Supplementary Methods- Bioinformatic Analyses

Significance Analysis of Microarrays (SAM)

SAM is a stringent bioinformatic analysis that uses specified fold change and false discovery rate (FDR) cutoffs, non-parametric statistics with repeated permutations of the data, and corrections for multiple comparisons to determine the significance of individual gene transcripts. The normalized microarray data were analyzed using SAM 3.0 software (Tusher et al. 2001) to derive a refined list of genes affected by IFN-alpha, or to identify those genes significantly different between subjects with low versus high MADRS (≥15) and MFI (≥75) scores. Differentially expressed genes were identified using a 1.5-fold cutoff and a less than 1% FDR with 500 permutations of the data.

Ingenuity Pathways Analysis (IPA)

Differentially regulated genes as identified by SAM were subsequently analyzed for cellular functions and pathways as well as imputed associations with medical illnesses using IPA (Ingenuity Systems, Redwood City, CA), and these results were used to determine genes for validation by RT-PCR. IPA evaluates changes in gene expression as they relates to known pathways associated with a variety of cellular functions and disease states.

Transcription Element Listening System (TELiS)

Activity of upstream signal transduction pathways were analyzed by TELiS (www.telis.ucla.edu) (Cole et al. 2005). The TELiS database contains information on the prevalence of transcription factor binding motifs (TFBMs) in the promoters of all human, mouse, and rat genes, and is used to determine the representation of TFBMs in the promoter regions of differentially expressed genes. Promoters are strings of 300, 600, or 1200 nucleotides upstream of each gene's transcription start site, as indicated in the NCBI RefSeq database. TFBMs are defined by 108 position-specific weight matrices from the JASPAR 2 database, or 192 matrices representing all

vertebrate transcription factors in the TRANSFAC database. Binding motifs are detected by the MatInspector algorithm. This study surveyed the TRANSFAC and JASPAR databases to assess TFBMs associated with IFN-alpha, CREB/ATF, and AP1/c-Fos signaling, as well as myeloid differentiation (see Table 2 of the manuscript for specific matrices).

TELiS and TOA analyses provide the most accurate results when focused on relatively large numbers of genes showing large biological differences in expression. Therefore, we used a slightly less stringent FDR of 5% to identify a larger list of initial "driver genes" for these second-stage bioinformatic analyses, and relied on the second stage of statistical testing at the level of specific TFBMs and/or candidate cell types of origin, to ensure statistical reliability (Bower et al. 2011; Cole et al. 2003; Miller et al. 2008*)*. The comprehensive lists were subsequently subject to the stringency of statistical analysis by TELiS, in conjunction with the PromoterStats statistical tool, to identify transcription factors driving gene expression dynamics. This study employed a 2-sample variant of the TELiS, comparing up- and down-regulated gene lists from the same sample/cell type, which removes biases that may arise from comparing to the entire genome. Aggregate results were pooled across 9 different technical specifications involving variations of promoter length (-300, -600, and -1000 to +200 base pairs relative to the RefSeq gene transcription start site) and TFBM match stringency (mat_sim .80, .90, .95), for both the TRANSFAC and JASPAR databases. P values were calculated using dependent-sample t tests (Miller 1986).

Transcript origin analysis (TOA)

Transcript origin analysis (Cole et al. 2011) was applied to identify the cellular source of differentially expressed genes. This analysis identified the cell types responsible for the pattern of differentially expressed genes observed. Some genes are more commonly expressed in one immune cell type compared to others, as established by a reference data set, and this analysis

determines whether these genes are significantly over or under represented in a list of differentially regulated transcripts. Therefore, this analysis determines the cell types that are transcriptionally sensitive to a particular manipulation (e.g. IFN-alpha administration) or behavioral or physiological state (e.g. depression/fatigue).

The TOA tests whether differentially expressed genes originated predominately from one or more of the major leukocyte subtypes (monocyte, plasmacytoid dendritic cell, CD4+ T cell, CD8+ T cell, B cell, NK cell). It quantifies a cell type diagnosticity score, Scg, based on reference data from physically isolated leukocyte subsets in the publicly available Human Gene Atlas, which can be found at [Gene Expression Omnibus (GEO) series GSE1133; http://www.ncbi.nlm.nih.gov/projects/geo/query/acc.cgi?acc=GSE1133]. Average cell-specific diagnosticity scores for differentially expressed genes were tested for enrichment relative to the genome-wide (null hypothesis) average score using a single-sample t-test. Similar results were obtained using log transformed diagnosticity scores (data not shown).

Supplemental Table 1. Gene transcripts significantly up- and down-regulated in subjects administered 12 weeks IFN-alpha and ribavirin (n=11) compared to controls (n=10) as identified by SAM.

Up-regulated Genes					
Symbol	**Probe ID**	**Accession**	**Fold change**	**p-value**	**q-value (%)**
IFI27	ILMN_2058782	NM_005532.3	173.71	6.15E-10	0
OTOF	ILMN_1663347	NM_194323.1	25.08	8.13E-04	0.00
IFIT1	ILMN_1707695	NM_001548.3	10.76	7.87E-06	0.00
IFI44L	ILMN_1723912	NM_006820.1	10.31	5.90E-08	0.00
IFIT3	ILMN_2239754	NM_001549.2	8.53	1.53E-06	0.00
IFIT3	ILMN_1701789	NM_001031683.1	7.96	6.43E-06	0.00
IFI6	ILMN_2347798	NM_022872.2	7.90	1.21E-05	0.00
RSAD2	ILMN_1657871	NM_080657.4	6.91	2.43E-05	0.00
IFITM3	ILMN_1805750	NM_021034.2	6.64	1.69E-09	0.00
CCL2	ILMN_1720048	NM_002982.3	5.74	1.24E-04	0.00
LGALS3BP	ILMN_1659688	NM_005567.2	5.56	2.47E-05	0.00
ISG15	ILMN_2054019	NM_005101.1	5.00	7.31E-04	0.00
IFIT3	ILMN_1664543	NM_001031683.1	4.98	2.25E-07	0.00
HERC5	ILMN_1729749	NM_016323.2	4.87	4.95E-06	0.00
IFI44	ILMN_1760062	NM_006417.3	4.77	2.95E-07	0.00
MX1	ILMN_1662358	NM_002462.2	4.74	1.68E-06	0.00
OASL	ILMN_1674811	NM_198213.1	4.66	2.49E-05	0.00
IFIT2	ILMN_1739428	NM_001547.4	4.52	5.34E-05	0.00
HESX1	ILMN_1742929	NM_003865.1	4.52	4.26E-04	0.00
OAS3	ILMN_1745397	NM_006187.2	4.49	2.47E-06	0.00
C1QB	ILMN_1796409	NM_000491.3	4.42	1.46E-02	0.41
EPSTI1	ILMN_2388547	NM_033255.2	4.40	2.66E-09	0.00
LOC26010	ILMN_1683678	NM_001100422.1	4.27	1.15E-06	0.00
LY6E	ILMN_1695404	NM_002346.1	4.10	3.80E-09	0.00
	ILMN_1835092	BQ437417	4.04	7.99E-07	0.00
HERC6	ILMN_1654639	NM_017912.3	4.04	7.31E-06	0.00
OAS1	ILMN_2410826	NM_001032409.1	4.03	9.96E-08	0.00
MX2	ILMN_2231928	NM_002463.1	3.81	5.63E-07	0.00
XAF1	ILMN_1742618	NM_199139.1	3.71	4.58E-06	0.00
CMPK2	ILMN_1783621	NM_207315.2	3.71	1.02E-06	0.00
OAS2	ILMN_1674063	NM_016817.2	3.70	4.15E-07	0.00
OAS1	ILMN_1675640	NM_001032409.1	3.60	1.30E-07	0.00
OAS2	ILMN_1736729	NM_002535.2	3.54	9.59E-08	0.00
DEFB1	ILMN_1686573	NM_005218.3	3.52	1.49E-03	0.00
OASL	ILMN_1681721	NM_003733.2	3.49	1.41E-05	0.00
HBA2	ILMN_2127842	NM_000517.3	3.40	7.05E-05	0.00
OAS1	ILMN_1658247	NM_002534.2	3.31	2.25E-02	0.80
JUP	ILMN_1733811	NM_002230.1	3.27	4.17E-05	0.00
XAF1	ILMN_2370573	NM_199139.1	3.27	8.72E-05	0.00
IRF7	ILMN_1798181	NM_004029.2	3.26	1.34E-07	0.00
C1QC	ILMN_1785902	NM_172369.2	3.26	2.53E-03	0.00
SIGLEC1	ILMN_1725320	NM_023068.3	3.25	2.77E-06	0.00
IRF7	ILMN_2349061	NM_004029.2	3.25	2.99E-07	0.00

CCL8	ILMN_1772964	NM_005623.2	3.16	5.28E-03	0.21
IFITM2	ILMN_1673352	NM_006435.2	3.14	3.92E-09	0.00
SERPING1	ILMN_1670305	NM_001032295.1	3.07	9.74E-04	0.00
PARP9	ILMN_1731224	NM_031458.1	3.06	7.81E-08	0.00
DDX60	ILMN_1795181	NM_017631.4	3.04	7.80E-07	0.00
CTSL1	ILMN_2374036	NM_145918.2	3.01	1.10E-05	0.00
CTSL1	ILMN_1812995	NM_001912.3	3.00	2.86E-05	0.00
HES4	ILMN_1653466	NM_021170.2	3.00	3.32E-04	0.00
RNASE2	ILMN_1730628	NM_002934.2	2.99	1.64E-06	0.00
EIF2AK2	ILMN_1706502	NM_002759.1	2.98	4.74E-06	0.00
AXL	ILMN_2364521	NM_021913.2	2.95	1.62E-04	0.00
PRIC285	ILMN_1787509	NM_033405.2	2.93	2.05E-05	0.00
IFIT1	ILMN_1699331	NM_001548.2	2.91	9.11E-06	0.00
LAMP3	ILMN_2170814	NM_014398.2	2.90	6.53E-05	0.00
PLSCR1	ILMN_1745242	NM_021105.1	2.89	1.90E-06	0.00
	ILMN_1910908	BG205162	2.88	7.94E-07	0.00
IFIH1	ILMN_1781373	NM_022168.2	2.82	4.89E-07	0.00
AXL	ILMN_1701877	NM_021913.2	2.82	1.97E-04	0.00
IFI35	ILMN_1745374	NM_005533.2	2.76	2.59E-06	0.00
MT2A	ILMN_1686664	NM_005953.2	2.68	1.63E-06	0.00
NEXN	ILMN_1783276	NM_144573.3	2.66	2.69E-04	0.00
TCN2	ILMN_1740572	NM_000355.2	2.63	3.80E-04	0.00
OAS2	ILMN_1709333	NM_016817.2	2.61	2.81E-07	0.00
RGL1	ILMN_1654398	NM_015149.3	2.60	8.24E-05	0.00
TMEM51	ILMN_1674985	NM_018022.1	2.56	6.56E-04	0.00
SAMD9L	ILMN_1799467	NM_152703.2	2.53	8.31E-05	0.00
FCGR1B	ILMN_2261600	NM_001017986.1	2.53	2.40E-03	0.00
APOBEC3A	ILMN_1680192	NM_145699.2	2.52	2.89E-04	0.00
ZBP1	ILMN_1765994	NM_030776.1	2.51	2.00E-05	0.00
IL8RBP	ILMN_1691507	XR_001023.1	2.51	4.02E-05	0.00
USP41	ILMN_1690365	XM_036729.5	2.50	7.25E-06	0.00
IFITM1	ILMN_1801246	NM_003641.3	2.47	9.16E-06	0.00
SAMD4A	ILMN_2119297	NM_015589.3	2.45	1.61E-05	0.00
KCTD14	ILMN_1731044	NM_023930.3	2.42	2.07E-04	0.00
IL1F7	ILMN_1697710	NM_014439.3	2.41	7.09E-06	0.00
DHX58	ILMN_1678422	NM_024119.2	2.41	2.28E-05	0.00
GMPR	ILMN_1729487	NM_006877.2	2.38	8.49E-04	0.00
H1F0	ILMN_1757467	NM_005318.2	2.37	7.05E-05	0.00
FFAR2	ILMN_1797895	NM_005306.1	2.36	3.49E-04	0.00
CXCL10	ILMN_1791759	NM_001565.2	2.34	6.11E-03	0.21
HBA2	ILMN_1667796	NM_000517.3	2.34	3.24E-03	0.00
SAMD9	ILMN_1814305	NM_017654.2	2.31	2.30E-05	0.00
SCO2	ILMN_1701621	NM_005138.1	2.30	7.41E-05	0.00
STAT1	ILMN_1690105	NM_007315.2	2.29	1.40E-05	0.00
E2F2	ILMN_1777233	NM_004091.2	2.27	2.58E-04	0.00
STAT1	ILMN_1691364	NM_139266.1	2.25	9.78E-05	0.00
EMP1	ILMN_1801616	NM_001423.1	2.25	1.33E-05	0.00
CCR1	ILMN_1678833	NM_001295.2	2.22	4.51E-06	0.00
LOC728216	ILMN_1740200	XM_001128283.1	2.22	1.36E-05	0.00

ECGF1	ILMN_1690939	NM_001953.2	2.19	1.05E-04	0.00
HBB	ILMN_2100437	NM_000518.4	2.18	4.08E-03	0.21
GBP1	ILMN_1701114	NM_002053.1	2.17	7.26E-04	0.00
ENDOGL1	ILMN_1709747	NM_005107.2	2.16	1.35E-05	0.00
LGALS9	ILMN_2412214	NM_009587.2	2.15	4.87E-08	0.00
OAS2	ILMN_2248970	NM_001032731.1	2.14	2.51E-04	0.00
TNFSF10	ILMN_1801307	NM_003810.2	2.14	1.62E-05	0.00
PLAC8	ILMN_1653026	NM_016619.1	2.13	1.86E-05	0.00
PARP12	ILMN_1718558	NM_022750.2	2.13	2.33E-05	0.00
BLVRA	ILMN_1691436	NM_000712.3	2.11	1.98E-06	0.00
MT1A	ILMN_1691156	NM_005946.2	2.11	4.32E-06	0.00
RTP4	ILMN_2173975	NM_022147.2	2.09	9.40E-06	0.00
LILRA3	ILMN_1786303	NM_006865.2	2.08	4.17E-03	0.00
HSH2D	ILMN_1788017	NM_032855.2	2.07	1.02E-05	0.00
PARP9	ILMN_2053527	NM_031458.1	2.07	1.24E-07	0.00
STAT1	ILMN_1777325	NM_007315.2	2.04	1.23E-07	0.00
GBP1	ILMN_2148785	NM_002053.1	2.01	7.26E-04	0.00
TRIM22	ILMN_1779252	NM_006074.3	2.01	2.31E-05	0.00
C3AR1	ILMN_1787529	NM_004054.2	2.01	2.06E-04	0.00
KIAA1618	ILMN_2289093	NM_020954.2	1.99	3.69E-04	0.00
RNASE1	ILMN_2333670	NM_198235.1	1.99	6.30E-03	0.21
PLAC8	ILMN_2093343	NM_016619.1	1.98	5.93E-06	0.00
NT5C3	ILMN_1769734	NM_001002010.1	1.98	4.64E-04	0.00
RNASE3	ILMN_2113126	NM_002935.2	1.98	9.30E-05	0.00
MS4A4A	ILMN_2370336	NM_148975.1	1.96	3.11E-05	0.00
LAP3	ILMN_1683792	NM_015907.2	1.95	3.97E-04	0.00
CD38	ILMN_2233783	NM_001775.2	1.95	3.11E-05	0.00
NCOA7	ILMN_1687768	NM_181782.2	1.94	4.87E-05	0.00
SP110	ILMN_2415144	NM_004510.2	1.93	3.36E-08	0.00
FBXO6	ILMN_1701455	NM_018438.4	1.93	5.12E-05	0.00
FCGR1A	ILMN_2176063	NM_000566.2	1.93	7.17E-03	0.21
DDX58	ILMN_1797001	NM_014314.3	1.93	7.32E-05	0.00
FCGR1B	ILMN_2391051	NM_001004340.1	1.92	1.59E-02	0.41
LGALS9	ILMN_1715760	NM_009587.2	1.92	4.57E-05	0.00
MARCKS	ILMN_1807042	NM_002356.5	1.90	4.73E-06	0.00
CHMP5	ILMN_1732534	NM_016410.3	1.90	1.04E-06	0.00
SP110	ILMN_1731418	NM_004510.2	1.88	1.76E-07	0.00
LILRA3	ILMN_1661631	NM_006865.2	1.88	8.11E-03	0.21
ECGF1	ILMN_2109708	NM_001953.2	1.87	3.72E-05	0.00
TRIM5	ILMN_1704972	NM_033034.1	1.87	1.48E-05	0.00
ACP2	ILMN_2104830	NM_001610.1	1.87	8.53E-07	0.00
LOC654346	ILMN_1766184	XM_934665.1	1.86	1.41E-06	0.00
PRKCDBP	ILMN_1793476	NM_145040.2	1.86	8.12E-03	0.21
ISG20	ILMN_1659913	NM_002201.4	1.86	6.37E-05	0.00
LOC649143	ILMN_1815895	XM_944822.1	1.85	2.04E-02	0.61
MARCO	ILMN_1731503	NM_006770.3	1.85	3.14E-03	0.00
C2	ILMN_1710740	NM_000063.3	1.84	2.36E-03	0.00
RRAS	ILMN_1780825	NM_006270.3	1.83	3.42E-05	0.00
C1QA	ILMN_1737918	NM_015991.1	1.82	1.74E-02	0.80

CHMP5	ILMN_2094166	NM_016410.2	1.80	1.77E-07	0.00
CASP5	ILMN_1722158	NM_004347.1	1.80	4.77E-03	0.21
TOR1B	ILMN_1724333	NM_014506.1	1.80	1.13E-04	0.00
ADAR	ILMN_2320964	NM_015840.2	1.80	2.41E-08	0.00
MT1E	ILMN_2173611	NM_175617.3	1.80	9.26E-06	0.00
TLR7	ILMN_1677827	NM_016562.3	1.79	2.39E-04	0.00
LILRB4	ILMN_2355953	NM_001081438.1	1.77	7.01E-05	0.00
GRN	ILMN_1724250	NM_002087.2	1.77	6.86E-06	0.00
TRIP6	ILMN_1713990	NM_003302.2	1.76	7.59E-06	0.00
FPR3	ILMN_2203271	NM_002030.3	1.76	3.04E-04	0.00
IFI30	ILMN_1807277	NM_006332.3	1.76	1.72E-03	0.00
IFI16	ILMN_1710937	NM_005531.1	1.76	4.58E-06	0.00
C5orf32	ILMN_1761566	NM_032412.3	1.76	2.54E-05	0.00
NT5C3	ILMN_2352121	NM_001002010.1	1.75	3.55E-03	0.00
LGALS9B	ILMN_2113333	NM_001042685.1	1.75	1.36E-05	0.00
OAS1	ILMN_1672606	NM_016816.2	1.75	4.23E-06	0.00
PPM1K	ILMN_2070044	NM_152542.2	1.75	2.62E-04	0.00
	ILMN_1845037	BC031266	1.74	1.15E-07	0.00
TDRD7	ILMN_1705241	NM_014290.1	1.74	3.86E-06	0.00
UBE2L6	ILMN_1769520	NM_004223.3	1.74	1.21E-05	0.00
SLC31A2	ILMN_1758938	NM_001860.2	1.74	3.20E-03	0.00
MAFB	ILMN_1764709	NM_005461.3	1.73	1.64E-04	0.00
ANXA2	ILMN_1711899	NM_001002857.1	1.72	3.11E-04	0.00
BST2	ILMN_1723480	NM_004335.2	1.72	2.82E-05	0.00
RNF213	ILMN_1749722	NM_020914.3	1.72	1.24E-02	0.41
TNFSF13B	ILMN_1758418	NM_006573.3	1.71	3.49E-04	0.00
ADAR	ILMN_1776777	NM_001111.3	1.70	4.25E-06	0.00
GBP4	ILMN_1771385	NM_052941.3	1.69	1.02E-03	0.00
FPR2	ILMN_1740875	NM_001005738.1	1.69	1.11E-04	0.00
IL4I1	ILMN_1659960	NM_172374.1	1.68	5.01E-03	0.21
LILRB2	ILMN_1695744	NM_001080978.1	1.67	7.14E-04	0.00
PHF11	ILMN_2390162	NM_001040443.1	1.67	1.27E-05	0.00
TMEM123	ILMN_1724139	NM_052932.2	1.66	2.35E-05	0.00
CFD	ILMN_1777190	NM_001928.2	1.66	1.65E-03	0.00
ARL4A	ILMN_1775405	NM_005738.3	1.65	5.98E-04	0.00
HIST3H2A	ILMN_1779648	NM_033445.2	1.65	3.04E-06	0.00
JUP	ILMN_1741970	NM_002230.1	1.65	1.03E-03	0.00
DRAP1	ILMN_2112301	NM_006442.2	1.65	7.02E-07	0.00
SDSL	ILMN_1750674	NM_138432.2	1.64	1.42E-03	0.00
FPR2	ILMN_2392569	NM_001462.3	1.64	9.61E-04	0.00
SHISA5	ILMN_2139100	NM_016479.3	1.64	3.58E-07	0.00
DTX3L	ILMN_1784380	NM_138287.2	1.64	6.90E-05	0.00
ACTA2	ILMN_1671703	NM_001613.1	1.63	1.96E-02	0.61
MERTK	ILMN_2138589	NM_006343.2	1.62	2.16E-04	0.00
CYSLTR1	ILMN_1733276	NM_006639.2	1.62	3.53E-05	0.00
GRN	ILMN_1811702	NM_002087.2	1.62	9.47E-06	0.00
TYMS	ILMN_1806040	NM_001071.1	1.62	6.56E-04	0.00
PARP10	ILMN_1710844	XM_001127571.1	1.62	3.27E-05	0.00
PARP14	ILMN_1691731	NM_017554.1	1.62	2.40E-03	0.00

BPGM	ILMN_2352921	NM_001724.3	1.61	2.50E-02	0.98
HIST1H2BD	ILMN_1651496	NM_138720.1	1.61	1.25E-02	0.41
LILRA5	ILMN_1726545	NM_181879.1	1.61	2.55E-03	0.00
HBZ	ILMN_1713458	NM_005332.2	1.61	6.49E-03	0.98
UBE2L6	ILMN_1703108	NM_004223.3	1.61	5.18E-06	0.00
GPBAR1	ILMN_1727709	NM_170699.2	1.60	8.35E-04	0.00
LILRA5	ILMN_2357419	NM_021250.2	1.60	1.28E-03	0.00
ATF5	ILMN_1669113	NM_012068.3	1.60	3.90E-04	0.00
GPBAR1	ILMN_2316386	NM_001077191.1	1.60	7.29E-04	0.00
MOV10	ILMN_1725700	NM_020963.2	1.60	1.84E-04	0.00
CYP2J2	ILMN_1758731	NM_000775.2	1.60	3.40E-05	0.00
PI4K2B	ILMN_1815134	NM_018323.2	1.60	2.21E-06	0.00
SP100	ILMN_2284998	NM_001080391.1	1.60	4.26E-07	0.00
ZNFX1	ILMN_1745148	NM_021035.2	1.60	8.66E-05	0.00
NMI	ILMN_1739541	NM_004688.1	1.59	2.35E-05	0.00
SP110	ILMN_1672661	NM_004510.2	1.59	1.13E-05	0.00
PTPRO	ILMN_1720113	NM_030667.1	1.59	1.53E-05	0.00
MTE	ILMN_2136089	NM_175621.2	1.59	1.35E-05	0.00
PARP10	ILMN_2262044	NM_032789.1	1.59	1.93E-04	0.00
ATOX1	ILMN_1670609	NM_004045.3	1.59	1.26E-04	0.00
PTPRO	ILMN_2316878	NM_030671.1	1.59	2.46E-03	0.00
GNGT2	ILMN_1671237	NM_031498.1	1.58	3.40E-05	0.00
HIST2H2AA3	ILMN_2144426	NM_003516.2	1.58	2.91E-03	0.00
LDLR	ILMN_2053415	NM_000527.2	1.58	4.00E-03	0.00
CLDN23	ILMN_1725338	NM_194284.2	1.58	1.49E-04	0.00
FER1L3	ILMN_2370976	NM_013451.2	1.57	7.74E-03	0.21
C9orf109	ILMN_1695485	XM_379665.2	1.57	1.11E-04	0.00
CALML4	ILMN_1757210	NM_001031733.1	1.57	2.06E-04	0.00
PHF11	ILMN_1776723	NM_001040443.1	1.57	4.76E-05	0.00
LOC441019	ILMN_1761281	XM_498969.2	1.56	2.55E-05	0.00
PARP10	ILMN_1721411	XM_001127571.1	1.56	1.44E-04	0.00
TIMP1	ILMN_1711566	NM_003254.2	1.55	2.21E-06	0.00
FER1L3	ILMN_1810289	NM_133337.1	1.55	4.66E-03	0.00
SP100	ILMN_2390586	NM_001080391.1	1.55	6.82E-06	0.00
FAM46A	ILMN_1740466	NM_017633.2	1.55	7.48E-04	0.00
SP110	ILMN_1813455	NM_080424.1	1.55	3.01E-06	0.00
HIST2H2AA3	ILMN_1659047	NM_003516.2	1.55	4.05E-03	0.00
P2RY6	ILMN_1660031	NM_176796.1	1.55	4.08E-03	0.21
CTSL1	ILMN_1694757	NM_001912.3	1.55	4.95E-06	0.00
RIN2	ILMN_1769546	NM_018993.2	1.55	2.91E-04	0.00
STAT2	ILMN_1690921	NM_005419.2	1.55	6.93E-04	0.00
C19orf66	ILMN_1750400	NM_018381.2	1.54	1.73E-04	0.00
BEX1	ILMN_2234697	NM_018476.3	1.54	4.77E-04	0.00
TNFSF13B	ILMN_2066858	NM_006573.3	1.54	9.86E-05	0.00
N4BP1	ILMN_2201966	NM_153029.3	1.53	3.80E-03	0.00
DNASE2	ILMN_1796245	NM_001375.2	1.53	1.00E-04	0.00
TRIM25	ILMN_1813625	NM_005082.4	1.53	1.25E-03	0.00
CAMK1	ILMN_2140990	NM_003656.3	1.53	2.50E-04	0.00
BATF2	ILMN_1690241	NM_138456.3	1.53	8.09E-04	0.00

GAS6	ILMN_1779558	NM_000820.1	1.53	9.66E-03	0.41
GCH1	ILMN_1812759	NM_001024071.1	1.53	3.51E-03	0.00
EPB41L3	ILMN_2109197	NM_012307.2	1.52	1.69E-03	0.00
AK2	ILMN_1716053	NM_001625.2	1.52	8.06E-05	0.00
IFIT5	ILMN_1696654	NM_012420.1	1.52	9.59E-04	0.00
CLEC7A	ILMN_1700610	NM_197948.2	1.51	4.87E-04	0.00
HIST2H2AC	ILMN_1768973	NM_003517.2	1.51	3.03E-03	0.00
ACOX2	ILMN_1685703	NM_003500.2	1.51	3.70E-04	0.00
MRPS18C	ILMN_1658416	NM_016067.1	1.51	7.43E-06	0.00
LAMP2	ILMN_1673282	NM_002294.1	1.51	1.60E-04	0.00
KIAA0101	ILMN_2285996	NM_014736.4	1.51	1.24E-02	0.41
OTOF	ILMN_2340886	NM_194322.1	1.50	4.06E-03	0.21
PSMB9	ILMN_2376108	NM_002800.4	1.50	2.64E-04	0.00

Down-regulated Genes

Symbol	Probe ID	Accession	Fold change	p-value	q-value (%)
HDC	ILMN_1792323	NM_002112.2	-3.95	3.40E-05	0.00
LYPD2	ILMN_1724266	NM_205545.1	-2.51	7.35E-03	0.42
PPBP	ILMN_1767281	NM_002704.2	-2.40	6.89E-03	0.22
SH3BGRL2	ILMN_1762764	NM_031469.2	-2.39	2.18E-02	0.98
LOC651149	ILMN_1660439	XM_940278.1	-2.39	5.21E-07	0.00
MPL	ILMN_1776640	NM_005373.1	-2.29	1.24E-02	0.61
TXNDC12	ILMN_1783753	NM_015913.2	-2.13	1.23E-11	0.00
FCER1A	ILMN_1688423	NM_002001.2	-2.08	4.02E-06	0.00
LOC650557	ILMN_1725170	XM_942240.1	-2.08	7.83E-04	0.00
LOC643031	ILMN_1743078	XM_926402.1	-2.06	2.11E-07	0.00
RPS23	ILMN_1772459	NM_001025.4	-1.98	4.56E-03	0.22
FCRL2	ILMN_1791329	NM_030764.2	-1.93	1.35E-03	0.00
EIF4B	ILMN_1655497	NM_001417.4	-1.91	8.98E-08	0.00
CNTNAP2	ILMN_1690223	NM_014141.4	-1.90	4.30E-03	0.22
EIF3EIP	ILMN_1762725	NM_016091.2	-1.90	5.15E-07	0.00
TCL1A	ILMN_1788841	NM_001098725.1	-1.88	6.45E-03	0.22
LOC91561	ILMN_1691053	XM_934176.1	-1.85	9.20E-08	0.00
EEF1G	ILMN_2262288	NM_001404.4	-1.85	1.26E-05	0.00
CLECL1	ILMN_1782729	NM_172004.2	-1.81	1.09E-02	0.42
	ILMN_1882953	AL833240	-1.81	2.93E-03	0.22
VENTX	ILMN_1782352	NM_014468.2	-1.80	3.54E-04	0.00
EEF1D	ILMN_2408039	NM_032378.2	-1.80	6.40E-06	0.00
LTA4H	ILMN_1690342	NM_000895.1	-1.79	3.12E-06	0.00
LOC158345	ILMN_1685538	XR_017130.1	-1.78	2.33E-06	0.00
MEF2D	ILMN_1763228	NM_005920.2	-1.78	1.42E-09	0.00
C19orf33	ILMN_1717793	NM_033520.1	-1.78	1.11E-02	0.61
RPL4	ILMN_1752285	NM_000968.2	-1.77	2.71E-07	0.00
	ILMN_1827736	BC038512	-1.77	4.68E-08	0.00
LOC220433	ILMN_1795243	XM_941684.2	-1.76	8.34E-05	0.00
LOC641848	ILMN_1679025	XM_935588.1	-1.75	1.21E-07	0.00
EEF2	ILMN_1738383	NM_001961.3	-1.74	2.44E-07	0.00
LOC389787	ILMN_1665823	XM_497072.2	-1.74	9.26E-07	0.00
PROS1	ILMN_1671928	NM_000313.1	-1.72	1.65E-02	0.98

C5orf39	ILMN_2098616	NM_001014279.1	-1.72	1.48E-07	0.00
LOC642934	ILMN_1653039	XM_942991.2	-1.71	1.66E-03	0.00
NELL2	ILMN_1725417	NM_006159.1	-1.71	6.76E-04	0.00
CD1C	ILMN_1654210	NM_001765.2	-1.70	2.30E-03	0.00
JAM3	ILMN_1769575	NM_032801.3	-1.70	2.09E-03	0.00
RTN1	ILMN_1756928	NM_021136.2	-1.69	4.59E-05	0.00
CACNA2D3	ILMN_1754076	NM_018398.2	-1.69	2.55E-05	0.00
HNRPA1P4	ILMN_1690586	XM_939887.2	-1.68	9.17E-07	0.00
LOC388275	ILMN_1676091	XM_928429.1	-1.68	1.20E-06	0.00
HLA-DOA	ILMN_1659075	NM_002119.3	-1.67	4.21E-04	0.00
CLC	ILMN_1654875	NM_001828.4	-1.67	1.21E-02	0.80
PDXK	ILMN_1672504	NM_003681.4	-1.67	6.95E-05	0.00
LOC643977	ILMN_1745599	XM_932991.1	-1.67	1.37E-05	0.00
ZNF91	ILMN_1802053	NM_003430.2	-1.66	1.10E-04	0.00
LOC388532	ILMN_1656292	XM_939726.2	-1.65	3.97E-08	0.00
HNRPA1L-2	ILMN_2220283	NR_002944.2	-1.64	1.13E-06	0.00
LOC653820	ILMN_1723433	XM_935475.1	-1.64	1.10E-02	0.61
RGS2	ILMN_2197365	NM_002923.1	-1.64	2.19E-02	0.98
BANK1	ILMN_1661646	NM_001083907.1	-1.63	1.26E-03	0.00
RPL7	ILMN_1815292	NM_000971.3	-1.63	1.96E-06	0.00
CD19	ILMN_1782704	NM_001770.4	-1.62	3.97E-03	0.22
FAM101B	ILMN_1714418	NM_182705.2	-1.62	2.69E-05	0.00
RPL9	ILMN_2408415	NM_001024921.2	-1.62	5.15E-06	0.00
LOC647673	ILMN_1757702	XM_936731.1	-1.62	1.24E-05	0.00
GLS	ILMN_2188722	NM_014905.2	-1.62	9.97E-06	0.00
CLDND2	ILMN_2077680	NM_152353.1	-1.62	3.33E-03	0.22
OLIG1	ILMN_1666089	NM_138983.1	-1.61	9.45E-03	0.42
PARVB	ILMN_1787919	NM_013327.3	-1.60	1.60E-02	0.80
GOLGA8B	ILMN_2103547	NM_001023567.2	-1.60	2.83E-03	0.00
PABPC1	ILMN_2136133	NM_002568.3	-1.59	3.73E-05	0.00
AHNAK	ILMN_1714567	NM_001620.1	-1.59	5.44E-04	0.00
LOC645968	ILMN_1695370	XM_928934.1	-1.59	2.48E-04	0.00
LOC648343	ILMN_1690295	XR_018327.1	-1.59	1.34E-06	0.00
CMTM2	ILMN_1799030	NM_144673.2	-1.59	1.25E-05	0.00
RPS4X	ILMN_2166831	NM_001007.3	-1.59	3.37E-04	0.00
BLK	ILMN_1668277	NM_001715.2	-1.58	2.32E-04	0.00
EEF1D	ILMN_1782543	NM_032378.2	-1.58	1.51E-06	0.00
LAMA5	ILMN_1773567	NM_005560.3	-1.57	7.77E-04	0.00
EEF1B2	ILMN_2318725	NM_001037663.1	-1.57	1.74E-08	0.00
LOC643949	ILMN_1692956	XR_018645.1	-1.57	3.37E-09	0.00
PABPC4	ILMN_1757343	NM_003819.2	-1.57	8.01E-07	0.00
DSC1	ILMN_2402640	NM_004948.2	-1.57	8.72E-04	0.00
RPL10A	ILMN_1808041	NM_007104.4	-1.57	8.99E-06	0.00
EIF3F	ILMN_1694398	NM_003754.2	-1.57	6.26E-08	0.00
SYNE2	ILMN_2391419	NM_015180.4	-1.57	5.45E-03	0.22
LOC439992	ILMN_1671045	XM_495839.2	-1.56	1.08E-04	0.00
RPL3	ILMN_2319994	NM_001033853.1	-1.56	1.30E-06	0.00
EMR3	ILMN_2348487	NM_032571.2	-1.56	2.40E-04	0.00
RPLP1	ILMN_1689725	NM_001003.2	-1.56	2.82E-05	0.00

	ILMN_1816342	CR612552	-1.56	1.37E-02	0.61
C9orf45	ILMN_1719998	XR_017862.1	-1.56	1.03E-04	0.00
RPL22	ILMN_2079386	NM_000983.3	-1.56	4.09E-06	0.00
RPS4X	ILMN_1810577	NM_001007.3	-1.55	4.68E-04	0.00
FCRL3	ILMN_1691693	NM_001024667.1	-1.55	2.45E-03	0.22
VNN2	ILMN_1758864	NM_004665.2	-1.55	9.48E-03	0.42
RPL21	ILMN_2290808	NM_000982.3	-1.55	4.14E-06	0.00
ITGAE	ILMN_1683927	NM_002208.4	-1.54	5.50E-09	0.00
SORL1	ILMN_1759818	NM_003105.3	-1.54	1.82E-03	0.00
RPL5	ILMN_2087080	NM_000969.3	-1.54	1.51E-07	0.00
CYBRD1	ILMN_1712305	NM_024843.2	-1.54	2.97E-03	0.22
LOC388621	ILMN_1677262	XM_941195.2	-1.54	1.45E-06	0.00
VNN2	ILMN_1678939	NM_004665.2	-1.53	4.10E-03	0.22
HNRPDL	ILMN_1653432	NR_003249.1	-1.53	2.63E-03	0.00
NRG1	ILMN_1737252	NM_013962.2	-1.53	6.00E-03	0.42
ELA1	ILMN_1805902	NM_001971.4	-1.53	2.65E-03	0.22
BRI3BP	ILMN_1693410	XM_941876.1	-1.53	3.71E-04	0.00
FBL	ILMN_1719205	NM_001436.2	-1.53	4.02E-06	0.00
C11orf2	ILMN_2077094	NM_013265.2	-1.53	6.99E-06	0.00
CYBRD1	ILMN_2087692	NM_024843.2	-1.53	6.15E-03	0.22
MATK	ILMN_1669321	NM_139355.2	-1.52	2.82E-04	0.00
LOC654194	ILMN_1755808	XM_942669.1	-1.52	1.30E-06	0.00
GNG7	ILMN_1728107	NM_052847.2	-1.52	8.99E-05	0.00
	ILMN_1898723	BC090942	-1.52	2.09E-05	0.00
OSBPL10	ILMN_1669497	NM_017784.3	-1.52	1.01E-03	0.00
EEF1B2	ILMN_1694587	NM_001959.2	-1.52	6.91E-06	0.00
TCTN1	ILMN_1685124	NM_001082538.1	-1.52	3.09E-04	0.00
SORL1	ILMN_2060115	NM_003105.3	-1.52	2.80E-03	0.00
KRT10	ILMN_1716093	NM_000421.2	-1.52	1.40E-04	0.00
RAB37	ILMN_2255579	NM_175738.3	-1.52	6.93E-05	0.00
RPS29	ILMN_2298818	NM_001030001.1	-1.51	6.54E-06	0.00
NAP1L1	ILMN_1699208	NM_139207.1	-1.51	4.58E-05	0.00
LOC649095	ILMN_1728645	XM_001131851.1	-1.51	4.53E-05	0.00
GVIN1	ILMN_1668526	XM_495863.3	-1.50	1.67E-02	0.80

Supplemental Table 2. Ingenuity canonical pathways analysis of genes differentially regulated by IFN-alpha.

Ingenuity Canonical Pathways	P-value	Ratio	Molecules
Role of Pattern Recognition Receptors in Recognition of Bacteria and Viruses	3.72E-10	1.51E-01	OAS1, OAS2, C1QC, C1QA, C1QB, OAS3 (includes EG:4940), IFIH1, CLEC7A, IRF7, DDX58, TLR7, EIF2AK2, C3AR1
Interferon Signaling	2.19E-08	2.67E-01	IFIT3, IFIT1, OAS1, IFITM1, MX1, IFI35, STAT2, STAT1
Activation of IRF by Cytosolic Pattern Recognition Receptors	7.76E-08	1.35E-01	DHX58, IFIH1, IRF7, DDX58, ZBP1, STAT2, STAT1, ADAR, IFIT2, ISG15
Complement System	1.15E-06	1.94E-01	CFD, SERPING1, C1QC, C1QA, C1QB, C3AR1, C2
Retinoic acid Mediated Apoptosis Signaling	2.63E-04	1.14E-01	PARP10, TNFSF10, PARP12, PARP9, PARP14
Role of RIG1-like Receptors in Antiviral Innate Immunity	7.76E-04	9.62E-02	DHX58, IFIH1, IRF7, DDX58, TRIM25
Dendritic Cell Maturation	1.48E-02	4.02E-02	HLA-DOA, STAT2, IL1F7, STAT1, CD1C, FCGR1A, FCGR1B
Oncostatin M Signaling	1.86E-02	8.57E-02	RRAS, MT2A, STAT1
Eicosanoid Signaling	2.04E-02	4.76E-02	GRN, LTA4H, FPR2, CYSLTR1
Role of NFAT in Regulation of the Immune Response	2.14E-02	3.59E-02	HLA-DOA, RRAS, MEF2D, FCER1A, FCGR1A, GNG7, FCGR1B
Systemic Lupus Erythematosus Signaling	2.40E-02	3.97E-02	RRAS, TLR7, IL1F7, FCGR1A, TNFSF13B, FCGR1B
Role of PKR in Interferon Induction and Antiviral Response	2.82E-02	6.52E-02	EIF2AK2, STAT1, FCGR1A
IL-17 Signaling	3.16E-02	5.41E-02	CXCL10, CCL2, RRAS, TIMP1
Communication between Innate and Adaptive Immune Cells	4.37E-02	4.44E-02	CXCL10, TLR7, IL1F7, TNFSF13B
Nitrogen Metabolism	4.47E-02	2.26E-02	VNN2, GLS, ADAR
Altered T Cell and B Cell Signaling in Rheumatoid Arthritis	4.57E-02	4.6E-02	HLA-DOA, TLR7, IL1F7, TNFSF13B
EIF2 Signaling	4.90E-02	4E-02	PABPC1, RRAS, EIF3F, EIF2AK2

Supplemental Table 3. Gene transcripts up- and down-regulated by 50% (≥1.5 fold) in IFN-alpha-treated subjects (n=11) compared to control (n=10), and in subjects with high (n=4) versus low (n=7) MADRS and MFI scores at 12 weeks IFN-alpha.

IFN-alpha vs. Control			**High vs. Low MADRS/MFI**		
Up-regulated			***Up-Regulated***		
Probe ID	Symbol	Fold	Probe ID	Symbol	Fold
ILMN_2058782	IFI27	173.71	ILMN_1796678	HBG1	3.76
ILMN_1663347	OTOF	25.08	ILMN_2084825	HBG2	3.43
ILMN_1815527	HBD	13.12	ILMN_1791534	LOC731682	2.98
ILMN_2367126	ALAS2	11.96	ILMN_1759155	IFIT1L	2.45
ILMN_1796678	HBG1	11.34	ILMN_2165753	HLA-A29.1	2.22
ILMN_2084825	HBG2	11.24	ILMN_1664464	PTGDS	2.18
ILMN_1707695	IFIT1	10.76	ILMN_1678238	ZNF683	2.13
ILMN_1696512	ERAF	10.38	ILMN_1731233	GZMH	2.10
ILMN_1723912	IFI44L	10.31	ILMN_2074762	FCRL6	2.08
ILMN_2239754	IFIT3	8.53	ILMN_1658399	KLRG1	2.05
ILMN_1701789	IFIT3	7.96	ILMN_1676575	IKZF1	2.04
ILMN_2347798	IFI6	7.90	ILMN_2336609	SYTL2	1.96
ILMN_1657871	RSAD2	6.91	ILMN_1663347	OTOF	1.92
ILMN_1805750	IFITM3	6.64	ILMN_1697377	LOC649841	1.89
ILMN_1652431	CA1	6.15	ILMN_1813191	LOC653080	1.87
ILMN_1720048	CCL2	5.74	ILMN_2189406	C15orf38	1.86
ILMN_1659688	LGALS3BP	5.56	ILMN_1784287	TGFBR3	1.83
ILMN_2054019	ISG15	5.00	ILMN_1791511	TMEM176A	1.83
ILMN_1664543	IFIT3	4.98	ILMN_2384122	GPR56	1.83
ILMN_1729749	HERC5	4.87	ILMN_2198408	MFF	1.80
ILMN_2091454	HBM	4.80	ILMN_1801216	S100P	1.79
ILMN_1760062	IFI44	4.77	ILMN_1761945	FGFBP2	1.78
ILMN_1662358	MX1	4.74	ILMN_2248970	OAS2	1.77
ILMN_1674811	OASL	4.66	ILMN_1768482	CD8A	1.74
ILMN_1739428	IFIT2	4.52	ILMN_1764573	XIST	1.72
ILMN_1742929	HESX1	4.52	ILMN_1651403	LOC642161	1.71
ILMN_1745397	OAS3	4.49	ILMN_1813338	LAG3	1.70
ILMN_1796409	C1QB	4.42	ILMN_2352097	GPR56	1.68
ILMN_2388547	EPSTI1	4.40	ILMN_2353732	CD8A	1.66
ILMN_1683678	LOC26010	4.27	ILMN_2109489	GZMB	1.66
ILMN_1695404	LY6E	4.10	ILMN_2399463	VAV3	1.66
ILMN_1835092		4.04	ILMN_1660343	LOC653080	1.65
ILMN_1654639	HERC6	4.04	ILMN_1701195	PLA2G7	1.64
ILMN_2410826	OAS1	4.03	ILMN_2054019	ISG15	1.63
ILMN_2231928	MX2	3.81	ILMN_1695187	GYPE	1.62
ILMN_1742618	XAF1	3.71	ILMN_2313901	PAM	1.61
ILMN_1783621	CMPK2	3.71	ILMN_1740633	PRF1	1.61
ILMN_1674063	OAS2	3.70	ILMN_1682929	SYTL2	1.61
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Down-Regulated

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ILMN_1759818		SORL1	-1.54
ILMN_1668092		ESAM	-1.54
ILMN_2087080		RPL5	-1.54
ILMN_1712305		CYBRD1	-1.54
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ILMN_1749403		TSPAN33	-1.54
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