Inflammasome activation underlies central nervous system deterioration in HIV-associated tuberculosis

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Abstract (143 words)

Tuberculosis meningitis (TBM) is a frequent cause of meningitis in HIV-infected individuals, resulting in death in ~ 40% of affected patients. A severe complication of antiretroviral therapy (ART) in these patients is neurological TB-immune reconstitution inflammatory syndrome (IRIS), but its underlying cause remains poorly understood. To investigate the pathogenesis of TBM-IRIS, we performed longitudinal whole blood microarray analysis of HIV-infected TBM patients and reflected the findings at the protein level. Patients who would eventually develop TBM-IRIS had significantly higher abundance of neutrophil-associated transcripts from prior to developing TBM-IRIS through to IRIS symptom onset. Following ART initiation, a significantly higher abundance of transcripts associated with canonical and non-canonical inflammasomes were detected in TBM-IRIS patients, compared to non-IRIS controls. Whole blood transcriptome findings complement protein measurement from the site-of-disease, which together, suggest a dominant role for the innate immune system in the pathogenesis of TBM-IRIS.

Keywords: Tuberculosis meningitis, HIV, microarray, inflammasomes, neutrophils

Introduction

Tuberculosis (TB) is the most common cause of death among people with HIV-1 infection [1]. The World Health Organization recommends early initiation of antiretroviral therapy (ART) to all patients co-infected with HIV and TB [2]. While increased coverage of ART has significantly improved the clinical outcome of patients with HIV-associated TB, it also leads to increased incidence of TB-immune reconstitution inflammatory syndrome (IRIS) [3]. Paradoxical TB-IRIS is a condition in which patients on TB treatment experience new, recurrent or worsening of previously stabilized TB symptoms following the commencement of ART. HIV-1 positive patients with TB meningitis (TBM) are at particularly high risk of developing neurological TB- IRIS (47%). TBM-IRIS is associated with a mortality rate of up to 30% [4-6].

It is well established that serum hypercytokinemia is a major pathological consequence of TB-IRIS [7]. Similar observations were also reported from cerebrospinal fluid (CSF) in neurologically compartmentalized TBM-IRIS, with significantly higher concentrations of pro- and anti-inflammatory cytokines and chemokines were detected in patients who developed IRIS compared to those who did not [8]. Recently, our group and others have reported that inflammasome activation underlies the immunopathogenesis of TB-IRIS and that its inhibition results in reduction of cytokine production [9-11]. Inflammasomes are immune complexes of receptors and sensors that mediate innate immune responses and induce inflammation. Canonical inflammasomes are mediated via Nod-like receptor proteins (e.g. NLRP3 or NLRC4) or AIM2 and activate Caspase-1 to cleave pro-IL-1β and pro-IL-18 into their mature forms [12]. Non-canonical inflammasomes, on the other hand, activate Caspase-4/5 (Caspase-11 in mice) to cleave pro-IL-1α into its mature form and induce pyroptosis [12]. *Mycobacterium tuberculosis* (*Mtb*) is known to activate NLRP3 inflammasome and contribute to the tissue-damaging innate inflammatory responses [13, 14].

In this study, we investigated whether inflammasome activation also characterizes the pathogenesis of the highly compartmentalized TBM-IRIS. We performed transcriptomic profiling using microarray on longitudinal whole blood samples from TBM patients who did, or

did not, develop IRIS following ART. We further performed protein immunoassays on serum and CSF in order to investigate whether TBM-IRIS is associated with a proinflammatory inflammasome-activated innate immune response.

Materials and Methods

Ethical approval. The study was approved by the University of Cape Town Human Research Ethics Committee (HREC No: 350/2013). All participants or their relatives provided written informed consent.

Study design and participant recruitment. Hospitalized patients with HIV-associated TBM were recruited into a prospective observational cohort study at GF Jooste Hospital, a district level hospital in Cape Town, South Africa, between March 2009 and October 2010 [8, 15]. Eligible patients were adults (age ≥18 years) with serologically confirmed HIV-1 infection and a diagnosis of TBM according to a published clinical case definition [16]. All patients received antitubercular therapy and prednisone (1.5mg/kg/day) from the time of TBM presentation and commenced ART 2 weeks after antitubercular therapy initiation. All *Mtb* isolates were susceptible to rifampicin and isoniazid, with the exception of one from a TBM-IRIS patient, that was susceptible to rifampicin but not isoniazid. Patients were tracked longitudinally for the development of TBM-IRIS, which was diagnosed according to a published definition [8, 17] (**Figure S1**). Patients who experienced TBM-IRIS received an increased dosage of, or were restarted on, prednisone. In patients who did not develop TBM-IRIS, the dosage of prednisone was weaned after 4 weeks of TB treatment. A further group of HIV-infected, ART naïve adults without TB and meningitis were enrolled as controls [8].

Blood and CSF sample collection. Paired blood and CSF samples were collected from patients longitudinally at the following timepoints: TBM presentation, 2 weeks later at time of starting ART, 2 weeks after starting ART and at time of TBM-IRIS presentation (5). Plasma and CSF were stored in -80°C until batch RNA analysis and protein determination were performed.

RNA extraction and processing for microarray analysis. RNA was extracted from whole blood in PAXgene tubes using PAXgene Blood RNA kits (QIAGEN, Valencia CA, USA) according to the manufacturer's protocol. Total RNA (2µg) was then globin reduced using the

GLOBINclear 96-well plate format kit (Thermo Fisher Scientific, Waltham MA, USA). The total RNA yield after globin reduction was determined in a NanoDrop 1000 spectrophotometer (Thermo Fisher Scientific) and its integrity assessed by Agilent 2100 Bioanalyzer (Agilent Technologies, Santa Clara CA, USA). All RNA samples had integrity number **>**6.0 and were determined to be acceptable for analysis. Approximately 250ng of globin-reduced RNA was used to prepare amplified and biotinylated antisense complementary RNA targets using the Illumina TotalPrep RNA amplification kit (Thermo Fisher Scientific). Seven hundred and fifty nanograms of labelled cRNA was hybridized overnight to Illumina human HT-12 v4 BeadChip arrays (Illumina Inc., San Diego CA, USA), which contained >47,000 probes (for transcripts). Some genes were represented by more than one probe/transcript. The arrays were then washed, blocked, stained and scanned on an Illumina BeadStation 500. Signal intensity values from the scans were generated by the Illumina BeadStudio v2 software. All samples were randomized during all stages of processing to avoid any batch effect. The microarray data from this study have been deposited in NCBI's Gene Expression Omnibus and are accessible through GEO Series accession number GSE83892.

Microarray data analysis. Raw microarray data were background subtracted, and scaled data were generated using Illumina BeadStudio v2 software. A stringent filter was implemented to select only those transcripts present in 100% of samples of either the IRIS or the non-IRIS group. The transcripts in TBM-IRIS samples were further filtered to have >1.5-fold expression change (FC) compared with the non-IRIS samples. The Mann–Whitney *U*-test with Storey's bootstrapping *post hoc* test was applied with $q<0.05$. The transcripts identified were then clustered using a hierarchical algorithm with Pearson's uncentred distance metric and average linkage. The weighted temporal molecular distance was used to determine whether the raw expression value of each differentially expressed transcript in each sample lay within or outside two standard deviations of the baseline control. Mean transcript abundance in patients without meningitis and off ART was used as baseline control. To quantify, transcripts had to differ by at least 200 units in raw signal intensity and at least 2 standard deviations from the baseline control. The weighted distance is the group mean of the sum of the total standard deviations for all transcripts meeting these criteria. Functional pathways

overrepresented by differentially abundant transcripts were analyzed using Ingenuity Pathway Analysis (IPA) (QIAGEN, Germantown, MD).

Quantitative PCR. Total RNA (500ng) was first reverse transcribed into complementary DNA (cDNA) using SuperScipt VILO Master Mix (Thermo Fisher Scientific) before used for quantitative PCR (qPCR). Expression of mRNA targets were measured using TaqMan Gene Expression Assays as previously described and expression of TATA-box binding protein (TBP) was used as housekeeping [7, 18].

Serum and CSF protein determination. The plasma and CSF concentrations of Caspases-1 (R&D Systems, Minneapolis MN, USA), Caspase-3 (eBioscience, San Diego CA, USA) and Caspase-4 (LifeSpan BioSciences, Seattle WA, USA) were determined according to manufacturers' instructions.

Statistical analysis. Statistical analyses were performed in GraphPad Prism 6.0 software. Patient baseline characteristics were compared by χ^2-test for contingency data or Kruskal–Wallis test for continuous data. The weighted temporal molecular distance between IRIS and non-IRIS patients was compared using the unpaired t-test with Welch's correction. Potential significance was inferred for results associated with a p-value < 0.05.

Results

Patient characteristics. We have previously described the clinical and laboratory findings of our cohort of 34 HIV-associated TBM patients who did (n=16) or did not (n=18) develop paradoxical TBM-IRIS (5,8). At time of TBM-IRIS presentation, 15 patients underwent brain imaging, including CT (n=14) or MRI (n=1). Imaging showed features of TBM in 14 of these patients and was normal in one. CT brain abnormalities (excluding generalized atrophy) included: extensive focal meningeal enhancement (n=3), tuberculoma (n=6), infarcts (n=4), basal meningeal enhancement (n=2) and hydrocephalus (n=2). Of 4 patients who had CT scans performed at TBM diagnosis and at TBM-IRIS presentation, 2 showed worsening radiological features of TBM at TBM-IRIS, including new ring-enhancing lesions (n=1) and increasing basal meningeal enhancement (n=1). Serial CT brain findings showed evolving basal ganglia infarcts in the other 2 patients. MRI spine was performed in 2 of 3 patients with paraparesis and both had features of radiculomyelitis.

Longitudinal blood samples for RNA analysis were available for 33 of these patients (TBM-IRIS=16, non-IRIS=17), who were included in this study. Seventeen HIV-1 patients without TB and meningitis were included as controls [8]. TB diagnosis was excluded in the control patients by lack of TB symptoms, normal chest X-ray and absence of TB treatment. Compared to TBM patients (TBM-IRIS and non-IRIS), control patients without TB or meningitis had a significantly lower HIV-1 viral load, CSF lymphocyte and neutrophil counts, and protein concentrations (**Table 1**). Patients in both TBM-IRIS and non-IRIS groups were similar in terms of gender, age and baseline CD4 count and HIV-1 viral load (**Table 1**). All but one individual (15/16), who eventually developed TBM-IRIS, had positive *Mtb* culture in their CSF at the time of TBM diagnosis, while only 6/17 non-IRIS patients were culture positive for *Mtb* in their CSF by comparison (5). Time to culture positivity in samples collected during the first study LP was similar between TBM-IRIS and non-IRIS patients (median: 14 days, range: 8-31 days and median:15 days, range: 4-32 days, respectively). Some TBM-IRIS patients remained culture positive after 2 weeks (n=7, median time to culture positivity 18 days, range: 16-24) and 4 weeks (n=2, time to culture positivity 16 and 27 days, respectively) of TB treatment. No non-IRIS patients were culture positive after starting TB treatment. In addition,

TBM-IRIS patients also had significantly higher CSF neutrophil counts and CSF protein levels both at the time of TBM diagnosis and 2 weeks post-ART (2wpART) (**Table 1**).

Changes in innate immunity precede the development of TBM-IRIS. We investigated the transcriptional profile associated with the development of TBM-IRIS using whole blood microarray, which has been previously used to characterize non-disease site-specific TB-IRIS by our group and others [9, 19]. Whole blood RNA samples were utilized due to the relatively low number of cells present in the CSF compartment, resulting in insufficient amount and quality of RNA available for analysis.

At the time of TBM diagnosis, we identified 373 transcripts that were differentially abundant (FC >1.5, q <0.05) in patients who would eventually develop TBM-IRIS, compared to those who did not (**Figure 1a and Table S1**). Gene ontology term analysis on these 373 transcripts indicated significant overrepresentation of immune response against *Mtb* bacteria and increased antigen processing and presentation (**Figure 1b**). We focused particularly on neutrophil-mediated immune responses, as elevated neutrophil counts in the CSF have been implicated to be prognostic of future TBM-IRIS development [8]. In keeping with the observation in the CSF, the whole blood transcriptional signature also reflected an increase in neutrophil-dependent inflammatory response with significantly higher abundance of myeloperoxidase (MPO), matrix metalloproteinase-8 and -9 (MMP8 and MMP9), cathepsin G (CTSG), lipocalin-2 (LCN2) and alpha-defensin (DEFA1/3/4) (**Table S1**). To investigate whether the whole blood transcriptional signature reflected pathology at the disease site, we measured the protein concentrations of these neutrophil mediators in the corresponding CSF samples. Significantly higher protein concentrations of MMP9, CTSG, LCN2 and the alpha-defensin 1-3 (HNP1-3; encoded by DEFA1 and 3) were detected in the CSF of patients who eventually developed TBM-IRIS when compared to non-IRIS (**Figure 1c**). The peripheral transcriptional signature also indicated significant downregulation of Natural Killer (NK) cell signaling, marked by decreased expression of killer cell immunoglobulin-like receptors 2 and 3 (KIR2DL/3DL) and killer cell lectin-like receptor 2 (KLRC2) (**Table S2**).

Following the diagnosis of TBM, patients were placed on antitubercular therapy and prednisone for 2 weeks before commencing ART. Transcriptomic analysis identified 282 differentially abundant (FC >1.5, q <0.05) transcripts associated with later development of TBM-IRIS at 2 weeks post-TB treatment (2wpTBRx) and prior to ART (**Figures 2a and Table S2**). Transcripts associated with neutrophil-dependent inflammation (MPO, MMP9 and LCN2) continued to be significantly upregulated despite the antitubercular and anti-inflammatory (prednisone) therapy (**Table S2**). Further functional analysis of the differentially abundant transcripts also indicated significant upregulation of several immunological pathways including inflammasome activation, antigen-presenting cell (APC) maturation and IL-8 signaling (**Figure 2b**), suggesting patients who would develop TBM-IRIS had differences in innate immune response prior to and following antitubercular therapy and ART.

TBM-IRIS onset is associated with transcripts involved in pathogen recognition and inflammasome activation. In patients who developed TBM-IRIS, the median onset time was 14 days (IQR: 4-20 days) following ART commencement. We identified 327 differentially abundant (FC >1.5, q <0.05) transcripts associated with TBM-IRIS (**Figure 3a and Table S3**) at 2 weeks post-ART (2wpART). Similar to earlier timepoints, neutrophil-dependent inflammatory responses (MMP9, CTSG and LCN2) continued to be transcriptionally upregulated (**Table S3**) in patients with TBM-IRIS. Inflammasome activation has recently been shown as an important mediator of TB-IRIS in two independent studies [9, 11]. In accordance with these results, functional analysis of the differentially abundant transcript also indicated significant upregulation of transcripts associated with inflammasome activation (**Figure 3b**). These included signaling via toll-like receptors (TLRs) and other pattern recognition receptors (PRRs) such as NOD2 and C-type lectins, increased expression of the interferon-induced guanylate-binding proteins (GBP1, 4, 5 and 6) and the noncanonical caspases 4 and 5 (CASP4/5). Elements of the canonical inflammasome, including caspase 1 (CASP1), GBP2, AIM2, NLRC4 and IL1B, were also upregulated in TBM-IRIS but with lower fold change (FC = 1.28 to 1.48, q < 0.05). The increased mRNA expression of a panel of inflammasome-related genes was validated using qPCR and confirmed that both canonical and noncanonical inflammasomes were transcriptionally activated in TBM-IRIS (**Figure 3c**).

We further measured the protein concentrations of several caspases in both serum and CSF. Significantly higher amounts of caspase-1 were detected in the CSF, but not serum, of TBM-IRIS patients compared to those from non-IRIS (**Figure 3d**). The concentrations of noncanonical caspase-4 were below limit of detection in both serum and CSF, while the apoptosis-associated caspase-3 did not differ between the two groups (**Figure 3d**). Together, the data suggest that pathology of TBM-IRIS is driven by an aberrant innate immune response, with neutrophils and inflammasome activation being key mediators.

TBM-IRIS development is associated with increased transcript perturbation over time. We next overlapped the transcript signature identified at each timepoint (**Figure 4a**) and found 22 transcripts consistently differentially abundant (21 up-regulated and 1 down-regulated) in TBM-IRIS both prior to and at the time of symptom onset (**Figure 4b**). These included the neutrophil-dependent effectors LCN2 and MMP9, proinflammatory mediator oncostatin M (OSM) and cytolytic protein granulysin (GNLY). We then applied a weighted temporal molecular distance algorithm [20] to measure the perturbation of these 22 transcripts in each patient sample per timepoint, relative to the non-meningitis control patients. The mean raw intensity values of these transcripts from a panel of 15 control patients, who did not have meningitis and were not on ART, was used as baseline controls and was given a score of 0. At each of the three timepoints, there were significant perturbations of these 22 transcripts in the TBM-IRIS patients compared to the non-IRIS samples (**Figure 4c**). Similarly, we also computed the temporal molecular distance for a list of 21 transcripts associated with both canonical and noncanonical inflammasomes that were significantly differentially expressed with FC>1.3 ($q < 0.05$) at 2wpART (**Table S4**). At the time of TBM diagnosis, inflammasome transcript perturbation did not differ between patients who would eventually develop TBM-IRIS to those who were non-IRIS. While the TBM non-IRIS group remained transcriptionally quiescent over time, inflammasome-associated transcripts became significantly more upregulated in the TBM-IRIS group following antitubercular and antiviral therapies (**Figure 4d**). Together, these data indicate an early transcriptional increase in proinflammatory mediators and effectors in peripheral blood that

antecedes the TBM-IRIS episode and that the immunopathology of IRIS is associated with increased inflammasome activation.

Discussion

Compared to pulmonary and other forms of extrapulmonary TB-IRIS, patients with neurological TB-IRIS often exhibit severe disease, a poorer outcome and have higher mortality rates [6, 21]. To better understand this advanced form of TB disease, we investigated the transcriptional response in TBM-IRIS using whole blood microarray as extraction of disease site-specific RNA was not feasible. Based on our past findings in pulmonary TB [9, 22], we speculate that whole blood transcriptome would also provide insights on the cellular signaling across the blood-brain-barrier. Furthermore, measuring transcriptional changes in whole blood provides a non-invasive approach to monitor disease prognosis and progress compared to using CSF samples.

We identified differentially abundant transcripts associated with TBM-IRIS both prior to and during disease onset, which indicated a key role for neutrophil-dependent and inflammasome-associated proinflammatory responses in the pathogenesis of TBM-IRIS. Previous analyses of CSF from this patient cohort have revealed that higher bacterial burden, raised neutrophil counts and elevated concentrations of the proinflammatory cytokine TNF-α at time of TBM diagnosis predicted future TBM-IRIS [5]. In accordance with the CSF data, whole blood microarray analysis in this study also identified several neutrophil-dependent inflammatory mediators, including MMP9, to have significantly higher transcriptional abundance in TBM-IRIS patients throughout the course of disease development. MMPs are known to cause lung tissue damage in pulmonary TB [23]. In the central nervous system, evidence suggests that MMP not only facilitates blood-brain-barrier disruption, which results in leukocyte influx [24, 25] but also upregulates microglial secretion of cytokines [26]. Furthermore, elevated CSF MMP9 concentrations have been associated with poorer outcome, including death [27] and neurological complications [28, 29], in TBM patients. In addition to increased CSF concentration of MMP9 associated with TBM-IRIS, elevated mRNA expression and increased serum concentrations of MMP9 have also been reported in pulomnary TB-IRIS [8, 30]. We

hypothesize that the consistently high abundance of MMP9 in TBM-IRIS suggests degradation of the extracellular matrix as a mechanism of tissue damage in both the central nervous system that is systemically reflected in the blood.

Furthermore, despite having a highly compartmentalized inflammatory response in the CSF, TBM-IRIS appears to share the same underlying pathogenic mechanism with other forms of TB-IRIS in which inflammasome activation plays a key role, and again, this is reflected in peripheral blood. We have previously shown that TLR signaling and inflammasome activation are key mediators of dysregulated cytokine production in a cohort of patients who developed heterogenous presentations of paradoxical TB-IRIS [9]. Most recently, Crowe and colleagues have also reported that monocytes from TB-IRIS patients displayed aberrant inflammasome activation and had greater cell death both prior to and following ART [11]. In keeping with these observations in general TB-IRIS, we also identified that both canonical and noncanonical inflammasomes activation was involved in the pathogenesis of TBM-IRIS. Whilst there was no discernable difference in the blood transcriptional activity of inflammasomes at the baseline (time of TBM diagnosis), significant transcript perturbations following antitubercular therapy were observed and continued following ART initiation in patients who would go on to develop TBM-IRIS. At the site of infection, CSF concentrations of caspase-1 were significantly higher in TBM-IRIS patients both at TBM diagnosis and also during the IRIS episode, demonstrating that inflammasome activation was both compartmentalized in the central nervous system and reflected systemically at an early stage. Given that inflammasome activation can contribute to pyroptosis [31], an inflammatory cell death distinctive from apoptosis, tissue injury (such as disruption of the central nervous system architecture and degradation of the extracellular matrix) observed in TBM-IRIS may be partly induced by inflammasome-mediated pyroptosis.

Finally, although patients were prescribed prednisone prior to any IRIS onset, repression of proinflammatory transcription factors (e.g. NF-κB and AP-1) by this anti-inflammatory glucocorticoid [32] was insufficient to prevent the production of inflammatory mediators. Given the unwanted side effects of prednisone, treatments more specific to the pathology of

TB/TBM-IRIS should be considered. The existence of a small molecule inhibitor (MCC950), which targets the NLRP3 inflammasome [33], suggests more effective ways to both prevent and treat the inflammatory symptoms of TB-associated IRIS and should be explored in future studies.

Author contribution

SM, RPJL, GM, AOG and RJW conceived and designed the study. SM recruited, sampled and collected data from patients. SM, RPJL and KAW performed the experiments. SM and RPJL analyzed the data. SM, RPJL and RJW wrote the manuscript, which was revised by GM, KAW and AOG.

Conflict of interest

All authors have no conflict of interest to declare.

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Figure and Table Legends

Table 1. Baseline characteristics of HIV-associated TBM patients. Thirty-three patients who presented with HIV-associated TBM were recruited to a prospective cohort, 17 of whom did not develop IRIS following ART (TBM non-IRIS). The other 16 patients were diagnosed with TBM-IRIS with a median onset time of 14 days (interquartile range = 14-20 days) post-ART. Gender, age, viral load and CD4 counts were similar between these two groups. TBM-IRIS patients however had a significantly higher count of neutrophils in the CSF at baseline (TBM diagnosis) and higher counts of both neutrophils and lymphocytes at 2 weeks post-ART (2wpART). A control group of 17 HIV-1 infected patients without TBM were also included in this study. Lumbar puncture was performed in the control patients to rule out a CNS infection. The final diagnoses of control patients were seizures (n=4), psychosis (n=4), non-specific headaches (n=4), HIV-associated neurocognitive disorder (n=2), meningioma (n=1), stroke (n=1) and Bell's palsy (n=1). The control and the TBM groups were matched in gender, age and CD4 counts. However, non-TBM control patients had a significantly lower HIV-1 viral load and lower CSF lymphocyte and neutrophil counts, and lower protein concentrations. *P*-values that are significant are colored in red. Numbers in parentheses are percentage for contingency data or median plus interquartile range for continuous data. N.A.: Not Applicable.

Figure 1. Blood transcriptional signature and CSF protein analysis at the time of TBM diagnosis. (a) Whole blood samples from 33 HIV-TB patients diagnosed with TBM were processed for microarray. A total of 373 transcripts were found to be differentially abundant with FC>1.5 in patients who would later develop TBM-IRIS (n=16, red bar), compared to those who did not (TBM non-IRIS; n=17, blue bar). On the heatmap, upregulated transcripts are shown as red and downregulated transcripts are green. (b) Gene ontology term analysis on the differentially abundant transcripts indicated an increased immune response against *Mtb* pathogen and activation of immune cells in the eventual TBM-IRIS patients, indicating that these patients had more active immune responses prior to commencing any treatment. (c) Transcripts (MMP9, GTSG, LCN2 and HNP1-3) associated with neutrophil-dependent inflammatory pathways were significantly upregulated in the microarray. The CSF protein

concentrations of these effectors were significantly higher in the future TBM-IRIS group when compared to those who did not later develop IRIS. Two-tailed Student's t-tests were performed and * $p<0.05$, ** $p<0.01$ and *** $p<0.001$.

Figure 2. Blood transcriptional signature following antitubercular therapy. Whole blood samples were taken from patients 2 weeks post-antitubercular therapy immediately prior to starting ART. (a) A total of 282 transcripts were found to be differentially abundant with FC>1.5 between future TBM-IRIS patients (n=16, red bar) and TBM non-IRIS patients (n=17, blue bar). Green color on the heatmap represents decreased relative abundance and red represents increased relative abundance. (b) Functional analysis identified innate signaling pathways were overrepresented by the 282 transcripts. These include activation of inflammasomes, which have been shown to be mediators of pathogenesis in TB-IRIS in general.

Figure 3. Blood transcriptional signature at the median time of TBM-IRIS onset. The median time of IRIS onset was 14 days post ART initiation (2wpART) (a) A total of 327 transcripts were found to be differentially abundant with FC >1.5 in TBM-IRIS. TBM-IRIS patients (n=16) are indicated in red and TBM non-IRIS patients (n=17) are indicated in blue. Downregulated transcripts are shown in green and upregulated transcripts are shown in red. (b) Functional analysis of the transcripts indicated strong involvement of innate immunity at time of symptom onset in TBM-IRIS. These include inflammasome activation mediated by pattern recognition receptors (specifically, TLR1,2,6 and 8 and NOD2). (c) Expression of a panel of transcripts associated with inflammasome activation was validated by qPCR. Red presents TBM-IRIS and blue for TBM non-IRIS. Elements of both canonical and noncanonical inflammasomes were more abundant in TBM-IRIS at 2wpART. Two-tailed Student's t-tests were performed and * $p<0.05$ and ** $p<0.01$. Abbreviations: TLR2/5 (toll-like receptor 2/5), AIM2 (absence in melanoma 2), NLRC4 (nod-like receptor family CARD domain-containing protein 4), GBP1/5 (interferon-induced guanylate-binding protein 1/5), CASP1/4 (caspase 1/4) and IL-1B (interleukin-1 beta). (d) In keeping with the transcriptomic data, the CSF concentration of Caspase-1 was significantly higher in TBM-IRIS patients (*** $p<0.001$).

Concentration of CSF Caspase-3, which mediates anti-inflammatory apoptosis, did not differ between the TBM non-IRIS and the TBM-IRIS patients (p = non-significant, n.s.).

Figure 4. Longitudinal transcriptional perturbation is associated with TBM-IRIS. (a) To identify conserved transcriptional features associated with TBM-IRIS development, differentially abundant transcripts at each timepoint were overlapped: 373 from TBM diagnosis (pink), 282 from 2wpTBRx (green) and 327 from 2wpART (blue). Twenty-two transcripts (center) were found to be consistently differentially abundant in TBM-IRIS over the course of disease development. (b) Heatmap showing the expression of each of the 22 transcripts overtime. TBM non-IRIS patients are shown in blue and TBM-IRIS patients in red. Upregulated transcripts are shown in red and downregulated in green. (c) The temporal molecular distance, which measures the perturbation of transcript expression, was calculated for the 22 transcripts. Mean expression of these transcripts in HIV-infected patients without meningitis and not on ART (n=15) was used as baseline reference. The transcriptional perturbations of these 22 transcripts were significantly higher in TBM-IRIS (red) than TBM non-IRIS (blue) at all three timepoints. (d) Temporal molecular distance was separately calculated for a list of 21 transcripts associated with inflammasome activation (see Table S4). There was significantly higher transcriptional perturbation in TBM-IRIS both at 2wpTBRx and 2wpART. Two-tailed Student's t-tests were performed on the temporal molecular distance and * $p<0.05$.

Supplementary Figure and Table Legends

Figure S1. Schematic diagram of drug regimens and samplings. At the time of TBM diagnosis, all thirty-three patients were placed on standard antitubercular therapy and prednisone (1.5mg/kg/day). Two weeks later, patients were placed on antiretroviral therapy (ART). TBM-IRIS symptom onset occurred at a median time of 14 days post-ART initiation. Thirteen of the 16 patients who developed TBM-IRIS were still receiving prednisone (0.75-1.5mg/kg/day) at the time of IRIS symptom onset; prednisone dose was increased in these patients to 1.5-2mg/kg/day. In the remaining 3 IRIS patients, prednisone was restarted at the

time of IRIS symptom onset at 1.5mg/kg/day. Cerebrospinal fluid and whole blood were sampled at the time of TBM diagnosis prior to any medication, then at 2 weeks post TB therapy initiation (2wpTBRx) but prior to starting ART, and finally at the time of IRIS diagnosis or 2 weeks following ART commencement (2wpART).

Table S1. Differentially abundant transcripts at the time of TBM Diagnosis. 373 transcripts differentially expressed between TBM-IRIS and TBM non-IRIS patients and their expression FC (relative to non-IRIS) are listed. Positive values indicate increased relative abundance and negative values indicate decreased relative abundance.

Table S2. Differentially abundant transcripts at the time of starting ART. 282 transcripts differentially expressed between TBM-IRIS and TBM non-IRIS patients and their expression FC (relative to non-IRIS) are listed. Positive values indicate increased relative abundance and negative values indicate decreased relative abundance.

Table S3. Differentially abundant transcripts 2 weeks after starting ART (median time of IRIS presentation). 327 transcripts differentially expressed between TBM-IRIS and TBM non-IRIS patients and their expression FC (relative to non-IRIS) are listed. Positive values indicate increased relative abundance and negative values for decreased relative abundance.

Table S4. Transcripts associated with inflammasome activation. 21 differentially expressed transcripts associated with inflammasome activation. All 21 transcripts were more abundant in TBM-IRIS with FC>1.3 ($q < 0.05$) at the time of IRIS onset (2wpART).

References

1. WHO. World Health Organization: Global Tuberculosis Report 2015. Http://Www.Who.Int/Tb/Publications/Global_Report/En/. **2015**.

2. WHO. A Guide to Monitoring and Evaluation for Collaborative Tb/Hiv Activities. Http://Apps.Who.Int/Iris/Bitstream/10665/150627/1/9789241508278_Eng.Pdf?Ua=1. **2015**.

3. Lai RP, Meintjes G, Wilkinson RJ. Hiv-1 Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. Semin Immunopathol **2016**; 38:185-98.

4. Asselman V, Thienemann F, Pepper DJ, et al. Central Nervous System Disorders after Starting Antiretroviral Therapy in South Africa. AIDS **2010**; 24:2871-6.

5. Marais S, Meintjes G, Pepper DJ, et al. Frequency, Severity, and Prediction of Tuberculous Meningitis Immune Reconstitution Inflammatory Syndrome. Clin Infect Dis **2013**; 56:450-60.

6. Pepper DJ, Marais S, Maartens G, et al. Neurologic Manifestations of Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: A Case Series. Clin Infect Dis **2009**; 48:e96-107.

7. Tadokera R, Meintjes G, Skolimowska KH, et al. Hypercytokinaemia Accompanies Hiv-Tuberculosis Immune Reconstitution Inflammatory Syndrome. Eur Respir J **2011**; 37:1248-59.

8. Marais S, Wilkinson KA, Lesosky M, et al. Neutrophil-Associated Central Nervous System Inflammation in Tuberculous Meningitis Immune Reconstitution Inflammatory Syndrome. Clin Infect Dis **2014**; 59:1638-47.

9. Lai RP, Meintjes G, Wilkinson KA, et al. Hiv-Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome Is Characterized by Toll-Like Receptor and Inflammasome Signalling. Nat Commun **2015**; 6:8451.

10. Tan HY, Yong YK, Andrade BB, et al. Plasma Interleukin-18 Levels Are a Biomarker of Innate Immune Responses That Predict and Characterize Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. AIDS **2015**; 29:421-31.

11. Tan HY, Yong YK, Shankar EM, et al. Aberrant Inflammasome Activation Characterizes Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. J Immunol **2016**.

12. Guo H, Callaway JB, Ting JP. Inflammasomes: Mechanism of Action, Role in Disease, and Therapeutics. Nat Med **2015**; 21:677-87.

13. Dorhoi A, Nouailles G, Jorg S, et al. Activation of the Nlrp3 Inflammasome by *Mycobacterium Tuberculosis* Is Uncoupled from Susceptibility to Active Tuberculosis. Eur J Immunol **2012**; 42:374-84.

14. Mishra BB, Rathinam VA, Martens GW, et al. Nitric Oxide Controls the Immunopathology of Tuberculosis by Inhibiting Nlrp3 Inflammasome-Dependent Processing of Il-1beta. Nat Immunol **2013**; 14:52-60.

15. Burman W, Weis S, Vernon A, et al. Frequency, Severity and Duration of Immune Reconstitution Events in Hiv-Related Tuberculosis. Int J Tuberc Lung Dis **2007**; 11:1282-9.

16. Bhigjee AI, Padayachee R, Paruk H, Hallwirth-Pillay KD, Marais S, Connoly C. Diagnosis of Tuberculous Meningitis: Clinical and Laboratory Parameters. Int J Infect Dis **2007**; 11:348-54.

17. Meintjes G, Lawn SD, Scano F, et al. Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome: Case Definitions for Use in Resource-Limited Settings. Lancet Infect Dis **2008**; 8:516-23.

18. Meintjes G, Skolimowska KH, Wilkinson KA, et al. Corticosteroid-Modulated Immune Activation in the Tuberculosis Immune Reconstitution Inflammatory Syndrome. Am J Respir Crit Care Med **2012**; 186:369-77.

19. Tran HT, Van den Bergh R, Vu TN, et al. The Role of Monocytes in the Development of Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. Immunobiology **2014**; 219:37-44.

20. Pankla R, Buddhisa S, Berry M, et al. Genomic Transcriptional Profiling Identifies a Candidate Blood Biomarker Signature for the Diagnosis of Septicemic Melioidosis. Genome Biol **2009**; 10:R127.

21. Meintjes G, Wilkinson RJ, Morroni C, et al. Randomized Placebo-Controlled Trial of Prednisone for Paradoxical Tuberculosis-Associated Immune Reconstitution Inflammatory Syndrome. AIDS **2010**; 24:2381-90.

22. Berry MP, Graham CM, McNab FW, et al. An Interferon-Inducible Neutrophil-Driven Blood Transcriptional Signature in Human Tuberculosis. Nature **2010**; 466:973-7.

23. Elkington P, Shiomi T, Breen R, et al. Mmp-1 Drives Immunopathology in Human Tuberculosis and Transgenic Mice. J Clin Invest **2011**; 121:1827-33.

24. Gurney KJ, Estrada EY, Rosenberg GA. Blood-Brain Barrier Disruption by Stromelysin-1 Facilitates Neutrophil Infiltration in Neuroinflammation. Neurobiol Dis **2006**; 23:87-96.

25. Sellner J, Leib SL. In Bacterial Meningitis Cortical Brain Damage Is Associated with Changes in Parenchymal Mmp-9/Timp-1 Ratio and Increased Collagen Type Iv Degradation. Neurobiol Dis **2006**; 21:647-56.

26. Nuttall RK, Silva C, Hader W, et al. Metalloproteinases Are Enriched in Microglia Compared with Leukocytes and They Regulate Cytokine Levels in Activated Microglia. Glia **2007**; 55:516-26.

27. Price NM, Farrar J, Tran TT, Nguyen TH, Tran TH, Friedland JS. Identification of a Matrix-Degrading Phenotype in Human Tuberculosis in Vitro and in Vivo. J Immunol **2001**; 166:4223-30.

28. Lee KY, Kim EH, Yang WS, et al. Persistent Increase of Matrix Metalloproteinases in Cerebrospinal Fluid of Tuberculous Meningitis. J Neurol Sci **2004**; 220:73-8.

29. Matsuura E, Umehara F, Hashiguchi T, Fujimoto N, Okada Y, Osame M. Marked Increase of Matrix Metalloproteinase 9 in Cerebrospinal Fluid of Patients with Fungal or Tuberculous Meningoencephalitis. J Neurol Sci **2000**; 173:45-52.

30. Ravimohan S, Tamuhla N, Kung SJ, et al. Matrix Metalloproteinases in Tuberculosis-Immune Reconstitution Inflammatory Syndrome and Impaired Lung Function among Advanced Hiv/Tb Co-Infected Patients Initiating Antiretroviral Therapy. EBioMedicine **2016**; 3:100-7.

31. Bergsbaken T, Fink SL, Cookson BT. Pyroptosis: Host Cell Death and Inflammation. Nat Rev Microbiol **2009**; 7:99-109.

32. Coutinho AE, Chapman KE. The Anti-Inflammatory and Immunosuppressive Effects of Glucocorticoids, Recent Developments and Mechanistic Insights. Mol Cell Endocrinol **2011**; 335:2-13.

33. Coll RC, Robertson AA, Chae JJ, et al. A Small-Molecule Inhibitor of the Nlrp3 Inflammasome for the Treatment of Inflammatory Diseases. Nat Med **2015**; 21:248-55.

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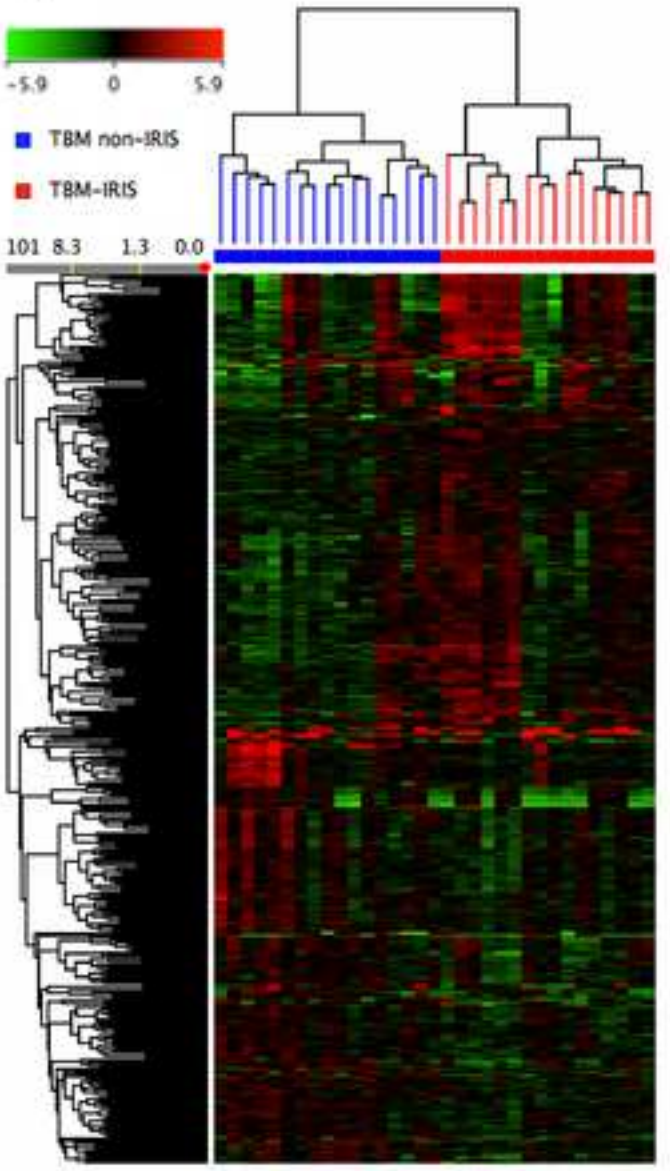
Table 1

Variables	Non-IRIS (n = 17)	IRIS (n = 16)	Controls (n = 17)	*P*-value (IRIS *vs.* non-IRIS)	*P*-value (All TBM *vs.* Controls)
Male sex	11 (65)	7 (44)	8 (47)	0.227	0.616
Age (years)	32.0 (25-42)	33.5 (30-46)	34 (26-40)	0.427	0.539
HIV viral load (log10 copies/ml)	5.45 (4.71-5.72)	5.39 (4.75-6.16)	4.85 (3.67-5.46)	0.788	0.030
CD4 baseline (cells/mm^3)	103 (77-291)	130 (52-168)	149 (94-354)	0.662	0.186
CSF count (TBM Diagnosis or time of symptom presentation)					
Lymphocyte (10^6 cells/L)	108 (50-276)	216 (120-419)	7 (3-17)	0.063	<0.0001
Neutrophil (10^6 cells/L)	4 (0-33)	38 (11-117)	0 (0-0)	0.016	<0.0001
Protein (g/L)	1.38 (1.07-2.13)	2.39 (1.88-4.08)	0.48 (0.37-0.70)	0.009	<0.0001
CSF count (2wpART)					
Lymphocyte (10^6 cells/L)	26 (5-57)	208 (90-363)	N.A.	<0.0001	N.A.
Neutrophil (10^6 cells/L)	0 (0-3)	52 (17-244)	N.A.	<0.0001	N.A.
Protein (g/L)	0.61 (0.37-2.04)	3.11 (2.01-22.83)	N.A.	0.0002	N.A.

Figure 1

a)



b)

Gene Ontology Term	*P*-value
Immune response	0.00E+00
Defense response to bacterium	0.00E+00
MHC class II protein complex	4.00E-03
Antigen processing & presentation	3.70E-02
Regulation of leukocyte activation	4.80E-02

c)

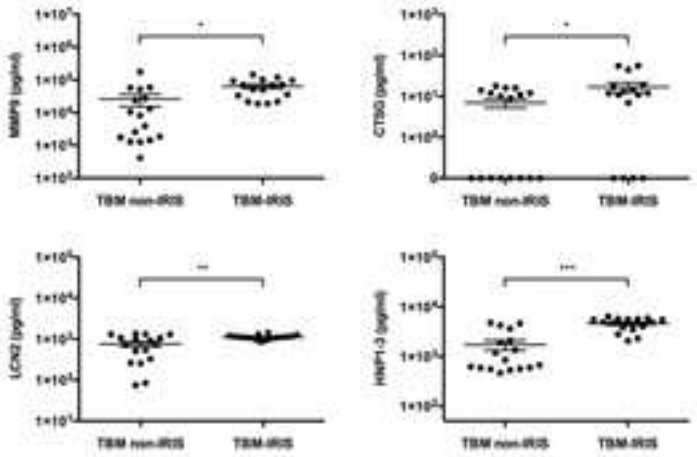
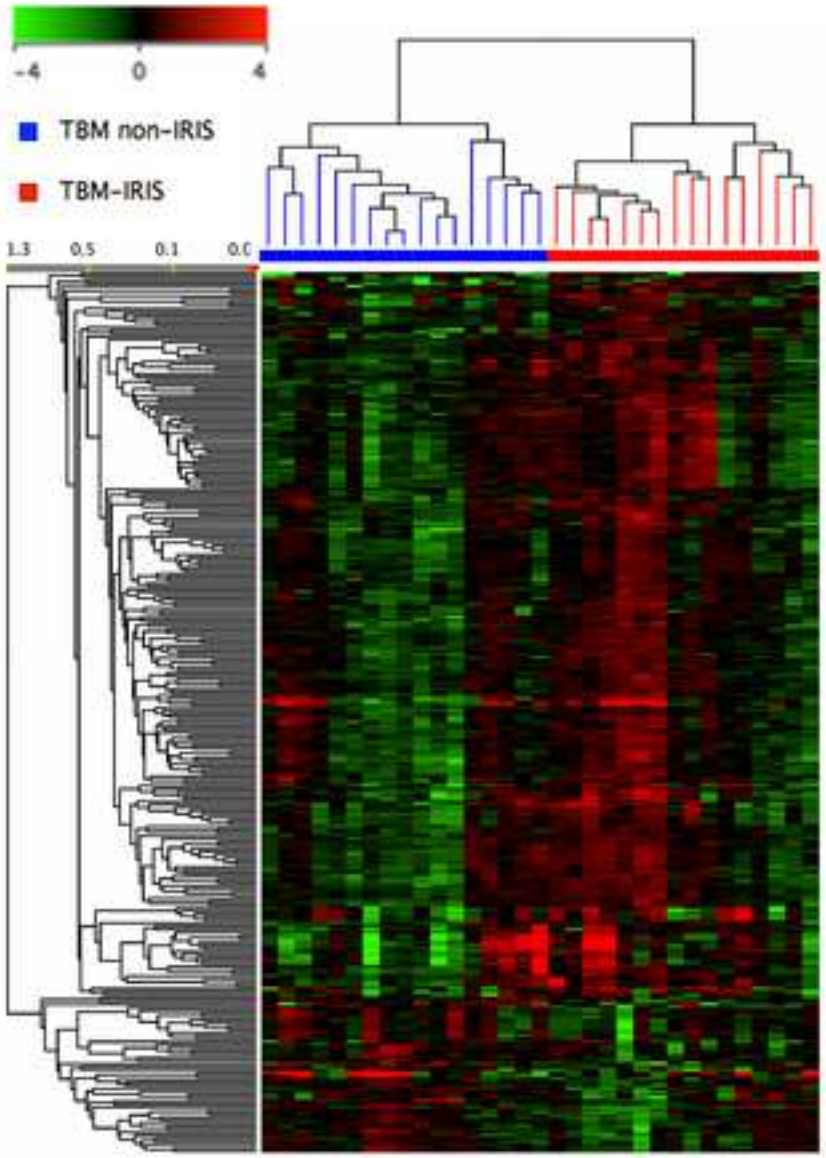


Figure 2

a)



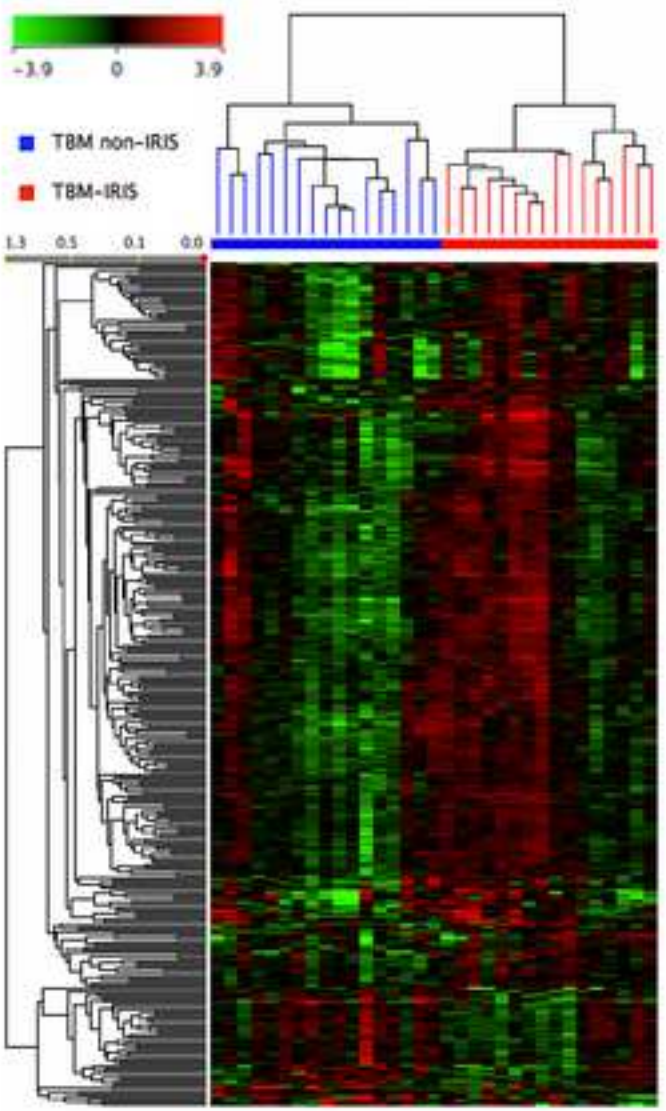
b)

Top 5 canonical pathways	*P*-value
Inflammasome activation	7.29E-03
IL-8 signaling	1.56E-02
HIF1α signaling	2.43E-02
Phagosome formation	2.58E-02
Role of JAK family kinases in IL-6-type cytokine signaling	3.03E-02

Figure 3

Figure 3

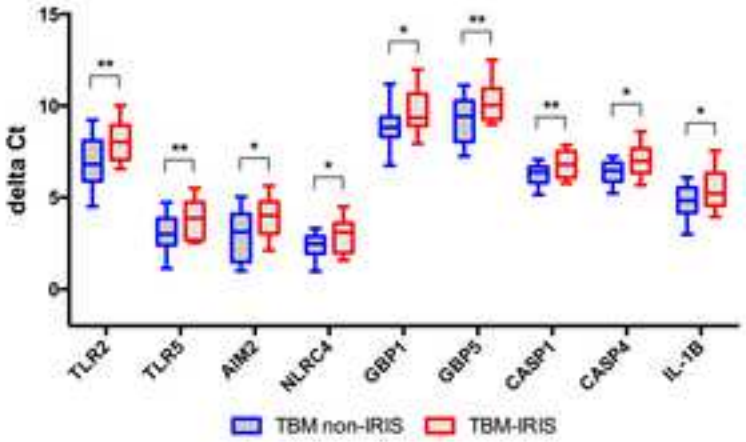
a)



b)

Top 5 canonical pathways	*P*-value
Inflammasome activation	3.72E-05
Phagosome formation	6.08E-05
Role of PRR in recognition of bacteria & viruses	1.80E-04
Role of JAK family kinases in IL-6-type cytokine signaling	2.98E-04
Tol-like receptor signaling	3.99E-04

c)



d)

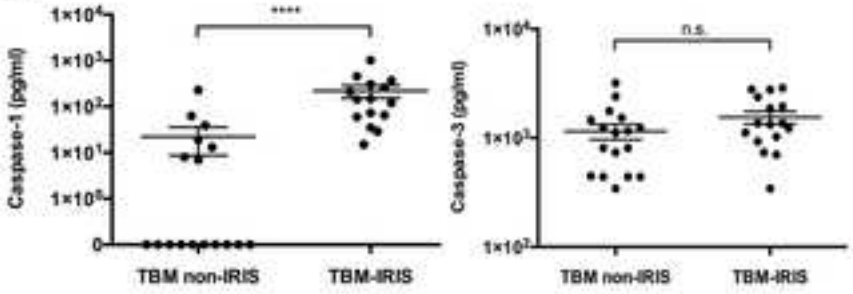
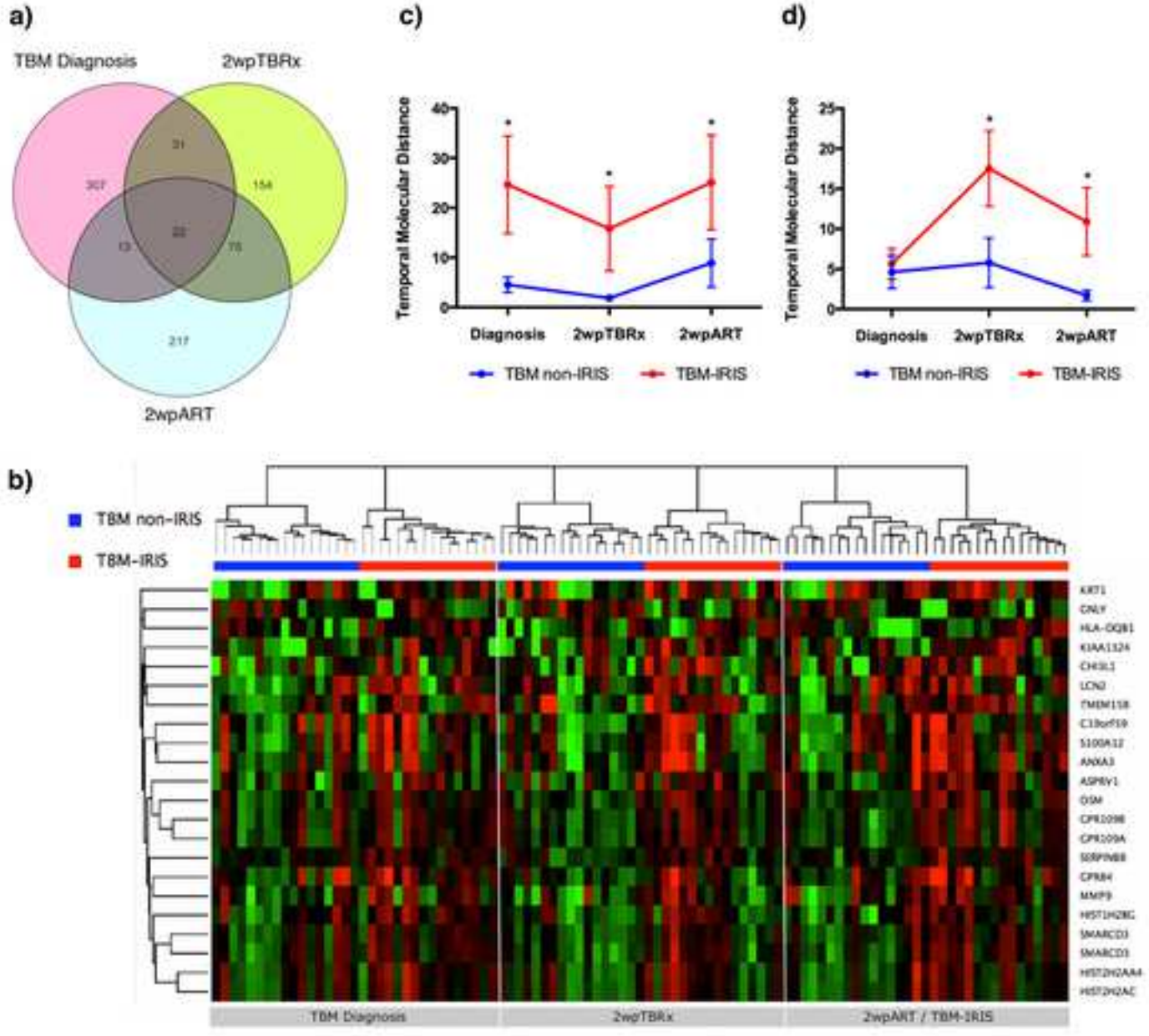


Figure 4



Supplementary Table S1

Illumina_ProbeID	Symbol	Regulation	FC	p -value	q-value
5050598	LOC645381	down	-2.07	1.19E-07	7.52E-08
1570086	B3GNTL1	up	1.51	9.27E-03	5.28E-05
6100356	ALPL	up	1.69	8.39E-02	1.65E-04
2070646	GPR84	up	1.69	6.02E-02	1.28E-04
620136	LILRA5	up	1.53	3.64E-02	9.50E-05
5860075	CAMP	up	1.72	9.78E-02	1.87E-04
2320152	ASB16	down	-1.73	2.94E-02	8.54E-05
4290731	KREMEN1	up	1.76	3.40E-02	9.21E-05
3130370	ZNF83	up	1.51	1.99E-02	7.28E-05
4590519	LOC100130332	up	1.55	1.30E-02	6.13E-05
450020	ORM2	up	1.54	2.28E-02	7.55E-05
3800600	MAGED1	down	-1.59	6.53E-03	4.79E-05
4540475	FABP5L2	down	-1.52	1.27E-02	6.03E-05
3830164	C14orf145	down	-2.01	3.25E-05	1.03E-05
6580041	GNLY	down	-1.50	1.20E-01	2.15E-04
580403	DFNA5	down	-1.64	4.29E-02	1.04E-04
5260484	HLA-DRB1	down	-6.38	3.92E-03	4.74E-05
6480131	ADAM15	up	1.58	1.24E-03	3.66E-05
3180220	GPR109B	up	1.52	3.64E-02	9.50E-05
4860255	ASPRV1	up	1.54	1.08E-01	1.99E-04
3390097	LOC728093	up	1.52	7.57E-02	1.52E-04
380102	TMEM51	down	-1.53	5.48E-02	1.23E-04
1010528	HES1	down	-1.52	1.14E-02	5.74E-05
2760500	CD38	down	-1.70	8.89E-03	5.24E-05
4200669	CR1	up	1.58	5.69E-02	1.24E-04
60674	LOC652102	down	-1.83	3.98E-02	9.94E-05
270136	RFX2	up	1.93	1.24E-02	5.99E-05
6550632	ZNF219	up	1.62	6.03E-03	4.74E-05
3390424	ITGAD	down	-1.77	5.05E-03	4.74E-05
1400474	MYO1D	down	-1.72	5.03E-03	4.74E-05
3850398	STX2	up	1.54	1.51E-02	6.54E-05
1090307	RNASE1	up	1.56	5.54E-02	1.23E-04
4920612	GNLY	down	-1.64	9.16E-02	1.77E-04
4060278	PLGLA	down	-1.60	3.13E-02	8.77E-05
3800021	LOC647506	down	-1.76	1.98E-02	7.28E-05
1450608	VWCE	up	1.72	1.83E-01	3.16E-04
1850687	PRKY	down	-2.96	4.00E-03	4.74E-05
2230678	ACACB	down	-1.53	4.39E-02	1.05E-04
6200196	SLC4A8	down	-1.61	4.86E-04	2.56E-05
2450270	PSORS1C1	down	-1.77	1.74E-02	6.92E-05
1990706	LOC284648	up	2.23	4.13E-03	4.74E-05
380440	NA	up	1.58	3.22E-03	4.74E-05
1570743	METTL9	up	1.57	1.99E-02	7.28E-05
3830228	GPR109A	up	1.56	2.89E-02	8.51E-05
5310445	KREMEN1	up	1.56	1.33E-01	2.35E-04
3390301	KREMEN1	up	1.79	7.20E-02	1.47E-04
5310754	VNN1	up	1.57	1.52E-01	2.66E-04
6590224	WFS1	down	-1.68	6.25E-03	4.74E-05
7560170	LOC441864	up	1.64	1.48E-02	6.51E-05
6550164	DEFA4	up	3.09	1.96E-02	7.28E-05
510072	LOC100132317	up	1.54	7.09E-02	1.46E-04
4050376	GYPE	up	1.87	9.34E-04	3.30E-05
4640500	UCHL1	down	-1.54	5.93E-02	1.28E-04
2140719	KIR2DL4	down	-1.82	2.21E-02	7.42E-05
5310154	GRIP2	up	1.53	3.04E-02	8.58E-05
1260228	CLEC5A	up	2.40	5.93E-03	4.74E-05
6980192	HBZ	down	-2.50	7.26E-02	1.47E-04
1990037	CHI3L1	up	1.79	1.08E-01	1.99E-04
1580437	PGA5	up	1.55	4.65E-02	1.09E-04
2630711	MCM4	down	-1.56	3.63E-02	9.50E-05
6370315	HLA-DRB5	down	-1.91	3.34E-01	5.68E-04
6900241	ABCB9	down	-1.91	7.12E-04	2.99E-05
5290598	ABCB9	down	-2.17	7.16E-05	1.13E-05
3170068	APOBEC3B	down	-1.67	2.13E-02	7.40E-05
2070224	BUB1	down	-1.65	5.79E-02	1.25E-04
5080692	HLA-A29.1	up	2.08	2.41E-01	4.14E-04
3710553	SMOX	up	1.63	1.41E-01	2.49E-04
2600121	OR4K15	up	1.80	1.53E-02	6.57E-05
4390398	LCN2	up	2.37	1.87E-02	7.21E-05
7050201	NA	down	-2.25	1.23E-02	5.99E-05
6840301	NT5DC2	down	-1.50	5.52E-02	1.23E-04
7650497	ELANE	up	2.92	1.87E-02	7.21E-05
7150609	ADAMTS2	up	1.77	3.58E-03	4.74E-05
520360	MS4A6A	up	1.52	5.17E-03	4.74E-05
6330184	HBBP1	up	1.53	8.06E-02	1.59E-04
6590131	HP	up	2.06	1.13E-01	2.06E-04
430328	LOC100130520	down	-1.81	4.01E-02	9.97E-05
1820747	DAAM2	up	1.67	1.27E-02	6.03E-05
7040161	HELLS	down	-1.66	2.66E-03	4.58E-05
3780100	OSBP2	up	1.62	2.67E-01	4.56E-04
2100458	LOC729010	up	1.51	3.52E-02	9.49E-05
3360615	FCER1A	down	-1.81	7.27E-02	1.47E-04
4850168	SLC22A4	up	1.54	4.19E-02	1.03E-04
2850315	ORM1	up	2.49	2.86E-02	8.51E-05
6040398	SLC22A4	up	1.55	4.47E-02	1.06E-04
2710452	POU2AF1	down	-1.67	6.90E-03	4.82E-05
5270753	ARG1	up	1.94	7.61E-02	1.52E-04
2570497	LOC100134379	up	2.11	2.30E-02	7.55E-05
5420066	H6PD	up	1.56	1.06E-02	5.64E-05
940673	PACAP	down	-1.62	3.84E-02	9.82E-05
2370072	PRR11	down	-1.51	9.26E-03	5.28E-05
6650333	LOC653867	up	1.64	1.64E-02	6.84E-05
7380273	GPR114	down	-1.58	7.43E-03	4.94E-05
1190528	MANSC1	up	1.52	1.18E-01	2.13E-04
3840561	UTY	down	-1.56	1.32E-01	2.34E-04
270068	SMOX	up	1.62	1.32E-01	2.35E-04
6580072	SMOX	up	1.82	7.49E-02	1.51E-04
1430484	C21orf81	down	-1.69	4.99E-02	1.15E-04
1500296	LOC283392	up	2.05	6.92E-03	4.82E-05
780079	LOC654053	down	-1.67	1.18E-01	2.13E-04
6560079	SUCNR1	up	1.73	2.30E-02	7.55E-05
6250010	GPRIN3	down	-1.62	1.67E-02	6.90E-05
1780537	ABCA13	up	1.59	1.87E-02	7.21E-05
650689	CLIP3	down	-1.52	4.66E-03	4.74E-05
4890181	RAP1GAP	up	1.77	3.88E-01	6.58E-04
3460594	C14orf68	down	-1.69	2.40E-02	7.67E-05
2710142	IER5L	up	1.56	5.36E-03	4.74E-05
6580482	ADORA3	down	-2.29	6.25E-03	4.74E-05
5960132	NOLC1	down	-1.53	1.10E-02	5.66E-05
3400762	LOC643870	up	1.67	3.67E-02	9.52E-05
4180524	EZH2	down	-1.58	1.38E-02	6.29E-05
7150630	HLA-C	down	-2.24	1.63E-01	2.84E-04
4290133	PACSIN1	down	-1.60	1.27E-02	6.03E-05
6980592	NA	up	1.51	8.66E-03	5.20E-05
3780673	EMR4	down	-1.55	5.19E-02	1.19E-04
4220110	LOC647450	down	-1.57	2.98E-02	8.54E-05
3520102	CCL4L1	down	-1.56	4.98E-03	4.74E-05
4050717	MYOM2	down	-2.72	4.10E-03	4.74E-05
5550367	LTF	up	1.86	6.02E-02	1.28E-04
6450102	LOC642113	down	-1.53	5.08E-02	1.16E-04
2000128	C4BPA	up	3.68	4.11E-03	4.74E-05
2450544	IL5RA	down	-1.83	9.29E-03	5.28E-05
6280594	MMP8	up	3.55	5.61E-03	4.74E-05
6370474	CDCA3	down	-1.59	2.83E-02	8.51E-05
5390427	NAIP	up	1.67	2.20E-02	7.42E-05
5340240	NAIP	up	1.59	4.29E-02	1.04E-04
5290100	MAK	up	1.57	4.48E-02	1.06E-04

2190671	CCR3	down	-1.97	2.56E-02	8.01E-05
6860706	LOC729891	up	1.51	2.69E-02	8.24E-05
7320324	EMR4P	down	-1.85	3.93E-02	9.90E-05
1510735	NTN3	up	1.69	1.05E-01	1.97E-04
2320441	LOC23117	down	-1.53	3.94E-02	9.90E-05
150609	LOC652493	down	-1.66	1.43E-02	6.37E-05
1580360	LOC651612	up	1.74	4.38E-02	1.05E-04
2570605	ARHGAP5	up	1.63	8.65E-03	5.20E-05
5550019	GPRC5D	down	-1.66	2.01E-02	7.28E-05
6560408	NA	up	1.53	3.27E-03	4.74E-05
3390253	TMEM156	down	-1.55	1.10E-02	5.66E-05
3870497	FUT8	down	-1.54	1.37E-02	6.29E-05
1400348	NMUR1	down	-1.58	1.56E-02	6.59E-05
4890750	DDX11	down	-1.78	2.90E-03	4.74E-05
7380047	THRA	up	1.51	4.29E-03	4.74E-05
3840113	PRDM1	down	-1.61	1.91E-03	4.09E-05
5260278	PPAPDC3	up	1.73	3.55E-02	9.49E-05
2760678	RCVRN	up	1.58	1.05E-02	5.64E-05
5870739	JARID1D	down	-2.80	7.75E-03	4.94E-05
2450647	KRT1	up	1.71	2.46E-01	4.22E-04
7210632	AKR1C3	down	-1.52	9.41E-02	1.82E-04
1400093	LOC401845	down	-1.63	3.99E-02	9.94E-05
4210397	GLDC	down	-1.82	2.35E-02	7.67E-05
7160474	HLA-DQB1	up	2.44	6.42E-03	4.76E-05
5390497	C7orf53	up	1.75	2.58E-02	8.02E-05
6280086	LGALS2	down	-1.96	4.14E-03	4.74E-05
5890653	CDKN1C	down	-2.51	4.35E-04	2.49E-05
4780619	AKAP7	down	-1.55	1.45E-01	2.54E-04
2350546	GPR55	down	-1.59	3.01E-02	8.54E-05
5560400	SLC14A1	up	1.74	5.73E-02	1.25E-04
2690181	NECAB2	up	1.54	1.27E-01	2.28E-04
5670739	AZU1	up	2.77	2.02E-02	7.29E-05
5260008	C1orf183	up	1.59	5.76E-02	1.25E-04
1340670	KIR2DL3	down	-1.80	9.99E-03	5.46E-05
3140242	KIR2DL3	down	-1.74	6.31E-03	4.74E-05
1070367	C19orf59	up	1.76	1.01E-01	1.90E-04
6520593	RNF182	up	1.95	1.12E-01	2.05E-04
780035	SYTL2	down	-1.58	5.95E-03	4.74E-05
4180647	SHPRH	down	-1.54	1.47E-03	4.03E-05
1940368	NRSN2	down	-1.83	3.41E-03	4.74E-05
7050639	LOC100130520	down	-1.74	6.63E-02	1.39E-04
1190446	DLC1	down	-1.61	4.07E-01	6.89E-04
2100725	KIR3DL3	down	-1.50	1.16E-01	2.12E-04
2810692	KIAA1881	up	1.54	1.11E-01	2.05E-04
6380411	IKZF3	down	-2.12	2.94E-02	8.54E-05
5050148	CDRT4	down	-1.56	3.63E-03	4.74E-05
780504	LOC442535	down	-2.17	6.73E-03	4.82E-05
270114	FAM134B	up	1.91	7.53E-03	4.94E-05
1410730	VSIG4	up	1.68	9.02E-02	1.76E-04
4610543	TLE1	down	-1.61	2.01E-03	4.09E-05
2850471	KCTD12	up	1.96	1.05E-01	1.97E-04
6960553	TERF1	down	-1.57	5.96E-05	1.13E-05
6100687	RPS4Y1	down	-3.55	2.00E-02	7.28E-05
940747	CAMK1G	down	-1.50	4.53E-02	1.07E-04
4570451	LOC401233	up	2.41	1.83E-03	4.09E-05
6650193	PTPRC	down	-1.51	7.27E-02	1.47E-04
2030678	HIST2H2AB	up	1.71	8.19E-02	1.61E-04
1470673	RFX2	up	1.80	3.55E-02	9.49E-05
2680189	LAG3	down	-1.52	4.30E-02	1.04E-04
6590575	SPRY2	down	-1.58	7.54E-03	4.94E-05
2760307	NA	down	-1.87	2.37E-03	4.58E-05
1070215	CAV1	down	-1.67	4.45E-03	4.74E-05
6330440	MSH5	up	1.53	3.86E-03	4.74E-05
7380452	KLHDC8A	up	1.51	1.73E-01	3.00E-04
5910632	SMARCD3	up	1.52	2.87E-02	8.51E-05
6100484	TNNI2	up	1.79	3.32E-04	2.49E-05
5340201	LOC100132535	down	-1.84	1.86E-03	4.09E-05
2070561	KIR2DS5	down	-1.54	3.40E-02	9.21E-05
540647	TMEM56	up	1.65	7.67E-02	1.53E-04
7400377	CEACAM6	up	3.04	1.70E-02	6.92E-05
1690440	XIST	up	1.73	3.19E-02	8.89E-05
2000669	ARHGAP10	down	-1.60	5.70E-03	4.74E-05
5080180	CACNG6	down	-1.99	1.98E-02	7.28E-05
6480468	BEX1	up	1.72	6.76E-02	1.40E-04
5360048	CCL23	down	-2.86	3.15E-03	4.74E-05
7040735	CYP27A1	up	1.72	5.37E-02	1.21E-04
4050156	ERBB2	down	-1.50	2.72E-02	8.25E-05
3440327	LOC653061	up	2.49	5.95E-03	4.74E-05
3780647	KIAA0125	down	-1.53	1.77E-02	6.96E-05
290669	SLC1A7	down	-1.60	2.63E-02	8.09E-05
6110343	CCL23	down	-3.41	1.16E-02	5.76E-05
2320358	SLC39A8	down	-1.56	6.72E-02	1.40E-04
6370646	CEACAM4	up	1.50	7.96E-02	1.58E-04
2900360	KIR2DL4	down	-1.79	3.15E-03	4.74E-05
4920075	TGM3	up	1.74	2.85E-02	8.51E-05
4290148	HIST2H2AA4	up	1.53	5.35E-02	1.21E-04
5420725	PNPLA1	up	1.55	4.90E-02	1.14E-04
3130220	TMEM158	up	1.61	1.06E-01	1.98E-04
450609	IGLL3	down	-1.94	9.12E-04	3.30E-05
1500735	CTSG	up	2.13	1.15E-01	2.10E-04
4640553	KIR3DL1	down	-1.59	3.40E-02	9.21E-05
2360164	KLRC2	down	-1.78	3.38E-02	9.21E-05
4830541	HBE1	up	1.73	2.21E-01	3.80E-04
3400672	SERPINB8	up	1.52	1.17E-03	3.66E-05
4260338	LOC647307	down	-1.52	9.74E-03	5.39E-05
7650736	NA	up	1.62	2.43E-03	4.58E-05
5570711	IDO1	down	-1.91	9.97E-02	1.89E-04
6280646	LOC100133662	down	-2.87	2.00E-02	7.28E-05
6580626	CXorf57	down	-1.53	7.97E-03	5.03E-05
620484	TNFRSF13B	down	-1.75	1.37E-02	6.29E-05
1050008	MMRN1	up	1.74	1.08E-01	1.99E-04
110397	LOC652755	up	1.62	6.08E-03	4.74E-05
4540239	DEFA1	up	1.95	6.34E-02	1.33E-04
7400402	HIST1H4D	up	1.52	9.77E-02	1.87E-04
7000546	LILRA6	up	1.81	5.42E-03	4.74E-05
6180743	LAIR2	down	-2.12	2.18E-02	7.42E-05
6020037	JSRP1	down	-1.64	2.59E-02	8.02E-05
2260349	MIR1974	up	1.51	5.36E-02	1.21E-04
4200746	BPI	up	1.89	8.59E-02	1.68E-04
4570612	FASLG	down	-1.51	3.27E-02	9.08E-05
2120634	CMTM4	up	1.51	2.08E-02	7.33E-05
1740328	KIR2DL5A	down	-1.61	5.25E-03	4.74E-05
830615	ZDHHC19	up	2.03	1.57E-01	2.74E-04
3170066	FANCI	down	-1.51	2.70E-02	8.24E-05
2360356	FSTL3	up	2.07	3.88E-04	2.49E-05
4290026	C20orf103	down	-2.40	2.04E-04	1.95E-05
6290471	LOC100134424	up	1.78	2.16E-04	1.95E-05
2490463	MXI1	up	1.56	2.10E-01	3.62E-04
1850523	GZMB	down	-1.65	4.94E-03	4.74E-05
1780239	OLIG2	down	-2.02	4.65E-02	1.09E-04
940670	TRAM2	down	-1.58	1.60E-02	6.74E-05
6290328	MAFG	up	1.53	5.80E-04	2.81E-05
1050360	HLA-DPB1	down	-1.51	4.08E-02	1.01E-04
870497	CCNE1	down	-1.50	2.06E-02	7.31E-05
4570220	LOC100130422	down	-1.54	2.11E-02	7.40E-05
6270138	TACSTD2	up	2.39	1.47E-02	6.51E-05
7610348	LOC652775	down	-1.68	2.27E-02	7.55E-05
6450619	SPON2	down	-1.86	1.00E-02	5.46E-05

380259	INDO	down	-2.10	7.16E-02	1.47E-04
6250615	PGLYRP1	up	1.63	1.06E-01	1.98E-04
3850647	PTPN20	up	2.73	1.92E-03	4.09E-05
7150170	DEFA1B	up	2.82	2.21E-02	7.42E-05
870477	DEFA1B	up	2.52	2.98E-02	8.54E-05
4860128	DEFA1B	up	2.29	4.42E-02	1.06E-04
4010296	RNASE1	up	1.71	9.87E-02	1.87E-04
6350437	CELSR3	down	-1.55	7.66E-03	4.94E-05
5050180	LOC652113	down	-2.03	1.98E-03	4.09E-05
6900523	EMR4	down	-1.81	4.49E-02	1.06E-04
5870474	RHOBTB3	down	-2.08	1.06E-03	3.52E-05
6100022	HIST2H2AC	up	1.51	5.63E-02	1.24E-04
1190754	LOC650557	down	-2.13	1.65E-02	6.84E-05
4610129	RETN	up	3.05	1.39E-02	6.29E-05
1770731	PRTN3	up	2.40	1.72E-02	6.92E-05
940519	GPR44	down	-2.44	8.85E-03	5.24E-05
1500725	CD1C	down	-1.57	2.58E-03	4.58E-05
770025	SPDYE1	up	2.23	1.28E-03	3.66E-05
540477	KIF19	down	-1.56	1.55E-02	6.59E-05
620301	TECPR2	up	1.53	4.13E-02	1.01E-04
2970747	DEFA3	up	2.29	4.85E-02	1.13E-04
6860102	CYorf15A	down	-2.23	4.31E-03	4.74E-05
2340743	CPA3	down	-1.73	3.37E-02	9.21E-05
3840072	PRG2	up	1.80	1.06E-02	5.64E-05
780538	ANRIL	up	1.54	2.93E-02	8.54E-05
580445	LOC649923	down	-1.57	1.40E-01	2.48E-04
7510132	OLR1	up	2.59	8.19E-03	5.06E-05
7570102	CYorf15B	down	-1.51	7.23E-03	4.94E-05
3830762	TMEM119	up	2.51	3.60E-02	9.50E-05
6770131	OLFM4	up	4.73	2.69E-03	4.58E-05
5560471	FCAR	up	1.53	6.02E-02	1.28E-04
130743	CLEC4C	up	1.52	1.99E-02	7.28E-05
7650008	NLRP12	up	1.68	6.18E-03	4.74E-05
430546	HIST1H2BG	up	1.73	1.75E-02	6.92E-05
1850402	LOC731007	down	-1.56	2.38E-02	7.67E-05
1580681	MS4A3	up	2.05	2.15E-02	7.40E-05
6290228	UTS2	up	1.62	5.80E-03	4.74E-05
6180687	SLC29A1	down	-1.81	1.99E-02	7.28E-05
5910424	SLC29A1	down	-2.27	7.55E-03	4.94E-05
2470364	PRSS33	down	-2.56	2.46E-02	7.81E-05
1770603	TCN1	up	2.00	2.57E-02	8.01E-05
3180528	MMP9	up	1.57	1.20E-01	2.16E-04
2760463	PKD2L1	up	1.52	2.04E-02	7.29E-05
460463	SMARCD3	up	1.68	1.10E-02	5.66E-05
460113	MAGED1	down	-1.52	6.67E-03	4.82E-05
770026	TMEM38A	up	1.55	1.11E-02	5.66E-05
4880553	MFSD9	up	1.51	7.74E-03	4.94E-05
5050333	RHAG	up	1.66	7.81E-02	1.55E-04
1070463	CYorf15B	down	-2.12	3.45E-03	4.74E-05
20075	NDUFAF3	up	1.52	9.81E-02	1.87E-04
4220692	CENTG2	down	-1.86	2.55E-03	4.58E-05
3870170	LOC728093	up	1.53	4.04E-02	1.00E-04
5050053	TXNDC5	down	-1.60	1.41E-02	6.34E-05
7330341	TXNDC5	down	-1.79	6.78E-02	1.40E-04
4560746	FCAR	up	1.55	3.92E-02	9.90E-05
1230615	WFDC1	up	1.67	2.16E-02	7.41E-05
4850398	TXNDC5	down	-1.90	1.10E-02	5.66E-05
2750706	NTSR1	up	2.05	6.17E-03	4.74E-05
770400	LOC653600	up	3.55	2.39E-02	7.67E-05
2810673	HOXA9	up	1.52	3.85E-02	9.82E-05
50278	LAIR2	down	-2.07	2.87E-02	8.51E-05
1010736	TOX2	down	-1.64	5.26E-03	4.74E-05
10333	LOC731682	up	2.64	5.70E-02	1.24E-04
5390168	SH2D1B	down	-1.74	5.54E-03	4.74E-05
3520601	MPO	up	1.96	6.08E-02	1.29E-04
580136	LOC652694	down	-1.91	1.71E-02	6.92E-05
1940632	NCAPG2	down	-1.54	1.74E-02	6.92E-05
1230524	ST6GALNAC3	up	1.51	1.33E-02	6.22E-05
1410221	S100A12	up	1.73	9.83E-02	1.87E-04
5050544	MS4A3	up	1.79	9.03E-02	1.76E-04
7200025	KIR2DL1	down	-1.67	9.05E-02	1.76E-04
4210458	KIR2DL1	down	-1.63	3.57E-02	9.49E-05
2230601	UTS2	up	1.58	2.47E-02	7.81E-05
6860048	UTS2	up	1.57	8.08E-03	5.05E-05
5890095	LILRA5	up	1.57	2.54E-02	8.01E-05
7100274	ALDH6A1	down	-1.77	6.54E-04	2.95E-05
4590551	TRA1P2	down	-1.83	1.99E-03	4.09E-05
770682	MGC29506	down	-1.67	1.86E-02	7.21E-05
2030142	CLC	down	-1.97	5.52E-02	1.23E-04
5290079	GLCCI1	down	-1.83	9.56E-05	1.21E-05
240594	ANXA3	up	1.62	1.03E-01	1.95E-04
3800132	TMPRSS9	down	-2.15	5.38E-02	1.21E-04
7330398	HLA-DRB4	up	2.09	2.78E-01	4.74E-04
4570398	F2R	down	-1.50	5.50E-03	4.74E-05
4780075	CEACAM8	up	2.61	2.95E-02	8.54E-05
3060767	MANEA	down	-1.64	1.51E-02	6.54E-05
5860138	RIPK4	up	1.63	4.04E-04	2.49E-05
4150600	EIF1AY	down	-2.48	6.04E-02	1.28E-04
20397	ALOX15	down	-1.85	3.77E-02	9.74E-05
1230722	ALOX15	down	-1.63	6.27E-02	1.32E-04
6280326	HDC	down	-1.81	3.36E-02	9.21E-05
1240554	TNFRSF17	down	-1.72	5.32E-02	1.21E-04
5900170	SLC11A1	up	1.53	1.19E-02	5.85E-05
2900669	RAB30	down	-1.82	3.12E-03	4.74E-05
7560593	OSM	up	1.51	3.09E-02	8.71E-05
4250059	HRASLS2	down	-1.52	2.05E-02	7.31E-05
2260189	FLJ14166	up	1.50	3.89E-02	9.89E-05
3780370	C9orf72	up	1.59	9.14E-03	5.28E-05
840253	ALDH2	up	1.55	1.50E-02	6.54E-05
990372	COL17A1	up	2.53	9.65E-03	5.38E-05
2120270	COL17A1	up	1.79	4.10E-03	4.74E-05
3170241	LOC651524	up	1.96	8.37E-03	5.13E-05
4210039	ABCB1	down	-1.50	2.15E-02	7.40E-05
520609	KIAA1324	up	2.52	6.95E-03	4.82E-05
2650220	FSTL1	up	1.69	6.64E-02	1.39E-04
4230102	SOCS3	up	1.57	5.62E-02	1.24E-04
3180719	FLJ10916	up	1.53	6.87E-02	1.42E-04
2030403	OLIG1	down	-1.64	1.25E-01	2.24E-04
6020273	RPS4Y2	down	-1.70	3.84E-02	9.82E-05
2640671	LOC642342	up	1.65	3.00E-02	8.54E-05
2680605	IGJ	down	-1.91	4.92E-03	4.74E-05
4040176	LAMA5	down	-1.52	2.37E-02	7.67E-05
5960068	PDGFRB	down	-1.93	9.51E-03	5.35E-05
10451	BEND7	up	1.52	4.97E-02	1.15E-04
1710673	LOC652126	down	-1.70	3.62E-02	9.50E-05
6420309	FAM134B	up	2.05	1.89E-03	4.09E-05
3180661	FAM134B	up	1.81	1.16E-02	5.76E-05
2480280	SORD	down	-1.70	9.41E-04	3.30E-05

Supplementary Table S2

Illumina_ProbeID	Symbol	Regulation	FC	p-value	q-value
770639	PDLIM7	up	1.50	3.39E-02	1.30E-04
2190349	KCNJ15	up	2.22	3.19E-03	8.33E-05
5570139	QPCT	up	1.62	1.84E-02	9.87E-05
540288	TMEM88	up	1.55	5.79E-02	1.73E-04
6550333	CXCR6	down	-1.57	2.59E-02	1.11E-04
3190189	TTRAP	up	1.52	4.39E-03	8.33E-05
6940086	GYPE	up	1.58	3.19E-01	6.94E-04
6100356	ALPL	up	1.55	1.47E-01	3.41E-04
380612	LOC644950	up	1.75	5.25E-03	8.33E-05
2070646	GPR84	up	1.51	9.15E-02	2.29E-04
130181	ANKRD22	up	1.70	6.70E-02	1.92E-04
5570398	FCGR1C	up	1.69	2.49E-02	1.11E-04
6620209	FCGR1B	up	1.79	1.80E-02	9.87E-05
5340161	TMEM217	up	1.52	7.18E-03	8.33E-05
1260348	MIR223	up	1.53	4.71E-02	1.53E-04
7100161	VNN2	up	1.63	3.63E-02	1.33E-04
110639	MAPK14	up	1.64	1.84E-02	9.87E-05
3180220	GPR109B	up	1.77	2.88E-03	8.33E-05
4860255	ASPRV1	up	1.57	7.99E-02	2.06E-04
1030463	PROK2	up	1.59	2.19E-02	1.05E-04
6560576	OCRL	up	1.53	5.62E-02	1.70E-04
3520327	LOC642161	down	-1.50	8.56E-02	2.17E-04
2760500	CD38	down	-1.72	2.51E-03	8.33E-05
7570196	TSPAN9	up	1.55	7.23E-02	2.01E-04
630167	SDCBP	up	1.53	1.81E-02	9.87E-05
2140707	SLPI	up	1.79	1.02E-01	2.49E-04
3850398	STX2	up	1.66	1.27E-03	8.33E-05
6290270	MNDA	up	1.54	8.06E-03	8.61E-05
4920612	GNLY	down	-2.06	1.44E-02	9.87E-05
6510333	LOC730286	up	1.55	3.64E-02	1.33E-04
1440209	RGS10	up	1.55	1.02E-01	2.50E-04
4220292	LOC646301	up	1.53	2.35E-02	1.09E-04
5090754	KIAA0101	down	-1.53	7.64E-02	2.02E-04
5130025	LOC100134703	up	1.53	1.44E-02	9.87E-05
3800021	LOC647506	down	-1.68	3.67E-02	1.33E-04
4880600	PTCRA	up	1.53	5.86E-02	1.73E-04
4670327	FBXO7	up	1.57	1.23E-01	2.89E-04
1740451	IL1R2	up	1.76	1.76E-01	4.01E-04
5560246	TPM1	up	1.66	8.32E-02	2.12E-04
4570255	LEF1	down	-1.53	6.89E-02	1.94E-04
3830228	GPR109A	up	1.79	1.49E-03	8.33E-05
5310445	KREMEN1	up	1.97	2.95E-02	1.18E-04
6550164	DEFA4	up	1.63	2.80E-01	6.19E-04
540703	RFESD	up	1.58	7.76E-02	2.03E-04
5080192	SERPINE2	up	1.57	3.68E-02	1.33E-04
460373	LACTB	up	1.51	1.89E-03	8.33E-05
1430711	KLF12	down	-1.51	2.93E-02	1.18E-04
1690706	HIST1H3H	up	1.58	5.81E-02	1.73E-04
380689	TSC22D1	up	1.52	4.52E-02	1.50E-04
6560398	NAT8B	up	1.73	2.81E-02	1.16E-04
1990037	CHI3L1	up	2.08	2.86E-02	1.17E-04
2030079	RUFY1	up	1.52	1.28E-02	9.78E-05
6900241	ABCB9	down	-1.85	7.52E-03	8.33E-05
5290598	ABCB9	down	-1.85	6.10E-03	8.33E-05
5080692	HLA-A29.1	up	2.09	1.77E-01	4.01E-04
3710553	SMOX	up	2.12	1.51E-02	9.87E-05
4640446	FHL1	up	1.53	7.82E-02	2.03E-04
7200044	SH3BGRL2	up	1.65	3.60E-02	1.33E-04
2000592	FTHL8	up	1.51	9.38E-02	2.34E-04
2230431	IRF5	up	1.63	5.64E-02	1.70E-04
4390398	LCN2	up	1.53	1.86E-01	4.18E-04
5360070	CCNB2	down	-1.51	6.21E-02	1.80E-04
3460053	SIPA1L2	up	1.51	7.39E-02	2.02E-04
3370594	LILRA2	up	1.54	1.85E-02	9.87E-05
7650497	ELANE	up	1.67	1.77E-01	4.01E-04
1260576	C1orf198	up	1.59	2.73E-02	1.13E-04
5310411	H2AFJ	up	1.64	1.59E-02	9.87E-05
5050402	HIST1H2BK	up	1.52	2.64E-02	1.11E-04
3440360	ZNF438	up	1.54	1.56E-02	9.87E-05
3780100	OSBP2	up	1.61	2.71E-01	6.01E-04
4060471	FAH	up	1.88	4.40E-03	8.33E-05
2750767	LOC100129960	up	1.57	1.92E-02	9.93E-05
540091	STEAP4	up	1.78	9.20E-03	8.78E-05
3420373	SOD2	up	1.74	8.55E-03	8.78E-05
3460376	RTN2	up	1.55	6.28E-03	8.33E-05
2190128	RAB32	up	1.59	2.26E-03	8.33E-05
940673	PACAP	down	-1.60	1.85E-02	9.87E-05
3830601	SLC2A11	up	1.55	3.07E-01	6.74E-04
150041	MANSC1	up	1.56	1.03E-01	2.51E-04
6580019	LOC731954	up	1.54	2.40E-02	1.09E-04
1050215	KCNJ15	up	1.93	6.40E-03	8.33E-05
270068	SMOX	up	1.90	2.09E-02	1.02E-04
1430484	C21orf81	down	-1.59	7.12E-02	1.99E-04
6960274	HAL	up	1.52	4.96E-02	1.56E-04
6280470	LOC728519	up	1.60	7.06E-02	1.98E-04
160070	C16orf30	down	-1.53	7.45E-02	2.02E-04
7550167	SV2A	up	1.57	4.12E-02	1.41E-04
7320424	HNRPA1L-2	down	-1.56	4.30E-02	1.45E-04
4670102	EGLN1	up	1.53	6.74E-03	8.33E-05
1050168	PI3	up	1.79	1.22E-01	2.89E-04
450753	HIST1H2BC	up	1.52	2.68E-02	1.12E-04
3390121	CASP5	up	1.59	8.12E-02	2.08E-04
6290747	NRGN	up	1.53	3.92E-02	1.36E-04
5890386	LOC642103	up	1.83	1.42E-02	9.87E-05
5420600	BEST1	up	1.56	1.99E-02	9.99E-05

2320689	LOC653610	up	1.81	1.06E-02	9.09E-05
4220110	LOC647450	down	-1.57	5.34E-02	1.65E-04
6290685	HIST1H2BJ	up	1.90	3.64E-04	8.33E-05
1770170	CTDSPL	up	1.51	1.09E-01	2.59E-04
4230678	HIST2H2BE	up	1.60	2.57E-02	1.11E-04
1340500	CLEC12A	up	1.55	7.47E-02	2.02E-04
3780358	CLEC12A	up	1.71	5.36E-02	1.65E-04
7150392	LOC100130623	down	-1.53	7.08E-03	8.33E-05
4860600	MAPK14	up	1.66	2.01E-02	9.99E-05
1770333	PDE5A	up	1.52	6.12E-02	1.79E-04
5270377	LOC728790	up	1.79	7.05E-03	8.33E-05
150609	LOC652493	down	-1.60	3.74E-02	1.33E-04
4010270	LOC440731	up	1.82	4.20E-03	8.33E-05
6620630	XK	up	1.90	1.76E-01	4.01E-04
4560021	LOC100132112	up	1.54	3.38E-02	1.30E-04
2710709	FCGR1B	up	1.82	1.57E-02	9.87E-05
4180079	CRISPLD2	up	1.55	3.69E-02	1.33E-04
2490142	C19orf35	up	1.51	7.38E-02	2.02E-04
7510253	ACRBP	up	1.54	5.65E-02	1.70E-04
4640092	IMPDH1	up	1.60	4.75E-04	8.33E-05
3450537	DGAT2	up	1.63	1.84E-02	9.87E-05
4670575	HTATIP2	up	1.52	2.52E-03	8.33E-05
3060523	NAMPT	up	1.52	4.65E-02	1.52E-04
2230379	NAMPT	up	1.56	3.66E-02	1.33E-04
1260482	GZMK	down	-1.69	5.32E-03	8.33E-05
2810280	SLC6A6	up	1.69	6.40E-03	8.33E-05
2450647	KRT1	up	2.09	1.00E-01	2.46E-04
1850546	FAM102A	down	-1.67	1.22E-02	9.50E-05
3440630	ESPN	up	1.71	7.75E-02	2.03E-04
7160474	HLA-DQB1	up	1.89	6.53E-02	1.88E-04
5390497	C7orf53	up	1.67	5.60E-03	8.33E-05
4640427	HIATL1	up	1.54	2.31E-03	8.33E-05
520523	CYP4F3	up	1.68	3.80E-02	1.34E-04
1070367	C19orf59	up	2.39	7.52E-03	8.33E-05
1050292	GP9	up	1.54	7.60E-02	2.02E-04
6480630	ATP9A	up	1.72	1.76E-02	9.87E-05
6330612	LOC100133875	up	1.55	3.53E-02	1.33E-04
70343	FRAT1	up	1.60	1.79E-02	9.87E-05
1500010	CDC20	down	-1.81	6.93E-03	8.33E-05
5560193	BCAS4	down	-1.51	2.37E-02	1.09E-04
4290079	BCAS4	down	-1.63	1.29E-02	9.78E-05
2480192	SESN3	up	1.63	1.78E-01	4.02E-04
3390612	TLR8	up	1.54	1.66E-02	9.87E-05
4880370	JUP	down	-1.87	6.26E-02	1.81E-04
3130541	CCNF	down	-1.53	1.17E-02	9.39E-05
150626	LOC641710	up	1.66	2.77E-03	8.33E-05
610154	CLDND2	down	-1.58	3.70E-02	1.33E-04
2360136	LOC440926	up	1.55	8.86E-03	8.78E-05
2360095	TNFRSF10B	up	1.54	1.67E-02	9.87E-05
4210280	PGCP	up	1.51	1.40E-02	9.87E-05
5260754	TSC22D1	up	1.68	3.44E-02	1.31E-04
1710553	HSPA6	up	1.51	1.79E-02	9.87E-05
2680189	LAG3	down	-1.78	4.83E-03	8.33E-05
50136	CMTM5	up	1.57	7.56E-02	2.02E-04
1230164		up	1.56	5.60E-03	8.33E-05
5050138	NT5M	up	1.61	5.74E-02	1.72E-04
5810612	ANPEP	up	1.60	4.81E-02	1.54E-04
3710025	RUFY1	up	1.55	8.90E-03	8.78E-05
5310437	MYL9	up	1.76	3.91E-02	1.36E-04
5340468	ITGA2B	up	1.58	1.49E-01	3.43E-04
3390048	LIMK2	up	1.68	1.09E-02	9.09E-05
5910632	SMARCD3	up	1.76	2.42E-03	8.33E-05
5260349	NGFRAP1	up	1.66	2.44E-02	1.09E-04
6860220	NGFRAP1	up	1.58	3.48E-02	1.32E-04
2230563	PPBP	up	1.55	7.73E-02	2.03E-04
1430524	LTA4H	up	1.52	1.90E-02	9.89E-05
1240358	RAB20	up	1.58	1.09E-02	9.09E-05
7040735	CYP27A1	up	1.72	4.40E-02	1.47E-04
4290243	ARHGAP24	up	1.52	1.61E-02	9.87E-05
4290148	HIST2H2AA4	up	1.79	1.10E-02	9.09E-05
3170601	CLEC12A	up	1.59	6.88E-02	1.94E-04
3130220	TMEM158	up	1.73	1.27E-01	2.97E-04
450609	IGLL3	down	-1.84	9.30E-03	8.78E-05
3780187	GYPB	up	1.67	3.07E-01	6.74E-04
4180544	ROPN1L	up	1.64	1.44E-02	9.87E-05
3460204	LOC730235	up	1.56	1.54E-02	9.87E-05
3400672	SERPINB8	up	1.61	2.68E-03	8.33E-05
4260338	LOC647307	down	-1.52	2.52E-03	8.33E-05
2070369	TREML1	up	1.69	4.57E-02	1.50E-04
3370327	MOSC1	up	1.78	6.24E-03	8.33E-05
1980431	DOK3	up	1.56	6.27E-03	8.33E-05
620091	LOC730234	up	1.78	6.81E-04	8.33E-05
1820592	HIST2H2AA3	up	1.76	1.20E-02	9.46E-05
610451	HIST2H2AA3	up	1.92	6.19E-03	8.33E-05
1940504	FKBP1A	up	1.53	9.33E-04	8.33E-05
7000546	LILRA6	up	1.61	5.26E-02	1.64E-04
3060092	LAT2	up	1.65	2.86E-03	8.33E-05
450348	GNG10	up	1.50	2.53E-02	1.11E-04
4570725	LOC653604	up	1.64	3.03E-03	8.33E-05
6420164	ST6GALNAC2	up	1.56	2.40E-02	1.09E-04
1470132	B3GNT8	up	1.51	3.35E-02	1.30E-04
1300431	LY6G6F	up	1.51	9.51E-02	2.36E-04
2000451	PYHIN1	down	-1.56	4.42E-02	1.47E-04
4200746	BPI	up	1.64	1.55E-01	3.56E-04
4200754	ST3GAL4	up	1.60	1.61E-02	9.87E-05
5050274	DHRS12	up	1.63	1.10E-02	9.09E-05

3710086	DHRS12	up	1.57	4.13E-02	1.41E-04
2230241	F13A1	up	1.53	5.41E-02	1.65E-04
620544	HLA-DRB6	down	-1.87	6.84E-02	1.94E-04
4010564	TRPM6	up	1.62	2.96E-02	1.18E-04
940274	GK	up	1.58	1.90E-02	9.89E-05
6520594	ARHGEF11	up	1.56	4.98E-03	8.33E-05
7150070	ARHGEF11	up	1.52	1.10E-02	9.09E-05
6380672	CA4	up	1.58	1.06E-01	2.56E-04
4290110	CYP4F3	up	1.61	2.18E-02	1.05E-04
1070450	PTGS1	up	1.53	7.63E-02	2.02E-04
6590437	FCGR2A	up	1.76	1.48E-03	8.33E-05
240441	IL1R2	up	1.63	1.25E-01	2.92E-04
2450110	MMP23B	down	-1.56	1.82E-02	9.87E-05
6900091	IKZF3	down	-1.66	2.53E-02	1.11E-04
5390246	CCR7	down	-1.53	1.40E-01	3.25E-04
6660162	LRG1	up	1.54	3.00E-02	1.18E-04
1450484	HIST1H2BE	up	1.51	4.28E-02	1.45E-04
990349	MCTP2	up	1.60	1.54E-02	9.87E-05
2340577	AQP10	up	1.83	7.79E-02	2.03E-04
3180609	LOC100008588	down	-1.62	3.97E-01	8.58E-04
1240450	CD27	down	-1.71	5.20E-03	8.33E-05
6100022	HIST2H2AC	up	1.70	1.30E-02	9.78E-05
6280170	PDCD1	down	-1.53	5.97E-02	1.76E-04
3060682	BPGM	up	1.54	3.78E-01	8.19E-04
4920523	HOXC6	up	1.57	1.05E-02	9.09E-05
5260424	GPR97	up	1.55	5.37E-02	1.65E-04
3940438	NCF1	up	1.53	7.47E-03	8.33E-05
5870136	CLIC3	down	-1.51	5.07E-02	1.59E-04
6400674	LOC730387	up	1.53	3.94E-02	1.36E-04
2650114	ITGB5	up	1.51	7.49E-02	2.02E-04
520086	FCGR1A	up	1.71	3.24E-02	1.27E-04
6840674	ZNF185	up	1.60	2.02E-02	9.99E-05
630619	HPSE	up	1.61	2.24E-02	1.06E-04
6290672	LOC728417	up	1.61	6.47E-03	8.33E-05
430546	HIST1H2BG	up	1.76	1.58E-02	9.87E-05
5570039	LOC728744	up	1.93	2.43E-02	1.09E-04
4860220	SRGAP2	down	-1.65	9.37E-03	8.78E-05
3180528	MMP9	up	1.88	4.30E-02	1.45E-04
6130075	LOC391769	up	1.62	5.81E-03	8.33E-05
7320270	PNMA3	down	-1.76	4.83E-03	8.33E-05
5560414	LOC440093	up	1.53	1.09E-02	9.09E-05
460463	SMARCD3	up	1.94	2.88E-03	8.33E-05
1260133	LOC642334	up	1.51	2.04E-02	1.00E-04
6480142	LAMP2	up	1.55	1.86E-02	9.87E-05
5870678	LOC441763	down	-1.56	3.19E-01	6.94E-04
7320678		up	1.58	9.45E-02	2.35E-04
3850112	RBP7	up	1.65	4.47E-03	8.33E-05
2490333	ZNF467	up	1.50	7.34E-03	8.33E-05
7100703	LOC100132287	up	1.64	1.50E-02	9.87E-05
2810162	LAT2	up	1.72	1.47E-03	8.33E-05
4210113	CMTM2	up	1.58	7.28E-02	2.01E-04
5860551	BTNL8	up	1.88	7.84E-03	8.53E-05
270240	SLC26A8	up	1.57	9.93E-02	2.45E-04
4850398	TXNDC5	down	-1.77	3.76E-02	1.33E-04
2060411	LOC652616	up	1.64	3.51E-03	8.33E-05
4220187	DYSF	up	1.58	1.94E-02	9.93E-05
6200370	LILRA3	up	1.62	2.31E-02	1.08E-04
3930008	RPL14	down	-1.81	6.22E-02	1.80E-04
4120367	LPCAT2	up	1.59	4.85E-02	1.54E-04
610519	TPM1	up	1.62	1.09E-01	2.59E-04
3520601	MPO	up	1.76	8.72E-02	2.20E-04
580136	LOC652694	down	-1.67	2.99E-02	1.18E-04
1430435	C3orf34	up	1.51	8.29E-03	8.70E-05
1410221	S100A12	up	1.78	8.05E-02	2.07E-04
3940685	SIGLEC9	up	1.52	6.86E-03	8.33E-05
1740360	USP18	down	-1.68	8.97E-02	2.26E-04
6040259	ALOX12	up	2.00	6.88E-03	8.33E-05
770682	MGC29506	down	-1.71	2.64E-02	1.11E-04
4150369	GK	up	1.56	1.83E-02	9.87E-05
4900309	MGC13057	up	1.67	1.23E-01	2.89E-04
2260725	MGAM	up	1.70	2.61E-02	1.11E-04
4670458	Sep-04	up	1.50	2.68E-01	5.97E-04
240594	ANXA3	up	2.17	2.27E-02	1.07E-04
5270338	ALAS2	up	1.53	2.98E-01	6.57E-04
4610538	SUMO1P1	up	1.58	4.67E-02	1.52E-04
2120682	GPR89C	down	-1.50	1.54E-02	9.87E-05
6400603	PVRIG	down	-1.65	9.29E-03	8.78E-05
6130441	ASPM	down	-1.58	2.90E-02	1.18E-04
7560593	OSM	up	1.64	1.03E-02	9.09E-05
4540241	C5orf32	up	1.60	1.05E-01	2.54E-04
2260189	FLJ14166	up	1.60	2.59E-02	1.11E-04
2340241	IMPA2	up	1.60	1.96E-02	9.96E-05
7610767	F5	up	1.58	4.82E-02	1.54E-04
840253	ALDH2	up	1.70	1.68E-02	9.87E-05
520609	KIAA1324	up	2.22	1.66E-02	9.87E-05
2100528	HIST1H3F	up	1.54	4.79E-02	1.54E-04
2970019	HIST1H4H	up	1.60	7.38E-02	2.02E-04
4250753	TSPAN33	up	1.53	1.86E-02	9.87E-05
2190139	CA1	up	1.79	2.22E-01	4.97E-04
2680605	IGJ	down	-2.05	1.15E-02	9.30E-05
610437	CD24	up	1.55	1.22E-01	2.89E-04

Supplementary Table S3

Illumina_ProbeID	Symbol	Regulation	FC	p-value	q-value
2190349	KCNJ15	up	2.57	1.64E-03	1.56E-04
5570139	QPCT	up	1.53	4.76E-02	3.19E-04
5960653	TMEM55A	up	1.51	3.23E-02	2.48E-04
5900050	LOC653800	down	-1.69	1.81E-02	1.73E-04
380612	LOC644950	up	1.53	4.32E-02	2.99E-04
2070646	GPR84	up	1.61	7.75E-02	4.58E-04
130181	ANKRD22	up	2.93	1.29E-03	1.56E-04
430605	TMEM137	down	-1.56	7.01E-03	1.56E-04
4280026	ACAP2	up	1.51	2.12E-02	1.93E-04
4290368	PSTPIP2	up	1.57	3.29E-02	2.49E-04
70167	LY96	up	1.59	2.63E-02	2.22E-04
2630195	VAMP5	up	1.63	6.51E-03	1.56E-04
5570398	FCGR1C	up	1.94	7.78E-03	1.56E-04
6620209	FCGR1B	up	2.15	1.17E-02	1.62E-04
130609	FCGBP	down	-1.54	1.04E-01	5.71E-04
1510364	GBP5	up	1.79	8.00E-03	1.56E-04
6270681	BST1	up	1.58	2.19E-02	1.96E-04
1260348	MIR223	up	1.51	5.34E-02	3.41E-04
1850220	DAPP1	up	1.77	1.11E-03	1.56E-04
6560020	COMMD2	up	1.62	5.11E-03	1.56E-04
2490315	NA	up	1.54	1.21E-01	6.37E-04
7100161	VNN2	up	1.60	4.42E-02	3.01E-04
110639	MAPK14	up	1.74	8.46E-03	1.56E-04
3450349	CSF2RB	up	1.58	8.72E-03	1.56E-04
3180220	GPR109B	up	1.92	3.02E-03	1.56E-04
4860255	ASPRV1	up	1.82	1.79E-02	1.73E-04
2190452	PIM3	up	1.53	4.42E-03	1.56E-04
5860064	FCHO2	up	1.56	4.83E-02	3.20E-04
2940446	TGM2	up	1.69	1.31E-01	6.77E-04
2030309	SERPING1	up	1.80	9.08E-02	5.13E-04
6770707	SQRDL	up	1.50	1.51E-02	1.62E-04
3170273	FER1L3	up	1.95	1.42E-02	1.62E-04
7320377	LOC284422	up	1.65	1.95E-01	9.64E-04
3780017	SIRPB1	up	1.70	1.99E-03	1.56E-04
4780044	LOC389386	up	1.79	3.05E-02	2.42E-04
670470	SLK	up	1.69	1.84E-03	1.56E-04
4060021	SLK	up	1.62	6.46E-03	1.56E-04
4920612	GNLY	down	-1.89	2.82E-02	2.30E-04
1450504	NA	down	-1.64	9.61E-03	1.59E-04
4810468	SELP	up	1.50	1.03E-01	5.70E-04
2190475	DNM3	up	1.64	2.09E-02	1.92E-04
3610743	SF1	down	-1.66	8.75E-03	1.56E-04
7650451	ZNF683	down	-1.65	1.34E-01	6.86E-04
4120561	LIMK2	up	1.53	2.50E-02	2.16E-04
4810112	HAUS4	up	1.57	8.96E-03	1.57E-04
1450608	VWCE	up	1.84	6.31E-02	3.92E-04
940220	NOD2	up	1.70	2.53E-03	1.56E-04
4670327	FBXO7	up	1.50	1.90E-01	9.45E-04
2940767	CEBPE	down	-1.55	8.73E-02	4.97E-04
4670592	MYOF	up	2.22	3.91E-03	1.56E-04
6290475	HECW2	up	1.51	1.32E-01	6.81E-04
4780600	RBM47	up	1.54	1.37E-02	1.62E-04
7650195	LOC727908	down	-1.57	1.06E-02	1.61E-04
3060520	LOC642073	up	1.59	1.06E-01	5.76E-04
5560246	TPM1	up	1.56	5.54E-02	3.51E-04
4590224	EVI2A	up	1.54	1.12E-02	1.62E-04
2680162	EVI2A	up	1.51	3.42E-02	2.54E-04
3830228	GPR109A	up	1.84	3.68E-03	1.56E-04
3400392	FPR2	up	1.81	1.58E-02	1.62E-04
3390301	KREMEN1	up	1.73	8.05E-02	4.65E-04
5310754	VNN1	up	1.71	1.08E-01	5.81E-04
6840035	GBP1	up	1.80	1.01E-02	1.61E-04
2190148	GBP1	up	1.77	6.40E-03	1.56E-04
240053	GCH1	up	2.06	2.32E-03	1.56E-04
3800398	FBXO6	up	1.54	1.23E-02	1.62E-04
460373	LACTB	up	1.57	2.75E-03	1.56E-04
770494	TSC22D3	up	1.51	1.06E-01	5.76E-04
4860280	NA	down	-1.53	3.90E-02	2.77E-04
240750	TELO2	up	1.54	1.17E-02	1.62E-04
4730059	BATF2	up	1.96	1.53E-02	1.62E-04
1990037	CHI3L1	up	1.61	1.68E-01	8.44E-04
5340427	TLR6	up	1.50	2.83E-02	2.30E-04
840068	C3AR1	up	1.62	3.87E-02	2.76E-04
7050519	CLEC4D	up	1.59	9.31E-02	5.22E-04
6510735	DDX60L	up	1.64	1.50E-02	1.62E-04
7510367	GPR160	up	1.54	8.30E-02	4.78E-04
4640446	FHL1	up	1.61	2.38E-02	2.09E-04
730528	PLAUR	up	1.58	3.61E-02	2.66E-04
830750	NCF1B	up	1.56	9.41E-03	1.59E-04
2230431	IRF5	up	1.53	1.10E-01	5.88E-04
4390398	LCN2	up	1.53	2.50E-01	1.21E-03
3460053	SIPA1L2	up	1.64	4.69E-02	3.16E-04
1240270	LMTK2	up	1.61	1.75E-02	1.71E-04
1580435	TGM2	up	1.51	1.69E-01	8.46E-04
1260576	C1orf198	up	1.52	2.15E-02	1.95E-04
4780128	ATF3	up	1.86	2.90E-02	2.33E-04
2320576	RBM47	up	1.51	1.14E-02	1.62E-04
160019	SORT1	up	1.61	7.74E-03	1.56E-04
5050402	HIST1H2BK	up	1.57	6.63E-02	4.07E-04
5900468	HDAC4	up	1.58	6.42E-03	1.56E-04
2850315	ORM1	up	1.68	1.34E-01	6.86E-04
6100136	CASP4	up	1.56	3.68E-02	2.70E-04
6420750	TLR2	up	1.63	6.67E-02	4.08E-04
540347	ITM2B	up	1.52	2.65E-02	2.22E-04
2750767	LOC100129960	up	1.54	2.75E-02	2.29E-04
5270753	ARG1	up	1.55	2.67E-01	1.28E-03
6520451	TLR1	up	1.58	4.89E-03	1.56E-04
540091	STEAP4	up	1.68	1.46E-02	1.62E-04
2750685	LOC392437	up	1.54	1.09E-02	1.61E-04
3420373	SOD2	up	1.61	1.56E-02	1.62E-04
6250497	FBXL5	up	1.58	5.51E-03	1.56E-04
730221	PTPLA	up	1.59	1.31E-01	6.77E-04
1410278	PF4V1	up	1.57	7.14E-02	4.29E-04
150041	MANSC1	up	1.53	1.10E-01	5.88E-04
1050215	KCNJ15	up	2.08	3.49E-03	1.56E-04
4570164	LOC389386	up	1.50	6.33E-02	3.92E-04
3850202	IGSF6	up	1.51	1.23E-02	1.62E-04
620403	LOC400759	up	1.66	3.42E-02	2.54E-04
6280470	LOC728519	up	1.60	7.40E-02	4.44E-04
1070593	KLHL2	up	1.55	4.02E-02	2.84E-04
4610184	NA	down	-1.51	4.34E-02	2.99E-04

4760747	TPST1	up	1.82	1.01E-01	5.63E-04
3800592	LOC100129697	up	1.68	1.31E-03	1.56E-04
520451	NA	down	-1.51	3.06E-02	2.42E-04
6370228	NA	down	-1.62	6.86E-02	4.17E-04
650743	C10orf11	up	1.59	3.27E-03	1.56E-04
6110634	ERLIN1	up	1.86	1.59E-02	1.62E-04
5310224	LOC100133678	up	1.74	1.04E-01	5.71E-04
3390121	CASP5	up	1.78	3.28E-02	2.49E-04
5890386	LOC642103	up	1.77	1.26E-02	1.62E-04
5960239	CCR2	up	1.51	5.38E-03	1.56E-04
3520438	ARAP2	up	1.52	1.70E-03	1.56E-04
2140288	FLJ22662	up	1.53	7.37E-03	1.56E-04
2320689	LOC653610	up	1.62	4.24E-02	2.95E-04
6290685	HIST1H2BJ	up	1.56	3.31E-02	2.49E-04
3780358	CLEC12A	up	1.53	1.13E-01	6.02E-04
6180543	GK5	down	-1.61	1.49E-02	1.62E-04
1230309	RPL26	up	1.57	8.34E-02	4.78E-04
4860600	MAPK14	up	1.82	1.10E-02	1.61E-04
5900594	CD58	up	1.66	5.63E-03	1.56E-04
3610035	CD58	up	1.59	1.45E-02	1.62E-04
4040519	LOC728059	up	1.51	2.27E-02	2.01E-04
5270377	LOC728790	up	1.60	4.14E-02	2.91E-04
4010270	LOC440731	up	1.51	4.94E-02	3.23E-04
460672	TMEM165	up	1.70	8.83E-04	1.56E-04
60470	STX11	up	1.76	7.16E-03	1.56E-04
1010592	CD36	up	1.67	3.21E-03	1.56E-04
2710709	FCGR1B	up	2.21	6.78E-03	1.56E-04
5490601	SLC40A1	up	1.63	9.04E-03	1.57E-04
4180079	CRISPLD2	up	1.59	1.39E-02	1.62E-04
3140520	TMOD1	up	1.66	2.10E-01	1.03E-03
7510253	ACRBP	up	1.60	1.52E-02	1.62E-04
2230379	NAMPT	up	1.62	1.25E-02	1.62E-04
2450647	KRT1	up	1.91	1.16E-01	6.14E-04
360132	LHFPL2	up	1.81	1.09E-02	1.61E-04
3780066	LOC646438	up	1.53	2.10E-02	1.92E-04
7160474	HLA-DQB1	up	2.47	7.92E-03	1.56E-04
4640427	HIATL1	up	1.71	6.58E-04	1.56E-04
3390689	SMCHD1	up	1.55	1.64E-02	1.64E-04
1440615	OTOF	down	-1.76	2.36E-01	1.15E-03
4640561	NA	down	-1.55	4.92E-02	3.23E-04
1070367	C19orf59	up	1.54	2.22E-01	1.09E-03
7100717	RPS15A	up	1.54	6.88E-02	4.17E-04
6330612	LOC100133875	up	1.51	6.95E-02	4.20E-04
2640670	IDI1	up	1.50	8.79E-03	1.56E-04
1030431	ACSL1	up	1.63	1.53E-02	1.62E-04
3360132	SNX20	up	1.53	1.55E-02	1.62E-04
1050068	F2RL1	up	1.60	1.14E-02	1.62E-04
5810047	F2RL1	up	1.65	1.36E-02	1.62E-04
5560075	MFGE8	down	-1.61	1.31E-02	1.62E-04
5560561	TNS3	up	1.56	4.97E-03	1.56E-04
7570600	FLJ33590	down	-1.67	1.41E-02	1.62E-04
60719	KCNJ2	up	1.54	1.06E-02	1.61E-04
7000307	ACSL4	up	1.63	5.97E-03	1.56E-04
5340767	CEACAM1	up	1.55	1.06E-01	5.76E-04
1230307	RRBP1	down	-1.79	6.03E-03	1.56E-04
110372	CSTA	up	1.60	1.23E-02	1.62E-04
1500010	CDC20	down	-1.56	8.03E-02	4.65E-04
2480192	SESN3	up	1.74	1.10E-01	5.88E-04
3390612	TLR8	up	1.66	9.45E-03	1.59E-04
3140064	C22orf34	down	-1.71	1.52E-02	1.62E-04
4060452	LOC648226	down	-2.21	2.67E-03	1.56E-04
3290730	LOC100133591	up	1.78	1.06E-01	5.76E-04
2640377	PGCP	up	1.57	4.63E-03	1.56E-04
4210280	PGCP	up	1.51	2.77E-02	2.29E-04
1400593	SIGLEC14	down	-3.10	4.91E-02	3.23E-04
3830497	KLF12	down	-1.65	1.59E-02	1.62E-04
4150543	FPR2	up	1.72	8.48E-03	1.56E-04
2030678	HIST2H2AB	up	1.90	2.90E-02	2.33E-04
3780594	LOC440345	down	-1.63	2.86E-03	1.56E-04
50136	CMTM5	up	1.53	9.25E-02	5.20E-04
3420026	FAS	up	1.86	8.76E-04	1.56E-04
5310437	MYL9	up	1.71	2.23E-02	1.99E-04
2480327	MYL9	up	1.95	1.73E-02	1.70E-04
7040142	KYNU	up	1.61	4.29E-03	1.56E-04
5910632	SMARCD3	up	1.82	1.63E-03	1.56E-04
5260349	NGFRAP1	up	1.52	1.99E-02	1.89E-04
6860220	NGFRAP1	up	1.52	1.68E-02	1.67E-04
2230563	PPBP	up	1.67	3.80E-02	2.72E-04
2450070	LOC440345	down	-1.53	5.08E-02	3.30E-04
4900747	C11orf75	up	1.61	5.04E-03	1.56E-04
6400332	CNIH4	up	1.53	1.56E-02	1.62E-04
1240358	RAB20	up	1.74	1.63E-02	1.64E-04
1990300	SOCS1	up	1.93	1.00E-02	1.61E-04
6250484	CFH	up	1.80	4.71E-02	3.17E-04
4290148	HIST2H2AA4	up	1.66	2.46E-02	2.13E-04
3130220	TMEM158	up	1.68	6.01E-02	3.78E-04
3290292	LAP3	up	1.59	3.26E-02	2.49E-04
1500735	CTSG	down	-1.62	2.95E-01	1.41E-03
4850592	P2RY14	up	2.25	8.57E-03	1.56E-04
6510170	IFIT3	up	1.57	1.54E-01	7.79E-04
3460204	LOC730235	up	1.52	3.08E-02	2.43E-04
3400672	SERPINB8	up	1.56	5.73E-03	1.56E-04
5570711	IDO1	up	1.80	1.61E-01	8.10E-04
3370327	MOSC1	up	1.51	5.81E-02	3.66E-04
4150270	ANKRD22	up	2.47	2.20E-03	1.56E-04
6420008	PROS1	up	1.93	1.27E-02	1.62E-04
2140524	HIST1H3D	up	1.56	9.08E-02	5.13E-04
3060358	NA	down	-1.72	8.35E-03	1.56E-04
3130543	RNASE3	down	-1.66	1.52E-01	7.71E-04
4780068	SULT1B1	up	1.51	1.13E-01	6.02E-04
610451	HIST2H2AA3	up	1.80	2.04E-02	1.89E-04
3310538	CD36	up	1.53	2.03E-02	1.89E-04
6370717	GNG10	up	1.71	7.47E-03	1.56E-04
450348	GNG10	up	1.73	1.57E-02	1.62E-04
4570725	LOC653604	up	1.61	1.37E-02	1.62E-04
2000286	C8orf16	down	-1.95	4.86E-03	1.56E-04
5050274	DHRS12	up	1.63	2.19E-02	1.96E-04
6590646	FAM26F	up	1.80	1.17E-02	1.62E-04
1070477	ALDH1A1	up	1.69	7.26E-03	1.56E-04
3780544	SF3B14	up	1.55	1.45E-02	1.62E-04
830615	ZDHHC19	up	1.62	2.51E-01	1.21E-03
2230241	F13A1	up	1.63	3.12E-02	2.43E-04

650563	FAHD1	up	1.52	6.10E-02	3.82E-04
3460685	KYNU	up	1.54	1.23E-02	1.62E-04
940274	GK	up	1.71	5.63E-03	1.56E-04
3940189	JAK2	up	1.59	1.44E-02	1.62E-04
1980523	PSCDBP	up	1.79	2.28E-04	1.56E-04
6590437	FCGR2A	up	1.52	2.01E-02	1.89E-04
2900139	FLJ20489	up	1.52	8.60E-02	4.91E-04
3450092	PELI1	up	1.51	7.76E-02	4.58E-04
6900091	IKZF3	down	-1.64	1.34E-02	1.62E-04
540392	REPS2	up	1.51	1.02E-01	5.66E-04
1450484	HIST1H2BE	up	1.56	4.44E-02	3.01E-04
2340577	AQP10	up	1.80	4.99E-02	3.26E-04
3180609	LOC100008588	down	-1.75	2.46E-01	1.20E-03
1240450	CD27	down	-1.68	8.32E-03	1.56E-04
6100022	HIST2H2AC	up	1.58	3.20E-02	2.47E-04
7510019	FOXP1	down	-1.52	3.69E-02	2.70E-04
4610129	RETN	up	1.66	1.87E-01	9.30E-04
2510551	STK3	up	1.61	1.42E-02	1.62E-04
1660113	FNDC3A	up	1.55	3.41E-03	1.56E-04
1230731	NFXL1	up	1.53	1.43E-01	7.33E-04
7400152	P2RY10	down	-1.51	3.11E-02	2.43E-04
3060747	CENTB2	up	1.53	1.03E-02	1.61E-04
360689	HEBP1	up	1.52	4.81E-03	1.56E-04
3140487	BMX	up	2.29	8.14E-03	1.56E-04
6760445	LAT1-3TM	down	-1.51	8.77E-03	1.56E-04
2490687	JMJD1C	up	1.51	4.87E-03	1.56E-04
5360243	ITGB5	up	1.58	3.18E-02	2.47E-04
520086	FCGR1A	up	1.92	1.03E-02	1.61E-04
4560047	CD74	up	1.67	1.71E-02	1.69E-04
6770131	OLFM4	up	1.71	3.20E-01	1.52E-03
5560471	FCAR	up	1.76	5.37E-02	3.42E-04
2810059	KLF4	up	1.59	1.33E-03	1.56E-04
6860164	CLEC1B	up	1.56	1.27E-01	6.63E-04
430546	HIST1H2BG	up	1.50	6.36E-02	3.92E-04
6480274	LOC730995	down	-1.54	4.42E-02	3.01E-04
1340128	HSDL2	up	1.56	1.76E-03	1.56E-04
1230068	PPP1R3D	up	1.54	1.35E-02	1.62E-04
5290068	SLFN13	down	-1.57	7.97E-03	1.56E-04
5570039	LOC728744	up	2.30	2.92E-03	1.56E-04
5870138	VWF	up	1.63	2.41E-02	2.11E-04
3710068	WARS	up	1.70	8.47E-03	1.56E-04
3180528	MMP9	up	1.67	7.95E-02	4.63E-04
7320270	PNMA3	down	-1.60	5.60E-03	1.56E-04
460463	SMARCD3	up	2.07	5.05E-04	1.56E-04
290301	LOC653352	down	-1.70	7.96E-03	1.56E-04
2000564	C6orf204	down	-1.51	9.91E-03	1.61E-04
5390487	SPTBN1	down	-1.78	2.56E-02	2.18E-04
6370458	TCP11L2	up	1.52	1.49E-01	7.58E-04
6220739	GRAMD1B	up	1.62	7.45E-02	4.45E-04
6510754	ALDH1A1	up	1.94	1.28E-03	1.56E-04
4060156	LOC100130492	down	-1.56	2.43E-02	2.12E-04
4210113	CMTM2	up	1.52	3.80E-02	2.72E-04
4860746	LOC642684	up	1.55	5.27E-02	3.41E-04
5960747	TRIM22	up	1.56	4.81E-02	3.20E-04
2060411	LOC652616	up	1.53	3.43E-02	2.54E-04
4860224	WARS	up	1.58	1.15E-02	1.62E-04
1770243	IGF2BP3	up	1.81	1.46E-03	1.56E-04
6450504	FLJ43093	down	-1.60	5.34E-02	3.41E-04
6200370	LILRA3	up	1.53	7.91E-02	4.63E-04
520408	IFIT3	up	1.58	1.27E-01	6.63E-04
4120367	LPCAT2	up	1.79	2.64E-02	2.22E-04
4260253	OBFC2A	up	1.51	9.58E-03	1.59E-04
610519	TPM1	up	1.51	7.86E-02	4.62E-04
1410221	S100A12	up	1.91	3.74E-02	2.71E-04
3460161	RAB3IL1	up	1.80	9.43E-02	5.27E-04
6270553	CXCL10	up	1.93	4.36E-02	2.99E-04
4150369	GK	up	1.69	5.59E-03	1.56E-04
2230204	OAS2	up	1.56	2.78E-02	2.29E-04
5270148	PLEK2	up	1.94	6.22E-02	3.88E-04
6350634	DYNLT1	up	1.64	2.56E-03	1.56E-04
3360634	SNX10	up	1.51	6.49E-03	1.56E-04
2260725	MGAM	up	1.88	7.35E-03	1.56E-04
4670458	Sep-04	up	2.05	3.72E-02	2.71E-04
240594	ANXA3	up	2.15	1.42E-02	1.62E-04
1260136	MEGF9	up	1.50	2.83E-02	2.30E-04
780403	HLA-DQA1	up	1.55	2.19E-01	1.08E-03
4780075	CEACAM8	up	1.61	3.11E-01	1.49E-03
4920328	SH3KBP1	down	-1.69	2.55E-02	2.18E-04
7380626	FLJ20273	up	1.59	1.64E-02	1.64E-04
3610343	NBN	up	1.55	1.28E-02	1.62E-04
510347	C9orf72	up	1.58	7.57E-03	1.56E-04
7570022	C9orf72	up	1.61	4.88E-03	1.56E-04
4730634	SLC31A2	up	1.59	1.09E-02	1.61E-04
3850441	MAZ	up	1.59	3.03E-02	2.42E-04
7560593	OSM	up	1.70	7.23E-03	1.56E-04
4540241	C5orf32	up	1.62	4.22E-02	2.95E-04
3890193	CLIC4	up	1.65	6.52E-03	1.56E-04
520609	KIAA1324	up	2.06	1.03E-02	1.61E-04
6220671	PLAUR	up	1.59	1.78E-02	1.72E-04
360475	PLAUR	up	1.51	1.29E-02	1.62E-04
2970019	HIST1H4H	up	1.55	1.26E-01	6.62E-04
870563	RNF138	up	1.81	1.11E-04	1.56E-04
1110102	HS2ST1	up	1.51	1.79E-03	1.56E-04
3780047	GBP6	up	1.99	5.33E-02	3.41E-04
3450736	LOC100133583	up	1.53	7.97E-02	4.63E-04
2190139	CA1	up	2.02	1.61E-01	8.11E-04
6060142	AFF1	up	1.57	1.53E-02	1.62E-04
2120451	CD46	up	1.55	1.20E-02	1.62E-04
2650605	C4orf18	up	1.59	3.80E-02	2.72E-04
2340500	KLC3	up	1.55	2.03E-01	1.00E-03
5050768	LONRF1	up	1.62	2.23E-03	1.56E-04
7160468	DHRS9	up	1.62	7.63E-02	4.54E-04
4070424	C16orf93	down	-1.57	5.53E-03	1.56E-04
2140242	TNFAIP6	up	1.61	2.01E-02	1.89E-04

Supplementary Table S4

Illumina_ProbeID	Symbol	Regulation	FC	p-value	q-value
6840035	GBP1	up	1.80	1.01E-02	1.78E-05
1510364	GBP5	up	1.79	8.00E-03	1.78E-05
940220	NOD2	up	1.70	2.53E-03	1.78E-05
3390612	TLR8	up	1.66	9.45E-03	1.78E-05
6520451	TLR1	up	1.58	4.89E-03	1.78E-05
840685	IL1B	up	1.47	1.64E-02	1.78E-05
2490161	CLEC2B	up	1.43	1.77E-02	1.78E-05
450491	CASP1	up	1.38	2.20E-02	1.78E-05
5340427	TLR6	up	1.50	2.83E-02	1.88E-05
3390121	CASP5	up	1.78	3.28E-02	1.90E-05
7050382	CASP1	up	1.38	3.19E-02	1.90E-05
6100136	CASP4	up	1.56	3.68E-02	1.95E-05
2570291	IFNGR2	up	1.31	3.95E-02	1.97E-05
2470358	IFNGR1	up	1.37	4.61E-02	2.02E-05
3780047	GBP6	up	1.99	5.33E-02	2.07E-05
1980524	GBP4	up	1.47	5.30E-02	2.07E-05
1050020	NLRC4	up	1.48	5.80E-02	2.11E-05
6420750	TLR2	up	1.63	6.67E-02	2.20E-05
1500180	TLR4	up	1.33	1.14E-01	2.73E-05
830440	TLR5	up	1.38	1.31E-01	2.97E-05
1260270	AIM2	up	1.41	1.54E-01	3.32E-05

Figure S1

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