.08E-29	C	A
rs2849017	6	32174048	6834	0.94	0.06	0.02	0.42	0.04	124.63	6.15E-29	A	G
rs2854047	6	32179432	6834	0.94	0.06	0.02	0.42	0.04	124.02	8.33E-29	G	T
rs2555469	6	32179494	6834	0.94	0.06	0.02	0.42	0.04	124.01	8.39E-29	C	G
rs2071285	6	32180431	6834	0.94	0.06	0.02	0.42	0.04	123.93	8.71E-29	A	T
rs2854051	6	32184050	6834	0.94	0.06	0.02	0.42	0.04	123.77	9.48E-29	G	T
rs2854050	6	32185605	6834	0.94	0.06	0.02	0.42	0.04	123.52	1.07E-28	G	A
rs2071800	6	32714143	6834	0.93	0.03	0.01	0.33	0.05	40.48	1.99E-10	G	A
rs34878595	6	32715333	6834	0.93	0.03	0.01	0.34	0.05	43.00	5.48E-11	G	C



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rs11759423	6	32730392	6834	0.93	0.04	0.01	0.37	0.05	59.39	1.29E-14	C	T
rs33998906	6	32733628	6834	0.95	0.03	0.01	0.47	0.05	80.23	3.33E-19	C	T
rs35439528	6	32733823	6834	0.93	0.04	0.01	0.36	0.05	58.72	1.82E-14	C	T
rs34153000	6	32747016	6834	0.95	0.04	0.01	0.37	0.04	70.67	4.22E-17	C	A
rs35520662	6	32748029	6834	0.95	0.04	0.01	0.37	0.04	70.68	4.20E-17	T	G
rs34043227	6	32748590	6834	0.95	0.04	0.01	0.37	0.04	70.67	4.22E-17	C	T
rs34408145	6	32755177	6834	0.95	0.04	0.01	0.37	0.04	71.01	3.55E-17	T	C
rs35486885	6	32763506	6834	0.95	0.04	0.01	0.36	0.04	70.42	4.80E-17	A	G
rs34710970	6	32768115	6834	0.95	0.04	0.01	0.36	0.04	70.44	4.76E-17	A	G
rs35921062	6	32774416	6834	0.95	0.04	0.01	0.36	0.04	70.34	4.99E-17	C	T
rs34422230	6	32776995	6834	0.96	0.04	0.01	0.46	0.05	93.36	4.37E-22	T	C
rs41258084	6	32780957	6834	0.95	0.04	0.01	0.36	0.04	70.22	5.32E-17	C	T
rs41316241	6	32782795	6834	0.95	0.04	0.01	0.36	0.04	70.13	5.57E-17	C	A
rs17213756	6	32787996	6834	0.95	0.04	0.01	0.36	0.04	69.14	9.15E-17	C	T
rs41316544	6	32792886	6834	0.95	0.05	0.01	0.36	0.04	71.40	2.91E-17	T	A
rs41316548	6	32797167	6834	0.95	0.05	0.01	0.35	0.04	67.54	2.07E-16	C	T
rs2228396	6	32797809	6834	0.91	0.07	0.01	0.20	0.03	35.79	2.20E-09	C	T
rs41317090	6	32802354	6834	0.96	0.03	0.01	0.49	0.05	85.28	2.59E-20	C	A
rs4148878	6	32822186	6834	0.94	0.05	0.01	0.34	0.04	64.09	1.19E-15	T	G
rs35571244	6	32853219	6834	0.93	0.05	0.01	0.35	0.04	71.03	3.53E-17	T	C
rs34975158	6	32853511	6834	0.94	0.05	0.01	0.34	0.04	64.60	9.17E-16	G	A
rs35599935	6	32886487	6834	0.94	0.04	0.01	0.35	0.04	65.47	5.90E-16	T	C
rs35029304	6	32909533	6834	0.96	0.03	0.01	0.36	0.05	53.60	2.46E-13	T	C

**e-Table 2.** Baseline demographic and clinical characteristics of FHS participants with longitudinal spirometry data (N=4136).

<b>Characteristic</b>	<b>Mean</b>	<b>SD</b>
Age (yr)	46.3	12.2
Height (in)	66.7	3.66
sRAGE concentration (pg/mL)	3598	1120
$\Delta$ FEV1 (L)	-0.18	0.23
$\Delta$ FVC (L)	-0.14	0.26
$\Delta$ (FEV1/FVC) (L/yr)	-0.015	0.031
	<b>N</b>	<b>%</b>
Women	2257	54.4
New-onset COPD	352	8.51
Current smoker at baseline	543	12.3
Former smoker at baseline	1400	33.9

Abbreviations: BMI=body mass index; COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FVC=forced vital capacity

**e-Table 3.** Baseline demographic and clinical characteristics of never-, former-, and current- smokers with baseline spirometry data.

Characteristic	Never smokers (N=3,266)		Former smokers (N=2,031)		Current smokers (N=979)	
	Mean	SD	Mean	SD	Mean	SD
Age (yrs)	45.8	13.4	54.1	12	45.0	11.85
Height (in)	66.8	3.78	66.3	3.62	67.0	3.64
BMI (kg/m <sup>2</sup> )	27.2	5.41	27.9	5.39	27.1	5.44
sRAGE (pg/mL)	3674	1140	3474	1163	3520	1129
FEV1 (L)	3.37	0.88	2.98	0.85	3.23	0.94
FVC (L)	4.36	1.09	4.01	1.02	4.33	1.11
FEV1/FVC	0.77	0.065	0.74	0.076	0.74	0.083
	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>	<b>n</b>	<b>%</b>
Women	1745	53.5	1103	54.3	511	52.3
COPD	418	12.8	493	24.3	249	25.5

Abbreviations: BMI=body mass index; COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; SD=standard deviation

**e-Table 4.** Demographic and clinical characteristics of 2,707 FHS participants with quantitative CT imaging phenotypes.

<b>Characteristic</b>	<b>MEAN</b>	<b>SD</b>
Age (yrs)	50.3	10.0
Height (in)	67.0	3.8
BMI (kg/m <sup>2</sup> )	27.6	5.1
Smoking (pack-yrs)	8.9	15.3
sRAGE (pg/mL)	3537.8	1124.7
baseline FEV1 (L)	3269.9	875.1
baseline FVC (L)	4320.5	1080.6
baseline FEV1/FVC	75.6	6.9
%LAA950	2.8	2.3
	<b>N</b>	<b>%</b>
Women	1313	48.5
Offspring cohort	1019	37.64
Baseline COPD	494	18.25
Current smoker	336	12.41
Never smoker	1323	48.87
Former smoker	1048	38.71

\*Demographic and clinical characteristics collected at the examination cycles nearest to the time of the CT scans (Offspring cohort exam 7, Third Generation cohort exam 1).

Abbreviations: BMI=body mass index; COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; %LAA950=percentage low attenuation area (below -950 Hounsfield units); SD=standard deviation



**e-Table 5.** Colocalization of sRAGE pQTL variants with GWAS SNPs for pulmonary traits at the *AGER* locus on chromosome 6.

Locus	Trait	N_SNPs	PPH0	PPH1	PPH2	PPH3	PPH4
<i>AGER</i>	FEV1	5234	1.47E-70	8.74E-24	1.68E-47	<b>1</b>	2.56E-16
	FVC	5234	3.32E-58	1.97E-11	5.26E-50	2.13E-03	<b>9.98E-01</b>
	FEV1/FVC	5234	5.52E-230	3.28E-183	3.01E-50	7.88E-04	<b>9.99E-01</b>
	%LAA-950	1382	1.68E-51	5.59E-05	3.08E-50	2.39E-05	<b>1</b>

Results of colocalization analyses conducted between sRAGE pQTL variants and GWAS SNPs for pulmonary traits<sup>1,2</sup> at the sRAGE *cis* (*AGER*) locus on chromosome 6. The *cis* locus was defined as within one megabase upstream or downstream from transcription start site. N\_SNPs refers to the number of overlapping pQTL variants and GWAS SNPs within the aforementioned defined genomic region. Posterior probabilities were generated for five hypotheses: no associated SNPs for sRAGE or pulmonary trait (PPH0), 1 associated SNP for sRAGE only (PPH1), 1 associated SNP for pulmonary trait only (PPH2), 2 distinct SNPs for sRAGE and pulmonary trait (PPH3), and 1 associated SNP for both sRAGE and pulmonary trait (PPH4). Significant posterior probabilities (>90%) are shown in **bold**.

Abbreviations: FEV1=forced expiratory volume in one second; FVC=forced vital capacity; GWAS=genome-wide association study; %LAA-950=percentage of low attenuation area (below -950 Hounsfield units by chest CT); pQTL=protein quantitative trait locus; SNP=single nucleotide polymorphism

**e-Table 6.** MR analyses for pleiotropy of instrumental variables

Exposure	Outcome	All 9 SNPs			Excluding rs2070600		
		egger_intercept	se	pval	egger_intercept	se	pval
sRAGE	FEV1	0.020	0.0036	<b>8.33E-04</b>	0.018	0.011	0.16
	FVC	0.010	0.0023	<b>3.97E-03</b>	0.017	0.007	0.05
	FEV1/FVC	0.023	0.0066	<b>9.49E-03</b>	0.006	0.020	0.76

**e-Table 7.** Cross-sectional associations between sRAGE and continuous spirometry measures by smoking status.

Outcome	Never smokers (N=3266)			Former smokers (N=2031)			Current smokers (N=979)		
	Beta*	SE	P value	Beta*	SE	P value**	Beta*	SE	P value
FEV1	0.036	0.0084	<b>2.2E-05</b>	0.031	0.0097	<b>1.3E-03</b>	0.059	0.015	<b>4.9E-05</b>
FVC	0.064	0.010	<b>2.1E-10</b>	0.054	0.011	<b>3.8E-06</b>	0.087	0.0167	<b>1.7E-07</b>
FEV1/FVC	-0.36	0.11	<b>1.5E-03</b>	-0.19	0.15	0.193	-0.10	0.24	0.69

Covariates: age, sex, BMI, height, study cohort

\*Regression coefficients for FEV1 and FVC are reported as change in volume (L) per SD increment in standardized log-transformed plasma sRAGE concentration. Regression coefficients for FEV1/FVC as change in FEV1/FVC are reported per SD increment in standardized log-transformed plasma sRAGE concentration.

All *P* values less than 0.05 are shown **bold**.

Abbreviations: BMI=body mass index; COPD=chronic obstructive pulmonary disease; FEV1=forced expiratory volume in one second; FVC=forced vital capacity; SD=standard deviation

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