

Figure S1. Principal component analysis plots showing (A) total data in the microarray experiment, and (B) filtered data after three outliers were removed.

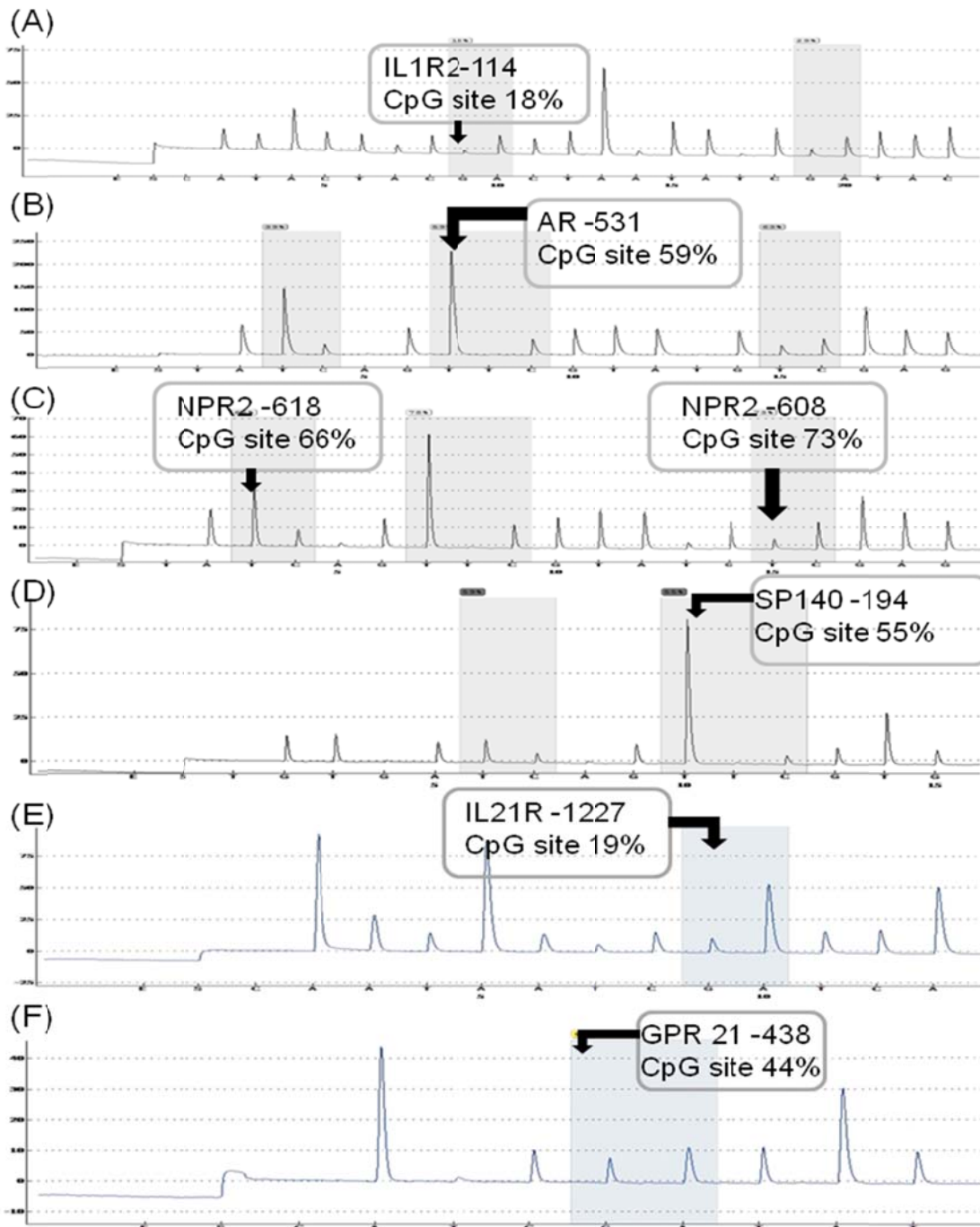


Figure S2. Representative programs showing the methylation at (A) -114 CpG site of the *IL1R2* promoter, (B) -531 CpG site of the *AR* promoter, (C) -608 and -618 CpG sites of the *NPR2* promoter, (D) -194 CpG site of the *Sp140* promoter region, (E) -1227 CpG site of the *IL21R* promoter region, and (F) -438 CpG site of the *GPR21* promoter region in a patient with OSA.

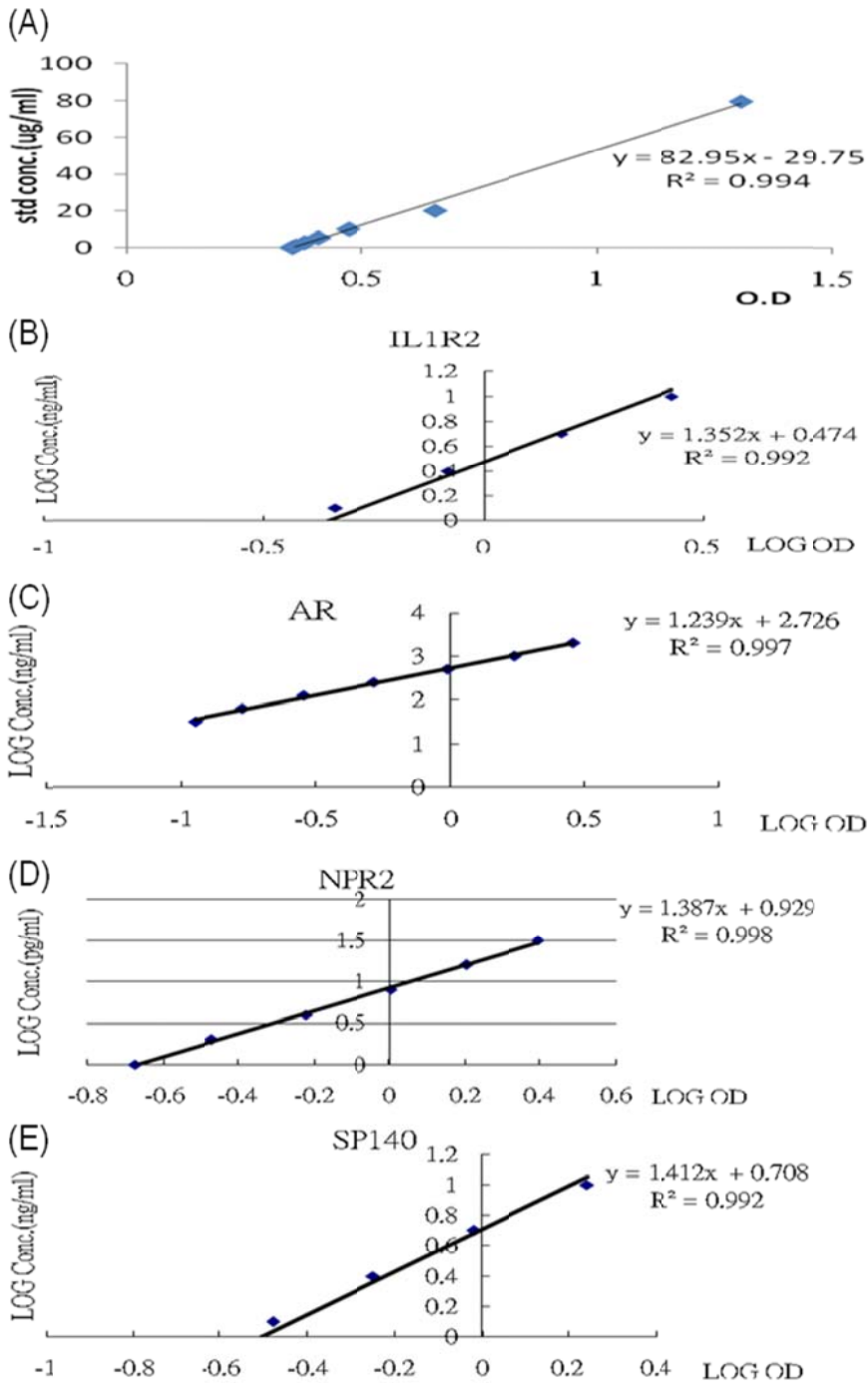


Figure S3. Standard curves for measuring total and specific protein levels of the peripheral blood mononuclear cells by the spectrophotometer and enzyme-linked immunosorbent assay methods. (A) Bovine serum albumin concentrations (Y-coordinate) from 0 to 80 $\mu\text{g/ml}$ were plotted against oxygen desaturation (OD) values at 595 nm (X-coordinate). The formulation was then used for the estimation of total protein concentrations of the peripheral blood mononuclear cell samples. (B) IL1R2, (C) AR, (D) NPR2, and (E) SP140 protein concentrations plotted against OD values after their logarithmic transformation.

Table S1. DNA Methylation Levels of the 20 CpG Sites Over the 16 Candidate Gene Promoter Regions in the Discovery Cohort

Column ID	Gene symbol	Distance to TSS	Healthy subjects N = 6			Patients with OSA N = 15		
			Mean, %	Median, %	β^b value	Mean, %	Median, %	β^b value
cg02656594 ^a	<i>IL21R</i>	1227	20.4	22	62.5	17.9	16	46.2
cg05564251 ^a	<i>SP140</i>	194	51.1	46	48.7	51.9	51	59.9
cg10266490	<i>ACOT11</i>	192	41	35	34.4	40.2	40	19.2
cg02519218	<i>CHFR</i>	490	61.6	59	74.7	58.5	60	86.3
cg19740969	<i>CXCL9</i>	949	77.9	76	70.3	65.7	62	86.6
cg22442090	<i>GIMAP5</i>	374	36.6	37	50.0	35	36	64.7
cg06796611	<i>IL24</i>	45	40.7	42	39.1	38.7	40	53.6
cg12876594 ^a	<i>NPR2</i>	608	30	30	73.5	25.4	26	55.9
cg12876594 ^a	<i>NPR2</i>	618	58.7	57	70.7	55.6	55	56.3
cg05019001 ^a	<i>AR</i>	531	34.3	33	9.2	35.9	35	20.8
cg17142183 ^a	<i>IL1R2</i>	114	21.8	21.5	80.2	18.1	18	72.9
cg06501084	<i>KCNH5</i>	389	85.2	85	54.4	83.2	85.5	65.1
cg00995520	<i>KCNA3</i>	627	41.2	39.5	62.0	50.5	47	46.0
cg03483626	<i>KCNA3</i>	621	53.5	60.5	42.9	66.9	67.5	39.6
cg22825487	<i>VNN3</i>	720	56.3	60.5	66.9	61.8	69	54.7
cg02218214	<i>ANGPTL3</i>	698	50	53	67.3	43.6	41	75.8
cg21409833	<i>ANGPTL3</i>	463	96.2	96.5	75.5	92.8	96	83.5
cg13578652	<i>UBASH3A</i>	156	67.5	57	38.3	69.3	61	45.3
cg00134539	<i>UBASH3A</i>	52	53.3	53	36.5	45.2	45	50.0
cg04784315 ^a	<i>GPR21</i>	438	33.5	37.5	62.7	28.3	28	49.9

^aThe changes in both the mean and median values of DNA methylation levels measured by the pyrosequencing method are in the same direction as the microarray results, and the difference in β value is $\geq 10\%$.

^bCalculated from the microarray results, as described in the Methods section.

OSA = obstructive sleep apnea; TSS = transcription start site.

Table S2. Primer sequences used for polymerase chain reaction and pyrosequencing of the six selected genes verified in the validation cohort

Gene	Primer	Sequences
<i>IL1R2</i>	Biotinylated forward PCR primer	TAATGGGGTTATAGTTGGGTAAA
	Reverse PCR primer	CCCCCAAACACTACAATACTAAATCTAAA
	Forward sequencing primer	CATAAATTTCCCTATTTTTCT
<i>AR</i>	Forward PCR primer	TTGAGGGTTTTTAGAGTAAATGGTATA
	Biotinylated reverse PCR primer	TACCTACTCCTAACTACCAAAAATTCTT
	Forward sequencing primer	TTTTTAGAGTAAATGGTATAATGT
<i>NPR2</i>	Biotinylated forward PCR primer	GAGGGAGGAGGAGAGGTA
	Reverse PCR primer	ACAAAAAAAACAAAAATAAATCTCCCTAT
	Reverse sequencing primer	AAACTCCTACTTAACTAA
<i>GPR21</i>	Biotinylated forward PCR primer	GGTTTGTATTAGTATTGATAGATATATTGT
	Reverse PCR primer	CCATAATATCCAAATTTACCCCAATAA
	Reverse sequencing primer	AACCAAATCAAAAAATACAC
<i>SP140</i>	Forward PCR primer	TAGGGGTAGATGGTAAGTGGA
	Biotinylated reverse PCR primer	ACAACCTCCAATCCAACCATTTACA
	Forward sequencing primer	GAGATAGTAATTTTAATTTTAGGTG
<i>IL21R</i>	Biotinylated forward PCR primer	AATGAGTTAGTAGGGAGAGTTATAAAT
	Reverse PCR primer	CCTACATAATCTCACTTTATCCCACAAAAT
	Reverse sequencing primer	ACAAATAAAAAAACTAAAACCCA

PCR = polymerase chain reaction.

Table S3. Top Differentially Methylated Loci in the Comparison Between Patients With OSA With and Without Hypertension (Comparison II)

	Column ID	Gene symbol	Chromosome	P value	q value	Difference in β value
Hypermethylated	cg10995925	<i>LTA</i>	6	0.005905	0.473535	0.1985
	cg10466917	<i>TRY1</i>	7	0.009324	0.473535	0.1513
	cg08843314	<i>CXCR3</i>		0.00373	0.473535	0.14915
	cg22442090	<i>GIMAP5</i>	7	0.009324	0.473535	0.13627
	cg24352688	<i>OFD1</i>		0.009324	0.473535	0.13422
	cg04183425	<i>ASF1A</i>	6	0.005905	0.473535	0.13095
	cg23276695	<i>CNR1</i>	6	0.00373	0.473535	0.12856
	cg22268164	<i>TRHR</i>	8	0.009324	0.473535	0.12566
	cg12513379	<i>OR10H2</i>	19	0.005905	0.473535	0.12333
	cg12682367	<i>FLJ46358</i>	13	0.009324	0.473535	0.12038
	cg12927617	<i>ORM1</i>	9	0.009324	0.473535	0.11887
	cg05564251	<i>SP140</i>	2	0.009324	0.473535	0.11775
	cg27622610	<i>ORIG1</i>	17	0.002176	0.473535	-0.11343
	cg04527989	<i>PTCD2</i>	5	0.005905	0.473535	-0.11167
	cg06154597	<i>MGC4618</i>	4	0.005905	0.473535	-0.11065
Hypomethylated	cg06812844	<i>TRPM2</i>	21	0.009324	0.473535	-0.115631
	cg01173186	<i>VMP</i>	6	0.009324	0.473535	-0.116092
	cg23265096	<i>CTSZ</i>	20	0.009324	0.473535	-0.122076
	cg20340242	<i>IL1R2</i>	2	0.00373	0.473535	-0.122983
	cg25882366	<i>HOXB2</i>	17	0.005905	0.473535	-0.127828
	cg12943082	<i>CCL26</i>	7	0.005905	0.473535	-0.138697
	cg21096966	<i>BTBD5</i>	14	0.005905	0.473535	-0.144355
	cg05556717	<i>CCL26</i>	7	0.000622	0.473535	-0.153207

Table S4. Products and Known Functions of the Genes With Top Differentially Methylated Loci in the Comparisons I and II

Symbol	Gene ontology process	Product
<i>ENTPDI</i>	Cell adhesion; cell-cell signaling; blood coagulation; antimicrobial humoral response	Ectonucleoside Triphosphate Diphosphohydrolase 1
<i>LGP1</i>	Molecular function unknown	LGP1 homolog
<i>NPR2</i>	cGMP biosynthesis; intracellular signaling cascade; regulation of blood pressure; protein amino acid phosphorylation; cell surface receptor linked signal transduction	Natriuretic peptide receptor B isoform a precursor
<i>SUSD1</i>	Calcium ion binding	Sushi domain containing 1
<i>IL21R</i>	Natural killer cell activation	Interleukin 21 receptor precursor
<i>KCNA3</i>	Potassium ion transport	Potassium voltage-gated channel; shaker-related subfamily; member 3
<i>ACOT11</i>	Fatty acid metabolism; response to temperature stimulus; intracellular signaling cascade	Thioesterase; adipose associated isoform BFIT1
<i>TFAP2E</i>	Regulation of transcription; DNA-dependent	Transcription factor AP-2 epsilon (activating enhancer binding protein 2 epsilon)
<i>RAB34</i>	Protein transport; small GTPase mediated signal transduction	RAB39
<i>APBA2</i>	Protein transport; nervous system development	Amyloid beta A4 precursor protein-binding; family A; member 2
<i>GIMAP5</i>	GTP binding; nucleotide binding	GTPase; IMAP family member 5
<i>ABCC12</i>	Nucleotide binding; ATPase activity; coupled to transmembrane movement of substances	ATP-binding cassette; subfamily C; member 12 isoform e
<i>LUM</i>	Visual perception; collagen fibril organization	Lumican precursor
<i>CRTAM</i>	Molecular function unknown	Class-I MHC-restricted T cell associated molecule

Symbol	Gene ontology process	Product
<i>EDA2R</i>	Cell differentiation; embryonic development; epidermis development; positive regulation of JNK cascade; activation of NF-kappa B transcription factor	X-linked ectodysplasin receptor
<i>CYSLTR2</i>	Immune response; signal transduction; G-protein coupled receptor protein signaling pathway	Cysteinyl leukotriene receptor 2
<i>RCHY1</i>	Protein ubiquitination	Ring finger and CHY zinc finger domain containing 1 isoform 1
<i>RNF36</i>	Protein ubiquitination	Ring finger protein 36 isoform b
<i>CXCL9</i>	Chemotaxis; cell-cell signaling; signal transduction; signal transduction; inflammatory response; cellular defense response; G-protein coupled receptor protein signaling pathway	Small inducible cytokine B9 precursor
<i>LTA</i>	Immune response; cell-cell signaling; signal transduction; induction of apoptosis	Lymphotoxin alpha precursor
<i>TRY1</i>	Proteolysis and peptidolysis	Trypsin X3
<i>CXCR3</i>	Chemotaxis; cell adhesion; go_process: cell motility signal transduction; G-protein coupled receptor protein signaling pathway; elevation of cytosolic calcium ion concentration; antimicrobial humoral response	Chemokine (C-X-C motif) receptor 3
<i>GIMAP5</i>	GTP binding; nucleotide binding	GTPase; IMAP family member 5
<i>OFD1</i>	Catalytic activity; biological process unknown	Oral-facial-digital syndrome 1
<i>ASF1A</i>	Loss of chromatin silencing	ASF1 anti-silencing function 1 homolog A
<i>CNR1</i>	Behavior; signal transduction; G-protein signaling; coupled to cyclic nucleotide second messenger	Central cannabinoid receptor isoform a
<i>TRHR</i>	Signal transduction; G-protein coupled receptor protein signaling pathway	Thyrotropin-releasing hormone receptor
<i>OR10H2</i>	Signal transduction; sensory perception of smell; G-protein coupled receptor protein signaling pathway	Olfactory receptor; family 10; subfamily H; member 2
<i>FLJ46358</i>	Molecular function unknown	Hypothetical protein LOC400110
<i>ORM1</i>	Acute-phase response; inflammatory response	Orosomuroid 1 precursor

Symbol	Gene ontology process	Product
<i>SP140</i>	Defense response; regulation of transcription; DNA-dependent	SP140 nuclear body protein isoform 1
<i>TRPM2</i>	Sodium ion transport; calcium ion transport	Transient receptor potential cation channel; subfamily M; member 2 isoform SSF-TRPM2
<i>VMP</i>	Molecular function unknown	Vesicular membrane protein p24
<i>CTSZ</i>	Proteolysis	cathepsin Z preproprotein
<i>IL1R2</i>	Blocking receptor activity; immune response	Interleukin 1 receptor; type II precursor
<i>HOXB2</i>	Circulation; development; regulation of transcription; DNA-dependent	Homeo box B2
<i>CCL26</i>	Chemotaxis; sensory perception; cell-cell signaling; signal transduction; inflammatory response	Chemokine (C-C motif) ligand 26 precursor
<i>BTBD5</i>	Protein binding	BTB (POZ) domain containing 5
<i>PLAT</i>	Proteolysis; blood coagulation; protein modification	plasminogen activator; tissue type isoform 1 preproprotein
<i>BTG3</i>	Negative regulation of cell proliferation; regulation of progression through cell cycle	B-cell translocation gene 3
<i>JAK2</i>	Cell motility; JAK-STAT cascade; mesoderm development; intracellular signaling cascade; protein amino acid phosphorylation; regulation of progression through cell cycle	Janus kinase 2
<i>ARID3A</i>	Regulation of transcription; DNA-dependent	AT rich interactive domain 3A (BRIGHT- like) protei
<i>CD9</i>	Cell adhesion; cell motility; go_process: platelet activation; paranodal junction assembly; fusion of sperm to egg plasma membrane	CD9 antigen
<i>GPR21</i>	G-protein coupled receptor protein signaling pathway	G protein-coupled receptor 21

Symbol	Gene ontology process	Product
<i>PITPNM2</i>	Calcium ion binding; transport; metabolism	Phosphatidylinositol transfer protein; membrane-associated 2
<i>VNN3</i>	Nitrogen compound metabolism	Vanin 3 isoform 2 precursor
<i>NRG4</i>	Growth factor activity	Neuregulin 4
<i>KRTCAP3</i>	Unknown	Keratinocyte associated protein 3
<i>SEC31L2</i>	Secretory pathway component Sec31B-1	Saccharomyces cerevisiae SEC31-like 2 isoform a
<i>PNPLA2</i>	Adipose triglyceride lipase; lipid metabolism	Patatin-like phospholipase domain containing 2
<i>PIP3-E</i>	Oxygen transport; response to oxidative stress	phosphoinositide-binding protein PIP3-E
<i>KLRG1</i>	Inflammatory response; cellular defense response; cell surface receptor linked signal transduction	Killer cell lectin-like receptor subfamily G; member 1
<i>FCGRT</i>	MHC class I receptor activity; pregnancy; antigen presentation	Fc fragment of IgG; receptor; transporter; alpha
<i>CCDC19</i>	Unknown biological process	Nasopharyngeal epithelium specific protein 1
<i>IL24</i>	Cytokine activity; apoptosis; immune response	Interleukin 24 isoform 2
<i>MOBP</i>	Nervous system development	Myelin-associated oligodendrocyte basic protein isoform c
<i>PTPRC</i>	Regulation of cell cycle; B cell receptor signaling; amino acid dephosphorylation; positive regulation of T cell proliferation; negative regulation of protein kinase activity; release of sequestered calcium ion into cytosol; negative regulation of T cell mediated cytotoxicity	Protein tyrosine phosphatase; receptor type; C isoform 1 precursor
<i>SLC25A26</i>	Transport; binding	Solute carrier family 25; member 26 isoform b
<i>UNQ9356</i>	Receptor activity	IVFI9356

Symbol	Gene ontology process	Product
<i>AHR</i>	Apoptosis; cell cycle; response to stress; response to xenobiotic stimulus; DNA-dependent; transcription from RNA polymerase II promoter	Aryl hydrocarbon receptor
<i>FASLG</i>	Tumor necrosis factor receptor binding; apoptosis; immune response; cell-cell signaling; induction of apoptosis; positive regulation of I- κ B kinase/NF- κ B cascade	Fas ligand
<i>UBASH3A</i>	Catalytic activity; metabolism	Ubiquitin associated and SH3 domain containing; A long form
<i>ITGB6</i>	Development; cell adhesion; cell-matrix adhesion; integrin-mediated signaling pathway	Integrin; beta 6
<i>RGS13</i>	Negative regulation of signal transduction	Regulator of G-protein signaling 13
<i>PIK3C2A</i>	Intracellular signaling cascade; phosphatidylinositol biosynthesis	Phosphoinositide-3-kinase; class 2; alpha polypeptide
<i>CYBB</i>	Ion transport; electron transport; inflammatory response; antimicrobial humoral response (sensu Vertebrata)	Cytochrome b-245; beta polypeptide
<i>KSR1</i>	Intracellular signaling cascade; protein amino acid phosphorylation; Ras protein signal transduction	Kinase suppressor of ras
<i>KRTAP19-6</i>	Unknown biological process	Keratin associated protein 19-6
<i>GPR87</i>	G-protein coupled receptor protein signaling pathway	G protein-coupled receptor 87
<i>RBM10</i>	RNA binding; zinc ion binding; nucleotide binding; nucleic acid binding	RNA binding motif protein 10 isoform 1
<i>CHFR</i>	Mitosis; cell cycle; cell division; mitotic checkpoint; protein ubiquitination	Checkpoint with FHA and Ring Finger
<i>KERA</i>	Visual perception; eye development	Keratocan
<i>EGFL11</i>	Calcium ion binding	EGF-like-domain; multiple 11
<i>POT1</i>	Protein amino acid dephosphorylation	Protein phosphatase 1M (PP2C domain containing)

Symbol	Gene ontology process	Product
<i>LCK</i>	Caspase activation; zinc ion homeostasis; induction of apoptosis; protein amino acid phosphorylation; Ras protein signal transduction; release of sequestered calcium ion into cytosol; positive regulation of T cell receptor signaling	Lymphocyte-specific protein tyrosine kinase
<i>SIAE</i>	Hydrolase activity; serine esterase activity; sialate O-acetylerase activity	Cytosolic sialic acid 9-O-acetylerase homolog
<i>NLN</i>	Zinc ion binding; hydrolase activity; metalloendopeptidase activity; proteolysis	Neurolysin
<i>KCNH5</i>	Cation transport; potassium ion transport; regulation of transcription; DNA-dependent; two-component signal transduction system (phosphorelay)	Potassium voltage-gated channel; subfamily H; member 5 isoform 1
<i>ORIG1</i>	Signal transduction; sensory perception of smell; G-protein coupled receptor protein signaling pathway	Olfactory receptor; family 1; subfamily G; member 1
<i>PTCD2</i>	Binding	Pentatricopeptide repeat domain 2
<i>MGC4618</i>	Unknown molecular function	hypothetical protein LOC84286

Table S5. Top 10 Pathways Enriched in the Comparison Between Patients With OSA With and Without Hypertension (Comparison II)

Pathway maps	Number in data/total	P value	q value	Differentially methylated loci involved in the pathway
Apoptosis and survival_Anti-apoptotic action of membrane-bound <i>ESR1</i>	4/38	9.824 E-04	1.138 E-01	<i>JNK(MAPK8-10)</i> , <i>L-type Ca(II) channel</i> , <i>alpha 1C subunit</i> , <i>Bcl-2</i> , <i>PI3K reg class IA (p85)</i>
Transcription_ <i>P53</i> signaling pathway	4/39	1.085 E-03	1.138 E-01	<i>JNK(MAPK8-10)</i> , <i>FHL2</i> , <i>Rb protein</i> , <i>Bcl-2</i>
Retinol metabolism / Rodent version	5/68	1.186 E-03	1.138 E-01	<i>DHA6</i> , <i>CYP2A6</i> , <i>DGAT1</i> , <i>ALIA1</i> , <i>ALDH2</i>
Immune response_ <i>HMGB1</i> release from the cell	4/41	1.312 E-03	1.138 E-01	<i>JNK(MAPK8-10)</i> , <i>PARP-1</i> , <i>PI3K reg class IA (p85)</i> , <i>PI3K reg class IA</i>
Retinol metabolism	5/72	1.534 E-03	1.138 E-01	<i>DHA6</i> , <i>CYP2A6</i> , <i>DGAT1</i> , <i>ALIA1</i> , <i>ALDH2</i>
Development_ <i>Notch</i> Signaling Pathway	4/43	1.570 E-03	1.138 E-01	<i>SKIP (Ski-interacting protein)</i> , <i>Furin</i> , <i>Histone H3</i> , <i>ADAM17</i>
Development_ Melanocyte development and pigmentation	4/49	2.555 E-03	1.588 E-01	<i>SOX10</i> , <i>Frizzled</i> , <i>PI3K reg class IA</i> , <i>PKA-reg (cAMP-dependent)</i>
<i>G-protein</i> signaling_ Proinsulin C-peptide signaling	4/52	3.178 E-03	1.646 E-01	<i>PI3K reg class IA (p85-alpha)</i> , <i>Bcl-2</i> , <i>PI3K reg class IA (p85)</i> , <i>PI3K reg class IA</i>
Immune response_ <i>HMGB1/RAGE</i> signaling pathway	4/53	3.406 E-03	1.646 E-01	<i>JNK(MAPK8-10)</i> , <i>PI3K reg class IA (p85-alpha)</i> , <i>PLAT (TPA)</i> , <i>PI3K reg class IA (p85)</i>
Development_ <i>Gastrin</i> in cell growth and proliferation	4/62	5.988 E-03	1.978 E-01	<i>JNK(MAPK8-10)</i> , <i>PI3K reg class IA (p85-alpha)</i> , <i>E-cadherin</i> , <i>PI3K reg class IA (p85)</i>