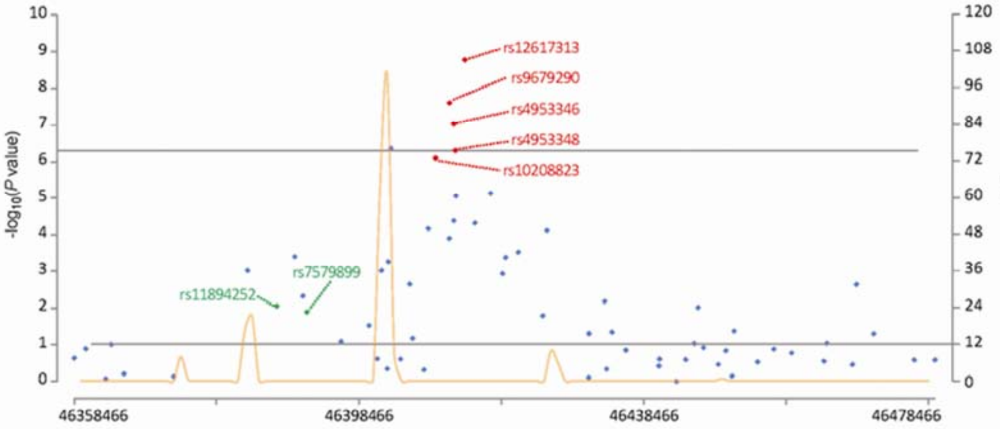
Supplemental Figure 1. Recombination hotspot analysis of a region of chromosome 2p21.

Illustration generated using SequenceLDhot shows the location of recombination hot spots (red peaks) in relation to the location of the new SNPs (red) and GWAS (green) SNPs.

Figure S1



Supplemental Table 1. pairwise r2 and LD between the old and new SNPs of interest

D’

r^2

	rs11894252	rs7579899	rs10208823	rs9679290	rs4953348	rs12617313
rs11894252		1	0.47	0.42	0.36	0.44
rs7579899	1		0.47	0.42	0.36	0.44
rs10208823	0.09	0.09		1	1	1
rs9679290	0.1	0.1	0.75		1	0.96
rs4953348	0.07	0.07	0.78	0.96		0.96
rs12617313	0.12	0.12	0.67	0.86	0.79	

Supplemental Table 2. Smoking by *EPAS1* SNP interaction

Region	SNP	Smoking Status	OR	95% CI	Association P-value	Interaction P-value
Reported in GWAS	rs7579899	NEVER	0.97	(0.81,1.16)	7.36E-01	0.036
		FORMER	1.34	(1.10,1.65)	4.22E-03	
		CURRENT	1.25	(1.05,1.49)	1.05E-02	
	rs11894252	NEVER	0.94	(0.74,1.20)	6.12E-01	0.199
		FORMER	1.26	(0.99,1.61)	6.30E-02	
		CURRENT	1.26	(1.01,1.57)	3.83E-02	
NEW	rs10208823	NEVER	0.75	(0.64,0.88)	4.84E-04	0.276
		FORMER	0.90	(0.76,1.07)	2.28E-01	
		CURRENT	0.82	(0.69,0.98)	2.81E-02	
	rs9679290	NEVER	1.38	(1.20,1.59)	7.60E-06	0.218
		FORMER	1.17	(1.00,1.38)	4.83E-02	
		CURRENT	1.20	(1.02,1.40)	2.62E-02	
	rs4953346	NEVER	1.36	(1.16,1.59)	1.39E-04	0.378
		FORMER	1.20	(1.00,1.43)	4.49E-02	
		CURRENT	1.18	(1.00,1.40)	5.51E-02	
	rs4953348	NEVER	1.33	(1.14,1.56)	3.79E-04	0.378
		FORMER	1.21	(1.01,1.44)	3.74E-02	
		CURRENT	1.15	(0.97,1.36)	1.16E-01	
	rs12617313	NEVER	1.42	(1.21,1.67)	1.87E-05	0.272
		FORMER	1.23	(1.03,1.48)	2.51E-02	
		CURRENT	1.21	(1.02,1.43)	3.10E-02	

ORs and P-values were calculated adjusting for age, sex, body mass index, study center, family history of cancer (any type of cancer), and hypertension

Supplemental Table 3. ***EPAS 1*** **variants and risk of having a** ***VHL*** **genetically altered RCC**

EPAS1 Region			RCC Cases						
			No Alteration	**(%)**	**Genetic Alteration**	**(%)**	**Odds Ratio** [1]	**(95% CI)**	**p-value**
New	**rs4953346**	GG	24	32.4	30	18.8	REF		
		GT	32	43.2	84	52.5	2.37	1.16-4.85	0.02
		TT	18	24.3	46	28.8	2.47	1.11-5.47	0.03
		Per allele-p-trend					*1.57*	*1.04-2.37*	*0.03*
		GT+TT	50	67.5	130	81.3	2.41	1.24-4.67	0.01
	rs12617313	TT	22	31.4	28	17.8	REF		
		AT	34	48.6	79	50.3	1.86	0.90-3.87	0.10
		AA	14	20.0	50	31.9	3.32	1.41-7.81	0.006
		Per allele-p-trend					*1.82*	*1.19-2.80*	*0.006*
		AT+AA	48	68.6	129	82.2	2.29	1.15-4.39	0.02
Reported in GWAS	**1867786**	GG	27	23.7	53	19.1	REF	0.78-2.50	
		GA	51	44.7	135	48.7	1.40	0.78-2.50	0.26
		AA	36	31.6	89	32.1	1.35	0.73-2.49	0.35
		Per allele-p-trend					*1.14*	*0.84-1.56*	*0.41*
		GA+AA	87	76.3	224	80.8	1.37	0.80-2.36	0.25
	rs7579899	GG	17	23.9	22	14.6	REF		
		AG	29	40.9	71	47.0	1.58	0.70-3.59	0.28
		AA	25	35.2	58	38.4	1.61	0.70-3.74	0.27
		Per allele-p-trend					1.23	0.81-1.86	0.33
		AG+GG	54	76.1	129	85.4	1.60	0.74-3.42	0.23

Adjusted for age, sex, country, tobacco status, and fruit intake