Supplementary Table 1. Clinical characteristics of the subjects were included in our study.

Characteristics	Discovery cohort		P	Control (n=75)	Validation cohort		P
	NORA (n=34)	CRA (n=53)			NORA (n=8)	CRA (n=18)	
Age (year)	56.74±12.98	57.94±10.55	0.635	51.61±7.72	61.25±8.48	58.28±8.27	0.410
Female,sex (n)	20	41	0.065	31	5	10	1.000
CRP (mg/L)	37.12±39.16	36.49±32.85	0.548	——	47.91±55.31	59.98±48.72	0.291
ESR (mm/h)	56.73±35.08	63.08±30.02	0.376	——	67.63±37.36	74.39±31.73	0.639
RF (U/ml)	269.51±217.67	277.74±403.03	0.401	——	231.81±453.51	359.60±230.48	0.046*
SJC28	10.10±7.41	6.33±6.92	0.014*	——	15.50±9.70	8.61±10.04	0.083
TJC28	11.65±7.75	9.72±8.19	0.218	——	16.00±11.05	10.39±10.99	0.261
DAS28(3)	5.56±1.39	5.35±1.23	0.358	——	5.79±1.69	4.99±2.10	0.350
IL-6 (pg/mL)	84.42±80.31	65.42±125.90	0.032*	——	——	——	——

Date presented as number mean±standard deviation.

NORA, new-onset rheumatoid arthritis; CRA, chronic rheumatoid arthritis; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; RF, rheumatoid factors; SJC28, 28 swollen joints count; TJC28, 28 tender joints count; DAS28, disease activity score; DAS28(3) = [0.56*sqrt(t28) + 0.28*sqrt(sw28) + 0.70*Ln(ESR)]*1.08 + 0.16; IL-6, Interleukin 6; *, $P \leq 0.05$.

Supplementary Table 2. Enrichment pathway of 6 differentially significant metabolites between NORA and CRA patients.

Metabolite	VIP	FC	P value
L-Phenylalanine	2.0842	1.1692	0.0305*
Trans-cinnamate	1.5284	1.3520	0.0183*
Alpha-N-Phenylacetyl-L-glutamine	1.6636	1.4605	0.0330*
1-Palmitoyl-sn-glycero-3-phosphocholine	1.8082	0.6142	0.0071**
1-Stearoyl-2-hydroxy-sn-glycero-3-phosphocholine	3.0471	0.6216	0.0002***
Glycerophosphocholine	1.9527	0.714	0.0042**

NORA, new-onset rheumatoid arthritis; CRA, chronic rheumatoid arthritis. *, $P < 0.05$; **, $P \leq 0.01$, ***, $P \leq 0.001$.

Supplementary Table 3. 9 gene sets were significantly enriched in the control, based on all protein-coding genes by GSEA analysis between NORA and control.

NAME	SIZE	ES	NES	P value
KEGG_NEUROACTIVE_LIGAND_RECEPTOR_INTERACTION	216	-0.35	-1.59	0.000
KEGG_TASTE_TRANSDUCTION	42	-0.53	-1.83	0.002
KEGG_GLYCOSYLPHOSPHATIDYLINOSITOL_ GPI_ANCHOR_BIOSYNTHESIS	24	-0.50	-1.66	0.008
KEGG_ARACHIDONIC_ACID_METABOLISM	48	-0.42	-1.58	0.016
KEGG_GLYCEROPHOSPHOLIPID_METABOLISM	73	-0.37	-1.54	0.020
KEGG_HEDGEHOG_SIGNALING_PATHWAY	53	-0.36	-1.43	0.032
KEGG_BASAL_CELL_CARCINOMA	54	-0.41	-1.54	0.032
KEGG_CALCIUM_SIGNALING_PATHWAY	162	-0.29	-1.36	0.035
KEGG_RNA_POLYMERASE	28	-0.45	-1.47	0.048

NORA, new-onset rheumatoid arthritis; CRA, chronic rheumatoid arthritis; GSEA, Gene Set Enrichment Analysis.

Supplementary Table 4. Significant enrichment of 3 gene sets in control, 16 gene sets in CRA, based on all protein-coding genes between CRA and controls by GSEA analysis.

3 gene sets enriched in control				
NAME	SIZE	ES	NES	P-value
KEGG_TASTE_TRANSDUCTION	42	-0.57	-1.74	0.012
KEGG_LINOLEIC_ACID_METABOLISM	25	-0.57	-1.62	0.002
KEGG_ARRHYTHMOGENIC_RIGHT_VENTRICULAR_CARDIOMYOPATHY_ARVC	73	-0.33	-1.40	0.038
16 gene sets enriched in CRA				
NAME	SIZE	ES	NES	P value
KEGG_CYSTEINE_AND_METHIONINE_METABOLISM	33	0.52	1.83	0.002
KEGG_PARKINSONS_DISEASE	121	0.62	1.81	0.034
KEGG_OXIDATIVE_PHOSPHORYLATION	126	0.61	1.80	0.036
KEGG_HUNTINGTONS_DISEASE	173	0.49	1.75	0.038
KEGG_LYSOSOME	118	0.52	1.74	0.006
KEGG_ALZHEIMERS_DISEASE	158	0.48	1.73	0.045
KEGG_GLUTATHIONE_METABOLISM	43	0.52	1.73	0.002
KEGG_CITRATE_CYCLE_TCA_CYCLE	28	0.62	1.73	0.016
KEGG_PROTEASOME	44	0.52	1.71	0.028
KEGG_ANTIGEN_PROCESSING_AND_PRESENTATION	69	0.48	1.67	0.010
KEGG_PROTEIN_EXPORT	23	0.59	1.67	0.029
KEGG_PATHOGENIC_ESCHERICHIA_COLI_INFECTION	54	0.52	1.65	0.021
KEGG_OOCYTE_MEIOSIS	107	0.38	1.59	0.014
KEGG_BIOSYNTHESIS_OF_UNSATURATED_FATTY_ACIDS	22	0.52	1.58	0.022
KEGG_PENTOSE_PHOSPHATE_PATHWAY	25	0.52	1.56	0.042
KEGG_SNARE_INTERACTIONS_IN_VESICULAR_TRANSPORT	38	0.42	1.52	0.047

Supplementary Table 5. KEGG and GO enrichment analysis of 196 differentially expressed genes between NORA and control.

ID	Pathway_Name	Count	Enrichment	p_Value
hsa04913	Ovarian steroidogenesis	3	0.0625	0.006492759
hsa04610	Complement and coagulation cascades	3	0.04	0.021789907
hsa04970	Salivary secretion	3	0.035294118	0.030145967
GO:0019373	epoxygenase P450 pathway	3	0.142857143	0.000771184
GO:0034754	cellular hormone metabolic process	5	0.043478261	0.003362224
GO:0046426	negative regulation of JAK-STAT cascade	3	0.058823529	0.009980307
GO:1904893	negative regulation of STAT cascade	3	0.058823529	0.009980307
GO:0019369	arachidonic acid metabolic process	3	0.056603774	0.011086064
GO:0050803	regulation of synapse structure or activity	5	0.028409091	0.01913541
GO:0019748	secondary metabolic process	3	0.044776119	0.020760376
GO:0006805	xenobiotic metabolic process	4	0.033333333	0.020971551
GO:0010951	negative regulation of endopeptidase activity	6	0.024	0.022504345
GO:0010466	negative regulation of peptidase activity	6	0.022813688	0.027947001
GO:0050906	detection of stimulus involved in sensory perception	9	0.018255578	0.029030265
GO:0010765	positive regulation of sodium ion transport	2	0.064516129	0.029796211
GO:0006730	one-carbon metabolic process	2	0.057142857	0.03727676
GO:0044344	cellular response to fibroblast growth factor stimulus	4	0.027777778	0.037446944
GO:0043271	negative regulation of ion transport	4	0.027586207	0.038257559
GO:0043267	negative regulation of potassium ion transport	2	0.055555556	0.039248174
GO:0071774	response to fibroblast growth factor	4	0.026490066	0.043332106
GO:0051588	regulation of neurotransmitter transport	3	0.033333333	0.04410979
GO:0051346	negative regulation of hydrolase activity	8	0.017621145	0.045733779
GO:0016125	sterol metabolic process	4	0.025974026	0.046004936
GO:0072503	cellular divalent inorganic cation homeostasis	8	0.01754386	0.046713745
GO:0042181	ketone biosynthetic process	2	0.05	0.047514063

Supplementary Table 6. KEGG and GO enrichment analysis of 211 differentially expressed genes between CRA and control.

ID	Pathway_Name	Count	Enrichment	p_Value
hsa00982	Drug metabolism - cytochrome P450	6	0.092307692	8.04E-05
hsa04020	Calcium signaling pathway	8	0.043715847	0.000966098
hsa00980	Metabolism of xenobiotics by cytochrome P450	5	0.072463768	0.0010045
hsa05204	Chemical carcinogenesis	5	0.064935065	0.001646987
hsa04726	Serotonergic synapse	5	0.044642857	0.008252113
hsa05322	Systemic lupus erythematosus	5	0.043103448	0.009530419
hsa04610	Complement and coagulation cascades	4	0.053333333	0.009773631
hsa00360	Phenylalanine metabolism	2	0.125	0.013470534
hsa04970	Salivary secretion	4	0.047058824	0.014971476
hsa04974	Protein digestion and absorption	4	0.046511628	0.01557085
hsa00140	Steroid hormone biosynthesis	3	0.055555556	0.022383946
hsa04750	Inflammatory mediator regulation of TRP channels	4	0.040816327	0.02395963
hsa00340	Histidine metabolism	2	0.090909091	0.024831356
hsa04921	Oxytocin signaling pathway	5	0.032894737	0.027571626
hsa04080	Neuroactive ligand-receptor interaction	7	0.025547445	0.033446169
hsa00830	Retinol metabolism	3	0.046875	0.034734996
hsa04919	Thyroid hormone signaling pathway	4	0.035714286	0.036665856
hsa04742	Taste transduction	3	0.044776119	0.039003143
hsa05031	Amphetamine addiction	3	0.044776119	0.039003143
hsa05214	Glioma	3	0.042857143	0.043526369
hsa00983	Drug metabolism - other enzymes	3	0.04109589	0.048300933
hsa05133	Pertussis	3	0.04109589	0.048300933
hsa04971	Gastric acid secretion	3	0.040540541	0.049947573
GO:0043271	negative regulation of ion transport	7	0.048275862	0.00050106
GO:1900371	regulation of purine nucleotide biosynthetic process	7	0.045454545	0.00071715
GO:0030808	regulation of nucleotide biosynthetic process	7	0.04516129	0.000745113
GO:0019373	epoxygenase P450 pathway	3	0.142857143	0.001014523
GO:0014065	phosphatidylinositol 3-kinase signaling	6	0.045801527	0.001655385
GO:0019369	arachidonic acid metabolic process	4	0.075471698	0.001656886
GO:0048015	phosphatidylinositol-mediated signaling	6	0.037735849	0.004342374
GO:2001257	regulation of cation channel activity	6	0.0375	0.004476564
GO:2000257	regulation of protein activation cascade	3	0.06122449	0.01155576
GO:0002544	chronic inflammatory response	2	0.105263158	0.014044865
GO:0052652	cyclic purine nucleotide metabolic process	4	0.038461538	0.01787916
GO:0008654	phospholipid biosynthetic process	7	0.024221453	0.021614065
GO:0046474	glycerophospholipid biosynthetic process	6	0.024489796	0.030932198

GO:0006171	cAMP biosynthetic process	3	0.041666667	0.031913732
GO:0030818	negative regulation of cAMP biosynthetic process	2	0.066666667	0.033361672
GO:0038111	interleukin-7-mediated signaling pathway	2	0.066666667	0.033361672
GO:0098761	cellular response to interleukin-7	2	0.064516129	0.035442037
GO:0071875	adrenergic receptor signaling pathway	2	0.0625	0.037571344
GO:0006644	phospholipid metabolic process	9	0.019067797	0.038471875
GO:0030814	regulation of cAMP metabolic process	3	0.037974684	0.040333433
GO:0050848	regulation of calcium-mediated signaling	3	0.037974684	0.040333433
GO:0007188	adenylate cyclase-modulating G-protein coupled receptor signaling pathway	5	0.025	0.043730329
GO:0009132	nucleoside diphosphate metabolic process	4	0.027777778	0.049994036
GO:0044344	cellular response to fibroblast growth factor stimulus	4	0.027777778	0.049994036

Supplementary Table 7. KEGG and GO enrichment analysis of 40 differentially expressed genes between NORA and CRA patients.

ID	Pathway_Name	Count	Enrichment	p_Value
hsa00564	Glycerophospholipid metabolism	2	0.020833333	0.007523158
hsa00604	Glycosphingolipid biosynthesis - ganglio series	1	0.071428571	0.01947223
hsa04964	Proximal tubule bicarbonate reclamation	1	0.043478261	0.031809201
GO:0050878	regulation of body fluid levels	5	0.01002004	0.001783292
GO:0048146	positive regulation of fibroblast proliferation	2	0.037735849	0.004040813
GO:0010001	glial cell differentiation	3	0.015228426	0.005161122
GO:0050891	multicellular organismal water homeostasis	2	0.03125	0.005839829
GO:0009247	glycolipid biosynthetic process	2	0.029411765	0.006569524
GO:0030104	water homeostasis	2	0.029411765	0.006569524
GO:0006643	membrane lipid metabolic process	3	0.013513514	0.00717923
GO:0050805	negative regulation of synaptic transmission	2	0.02739726	0.007536937
GO:0051702	interaction with symbiont	2	0.027027027	0.007737704
GO:2000027	regulation of organ morphogenesis	3	0.012048193	0.009820878
GO:0048145	regulation of fibroblast proliferation	2	0.022988506	0.010563645
GO:1902476	chloride transmembrane transport	2	0.022988506	0.010563645
GO:0048144	fibroblast proliferation	2	0.022727273	0.010797339
GO:0042063	gliogenesis	3	0.011538462	0.011039578
GO:0021782	glial cell development	2	0.021276596	0.012247256
GO:0052652	cyclic purine nucleotide metabolic process	2	0.019230769	0.014841957
GO:0009152	purine ribonucleotide biosynthetic process	3	0.010273973	0.015067585
GO:0009190	cyclic nucleotide biosynthetic process	2	0.019047619	0.015113421
GO:0098661	inorganic anion transmembrane transport	2	0.018867925	0.015387033
GO:0006164	purine nucleotide biosynthetic process	3	0.010135135	0.01562235
GO:0006821	chloride transport	2	0.018691589	0.015662786
GO:0060071	Wnt signaling pathway, planar cell polarity pathway	2	0.018181818	0.016502804
GO:0009260	ribonucleotide biosynthetic process	3	0.009836066	0.016912688
GO:0090175	regulation of establishment of planar polarity	2	0.017857143	0.017073371
GO:0072522	purine-containing compound biosynthetic process	3	0.00974026	0.0173558
GO:0046390	ribose phosphate biosynthetic process	3	0.009708738	0.017504952
GO:0019755	one-carbon compound transport	1	0.1	0.017769668

GO:0021670	lateral ventricle development	1	0.1	0.017769668
GO:0032429	regulation of phospholipase A2 activity	1	0.1	0.017769668
GO:0033131	regulation of glucokinase activity	1	0.1	0.017769668
GO:0060502	epithelial cell proliferation involved in lung morphogenesis	1	0.1	0.017769668
GO:0061140	lung secretory cell differentiation	1	0.1	0.017769668
GO:0106070	regulation of adenylate cyclase-activating G-protein coupled receptor signaling pathway	1	0.1	0.017769668
GO:0015791	polyol transport	1	0.090909091	0.019529734
GO:0046689	response to mercury ion	1	0.090909091	0.019529734
GO:0071474	cellular hyperosmotic response	1	0.090909091	0.019529734
GO:1902894	negative regulation of pri-miRNA transcription by RNA polymerase II	1	0.090909091	0.019529734
GO:1903299	regulation of hexokinase activity	1	0.090909091	0.019529734
GO:0001736	establishment of planar polarity	2	0.016393443	0.020050493
GO:0007164	establishment of tissue polarity	2	0.016393443	0.020050493
GO:0060456	positive regulation of digestive system process	1	0.083333333	0.021286748
GO:1900452	regulation of long term synaptic depression	1	0.083333333	0.021286748
GO:0006664	glycolipid metabolic process	2	0.015748031	0.021615076
GO:1903509	liposaccharide metabolic process	2	0.015748031	0.021615076
GO:0007596	blood coagulation	3	0.008797654	0.02266181
GO:0030157	pancreatic juice secretion	1	0.076923077	0.023040714
GO:0046415	urate metabolic process	1	0.076923077	0.023040714
GO:0046541	saliva secretion	1	0.076923077	0.023040714
GO:0050746	regulation of lipoprotein metabolic process	1	0.076923077	0.023040714
GO:0061029	eyelid development in camera-type eye	1	0.076923077	0.023040714
GO:0090179	planar cell polarity pathway involved in neural tube closure	1	0.076923077	0.023040714
GO:0090335	regulation of brown fat cell differentiation	1	0.076923077	0.023040714
GO:1900004	negative regulation of serine-type endopeptidase activity	1	0.076923077	0.023040714
GO:1902572	negative regulation of serine-type peptidase activity	1	0.076923077	0.023040714
GO:0007599	hemostasis	3	0.00867052	0.023535082
GO:0007586	digestion	2	0.015037594	0.023557703
GO:0050817	coagulation	3	0.008645533	0.02371193
GO:0030950	establishment or maintenance of actin cytoskeleton	1	0.071428571	0.024791638

	polarity			
GO:0042447	hormone catabolic process	1	0.071428571	0.024791638
GO:0072488	ammonium transmembrane transport	1	0.071428571	0.024791638
GO:0090178	regulation of establishment of planar polarity involved in neural tube closure	1	0.071428571	0.024791638
GO:0001738	morphogenesis of a polarized epithelium	2	0.01459854	0.024891501
GO:0090177	establishment of planar polarity involved in neural tube closure	1	0.066666667	0.026539526
GO:1900003	regulation of serine-type endopeptidase activity	1	0.066666667	0.026539526
GO:1902571	regulation of serine-type peptidase activity	1	0.066666667	0.026539526
GO:0035148	tube formation	2	0.013888889	0.027298545
GO:0030900	forebrain development	3	0.008174387	0.02740255
GO:0046467	membrane lipid biosynthetic process	2	0.013793103	0.027649865
GO:0009165	nucleotide biosynthetic process	3	0.008130081	0.027787703
GO:0060192	negative regulation of lipase activity	1	0.0625	0.028284381
GO:0071732	cellular response to nitric oxide	1	0.0625	0.028284381
GO:1901293	nucleoside phosphate biosynthetic process	3	0.008042895	0.028566778
GO:0009187	cyclic nucleotide metabolic process	2	0.013333333	0.029433947
GO:0002076	osteoblast development	1	0.058823529	0.03002621
GO:0042249	establishment of planar polarity of embryonic epithelium	1	0.058823529	0.03002621
GO:0043951	negative regulation of cAMP-mediated signaling	1	0.058823529	0.03002621
GO:0051262	protein tetramerization	2	0.013071895	0.030526126
GO:0035567	non-canonical Wnt signaling pathway	2	0.012987013	0.030893764
GO:1900371	regulation of purine nucleotide biosynthetic process	2	0.012987013	0.030893764
GO:0030808	regulation of nucleotide biosynthetic process	2	0.012903226	0.031263179
GO:0030952	establishment or maintenance of cytoskeleton polarity	1	0.055555556	0.031765017
GO:0070633	transepithelial transport	1	0.055555556	0.031765017
GO:1905276	regulation of epithelial tube formation	1	0.055555556	0.031765017
GO:0006497	protein lipidation	2	0.012578616	0.032758473
GO:0007517	muscle organ development	3	0.007575758	0.033272882
GO:0006833	water transport	1	0.052631579	0.033500807
GO:0015669	gas transport	1	0.052631579	0.033500807
GO:0033622	integrin activation	1	0.052631579	0.033500807

GO:0071731	response to nitric oxide	1	0.052631579	0.033500807
GO:1902170	cellular response to reactive nitrogen species	1	0.052631579	0.033500807
GO:0008361	regulation of cell size	2	0.012195122	0.034666733
GO:0042158	lipoprotein biosynthetic process	2	0.012195122	0.034666733
GO:0006665	sphingolipid metabolic process	2	0.012121212	0.035053535
GO:0014850	response to muscle activity	1	0.047619048	0.036963358
GO:0061436	establishment of skin barrier	1	0.047619048	0.036963358
GO:0097503	sialylation	1	0.047619048	0.036963358
GO:1901685	glutathione derivative metabolic process	1	0.047619048	0.036963358
GO:1901687	glutathione derivative biosynthetic process	1	0.047619048	0.036963358
GO:0006972	hyperosmotic response	1	0.045454545	0.038690128
GO:0007398	ectoderm development	1	0.045454545	0.038690128
GO:0009651	response to salt stress	1	0.045454545	0.038690128
GO:0042135	neurotransmitter catabolic process	1	0.045454545	0.038690128
GO:0060487	lung epithelial cell differentiation	1	0.045454545	0.038690128
GO:0001919	regulation of receptor recycling	1	0.043478261	0.040413902
GO:0006884	cell volume homeostasis	1	0.043478261	0.040413902
GO:0021952	central nervous system projection neuron axonogenesis	1	0.043478261	0.040413902
GO:0033561	regulation of water loss via skin	1	0.043478261	0.040413902
GO:0060479	lung cell differentiation	1	0.043478261	0.040413902
GO:0015698	inorganic anion transport	2	0.011111111	0.041055765
GO:1905330	regulation of morphogenesis of an epithelium	2	0.011049724	0.041468954
GO:0006688	glycosphingolipid biosynthetic process	1	0.041666667	0.042134685
GO:0021591	ventricular system development	1	0.041666667	0.042134685
GO:0032800	receptor biosynthetic process	1	0.041666667	0.042134685
GO:0071280	cellular response to copper ion	1	0.041666667	0.042134685
GO:0090103	cochlea morphogenesis	1	0.041666667	0.042134685
GO:0048839	inner ear development	2	0.010928962	0.042300101
GO:0051216	cartilage development	2	0.010928962	0.042300101
GO:0052547	regulation of peptidase activity	3	0.006802721	0.043586269
GO:0022011	myelination in peripheral nervous system	1	0.038461538	0.045567296
GO:0032292	peripheral nervous system axon ensheathment	1	0.038461538	0.045567296
GO:0042044	fluid transport	1	0.038461538	0.045567296
GO:0051346	negative regulation of hydrolase activity	3	0.00660793	0.046834206
GO:0006929	substrate-dependent cell migration	1	0.037037037	0.047279134
GO:1900542	regulation of purine nucleotide metabolic process	2	0.01025641	0.047417774

GO:0042157	lipoprotein metabolic process	2	0.01010101	0.0487314
GO:0031365	N-terminal protein amino acid modification	1	0.035714286	0.048988001
GO:0060292	long term synaptic depression	1	0.035714286	0.048988001
GO:0007188	adenylate cyclase-modulating G-protein coupled receptor signaling pathway	2	0.01	0.04961457