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## Transcriptome assists prognosis of disease severity in respiratory syncytial virus infected infants

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Respiratory syncytial virus (RSV) causes infections that range from common cold to severe lower respiratory tract infection requiring high-level medical care. Prediction of the course of disease in individual patients remains challenging at the first visit to the pediatric wards and RSV infections may rapidly progress to severe disease. In this study we investigate whether there exists a genomic signature that can accurately predict the course of RSV. We used early blood microarray transcriptome profiles from 39 hospitalized infants that were followed until recovery and of which the level of disease severity was determined retrospectively. Applying support vector machine learning on age by sex standardized transcriptomic data, an 84 gene signature was identified that discriminated hospitalized infants with eventually less severe RSV infection from infants that suffered from most severe RSV disease. This signature yielded an area under the receiver operating characteristic curve (AUC) of 0.966 using leave-one-out cross-validation on the experimental data and an AUC of 0.858 on an independent validation cohort consisting of 53 infants. A combination of the gene signature with age and sex yielded an AUC of 0.971. Thus, the presented signature may serve as the basis to develop a prognostic test to support clinical management of RSV patients.

Respiratory syncytial virus (RSV) causes infections that range from common cold to severe lower respiratory tract infection that in some instances may have a fatal outcome. Especially infants, elderly and patients with underlying chronic disorders suffer from severe RSV infections<sup>1,2</sup>. In infants, RSV is the leading cause of lower respiratory tract infections (LRTI) and is responsible for 80% of acute bronchiolitis cases<sup>3</sup>. RSV infections pose a huge burden on society in terms of disease, logistics and socio-economic sequelae. There is an unmet need for an RSV vaccine, despite considerable research efforts no licensed vaccine has been developed.

In industrialized countries, 1–5% of infants with RSV infection are hospitalized<sup>4–7</sup>. Some of these infants yet suffer from severe disease upon admittance, while others are admitted without severe symptoms since the course of bronchiolitis is highly variable and the need for supportive care cannot be predicted<sup>8,9</sup>. Several risk factors for developing severe RSV disease in infants have been identified, including preterm birth, young age, sex and environmental factors like in-house smoking<sup>10</sup>. Notwithstanding these known risk factors, current medical practice does not allow accurate prediction of whether an infant will further progress to severe RSV disease or not and could even be sent home safely. Genomic technologies have contributed to study the virus-host interaction, including virus discovery, pathogenesis studies, the design of antiviral strategies and identification of biomarkers to support clinical management of infectious diseases<sup>11–14</sup>. For RSV infections, this has supported the characterization of vaccine-induced skewed host responses upon infection<sup>15,16</sup>. Meijas *et al.*<sup>17</sup> recently used

<sup>1</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. <sup>2</sup>Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands. <sup>3</sup>Department of Pediatrics, Laboratory of Pediatric Infectious Diseases, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. <sup>4</sup>Center for Biomics, Erasmus Medical Center, Rotterdam, The Netherlands. <sup>5</sup>Department of Pediatrics, Erasmus Medical Center, Rotterdam, The Netherlands. <sup>6</sup>Research Institute for Infectious Diseases and Zoonoses, Veterinary University Hannover, Germany. <sup>\*</sup>These authors contributed equally to this work. Correspondence and requests for materials should be addressed to A.C.A. (email: a.andeweg@ erasmusmc.nl) blood transcriptome profiles obtained within 3 days of hospitalization to characterize the host response to RSV infection in infants compared with rhinovirus or influenza infections and identified transcriptional profiles that associate with RSV disease severity. However, a prognostic model for RSV severity based on gene expression profiles collected at admittance to the hospital has not been developed.

In this study we aim to identify and validate a gene signature that discriminates severe from less severe RSV LRTI that do not require advanced support. Such a signature together with other clinical parameters may improve the prognosis of less severe patients that could be safely sent home.

#### Material and Methods

**Study design.** Study subjects were recruited at Canisius Wilhelmina Hospital, Radboud University Medical Center, Nijmegen, and Erasmus Medical Center, Rotterdam, The Netherlands. Nasopharyngeal wash and blood samples were prospectively obtained from patients less than 2 years of age with a viral bronchiolitis. Patient enrolment occurred 7 days a week and samples were taken within 24 hours after first contact with the hospital. Seventy-three percent of all eligible bronchiolitis patients agreed to participate in the study. The major reasons for non-inclusion were parental availability to sign consent and the hesitancy for the venipuncture. Only patients with an RSV infection, as retrospectively determined by PCR were included in the study. Exclusion criteria were: immunodeficiency, systemic steroid treatment in the previous 2 weeks, blood transfusion, congenital heart and chronic lung disease. A Tempus tube (Tempus<sup>TM</sup>, Applied Biosystems, Austria) and sodium heparin tube were filled with 3 ml of blood. Medical history, demographic and clinical data were collected from medical records and questionnaires. The (hospitalized) patients were followed until recovery and were retrospectively classified as: mild for children without hypoxia, moderate for patients requiring supplemental oxygen (oxygen saturations <90%,  $\geq$ 10 minutes) and severe for children requiring mechanical ventilation due to apnea, exhaustion and/ or respiratory failure. Recovery samples were obtained after 4–6 weeks, during home visits. Blood samples were obtained from healthy controls (HC) without underlying diseases or medication subjected to elective surgery.

**Study approval.** The study protocol was approved by the Regional Committees on Research involving Human Subjects of Arnhem-Nijmegen and Rotterdam and were conducted in accordance with the principles of the Declaration of Helsinki. Written informed consent was obtained from the parents of all children prior to inclusion in the study.

**Sample processing and blood transcriptome profiling.** Inclusion of patients and sample collection was performed by a single MD at the hospitals. Multiplex RT-PCR was performed to test the nasopharyngeal washes on 15 different viral pathogens, as previously described<sup>18</sup>. Blood was collected in Tempus tubes for immediate stabilization of RNA and subsequently stored at -80 °C. Total RNA was isolated from each blood sample, processed, assessed, labelled and hybridized to a single Affymetrix Human Genome U133 plus 2 gene chips; and image analysis was performed in the same lab and by one technician as described in supplementary material. The raw data has been deposited in the ArrayExpress database under access number E-MTAB-5195.

**Data preprocessing.** Microarray data was preprocessed using R 3.1.2<sup>19</sup> and Bioconductor<sup>20</sup>. Upon initial quality control and VSN normalization (to render samples comparable), probeset (a combination of multiple probes) summarization was performed by median polish<sup>21,22</sup>. Unless otherwise stated, all probesets/genes present on the Affymetrix GeneChip were used for data analysis. Samples were labelled and hybridized in two batches which did not correspond to any biological variable as samples were randomly assigned to the batches. The normalized expression values were adjusted for a batch effect (see supplementary Fig. S1) using *ComBat*<sup>23</sup>. Additionally, we assessed confounding effects of clinical parameters age and sex on gene expression–severity relationship using "biasograms"<sup>24</sup>.

**Differential expression analysis.** To obtain a global view of the blood transcriptome changes in response to RSV infection (i.e. to evaluate whether whole transcriptome changes associate with severity), a principal component analysis (PCA) as an exploratory analysis was performed on the age by sex standardized data. Next, a differential expression (DE) analysis was performed on the normalized-batch-adjusted data controlling for an age by sex effect using empirical Bayes linear models<sup>25</sup> implemented in the R package *limma*<sup>26</sup>. Details of the models are found in supplementary material. We controlled for multiple testing via false discovery rate (FDR) using a Benjamini and Hochberg procedure<sup>27</sup>. Gene set enrichment analysis was performed using Ingenuity pathway analysis (IPA, www.qiagen.com/ingenuity).

**Identification and evaluation of prognostic biomarkers.** Since we are interested in identifying RSV-infected infants that will progress to severe stage upon presentation to the hospital, we grouped mild and moderate samples and aimed to separate these samples from infants that were presented with or progressed to severe disease after hospitalization. We chose to utilized probabilistic predictors (to predict the chance of an RSV-infected infant to be severe) because in clinical applications, probabilities are more informative than absolute yes or no predictions<sup>28</sup>. Several probabilistic predictors exist in the literature and their performance depends on the type of the data they are being applied on ref. 29. Using results of ref. 29,30 and observed correlations in the data, three probabilistic classification functions that could be optimal for this data were chosen as described in supplementary material. These functions were support vector machines (SVM)<sup>31</sup>, shrunken centroids discriminant analysis (SCDA)<sup>32</sup> and random forest (RF)<sup>33</sup>.

For each classification function, the experimental data was split into a learning set and a test set using leave-one-out cross-validation (LOOCV). Cross-validation reduces optimistic bias by ensuring that our models are evaluated on an independent dataset that was not used to constructed these models. Most probabilistic classification functions require hyper-parameters to perform variable selection among the huge number of variables

Parameters	Mild (n = 7)	Moderate (n = 14)	Severe (n = 18)
Age (days)	153 [84, 291]	185 [60, 333]	31 [17, 76]
Gestational age (weeks)	40 [29, 41]	40 [37, 41]	39 [37, 40]
Birth weight (kg)	3.5 [3.0, 4.2]	3.4 [3.1, 3.9]	3.3 [2.5, 4.0]
Symptomatic days	4 [2, 6]	4 [3, 6]	3 [2, 4]
Duration on O <sub>2</sub> (days)	0	3 [2, 5]	8 [7, 11]
Ventilation	None	Supplemental	Mechanical
Length of stay (days)	4 [2, 6]	5 [3, 8]	11 [9, 13]
Breastfeeding	4 (57)	11 (79)	12 (67)
Male gender	5 (71)	10 (71)	12 (67)
RSV + other virus(es)	4 (57)	8 (57)	3 (17)

**Table 1.** Patient characteristics (n represents the number of samples per group). Data are presented as median and interquartile range (IQR) in square brackets [.] or number and percentage in brackets (). The median age of the healthy controls was 536 days (IQR [472, 602]).

(probesets). Usually, the best values for these hyper-parameters are also determined by cross-validation. Thus, the parameter(s) of the function were optimized using an inner loop of five-fold cross-validation on the learning set. Next, a prognostic model was built with the optimal parameter(s) on the entire learning set and evaluated with the test set, as described in supplementary material. The following R packages; *CMA*<sup>34</sup>, *e1071*<sup>35</sup>, *pamr*<sup>36</sup> and *randomForest*<sup>37</sup> were utilized for class prediction. The best calibrated and refined function amongst the three functions was selected and its performance evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). Finally, the transcripts that maximized the binomial log-likelihood function, with the leave-one-out cross-validated data were retained as a gene signature from the selected function as described in supplementary material.

**Comparison of biomarkers to clinical parameters.** Age and sex are readily available clinical parameters that have been determined to be associated to RSV disease severity<sup>38</sup>. To assess the gain attained with a genomic model over a model with these clinical parameters, and the effect of standardization, the leave-one-out cross-validated predicted probabilities of progressing to severe for all samples were transformed to genomic scores (a genomic score is single measure of the genome of a sample as predicted by a model) for models with unstandardized and standardized data. Logistic regression models (see supplementary material) were then fitted with the genomic scores and/or clinical parameters and their AUCs compared.

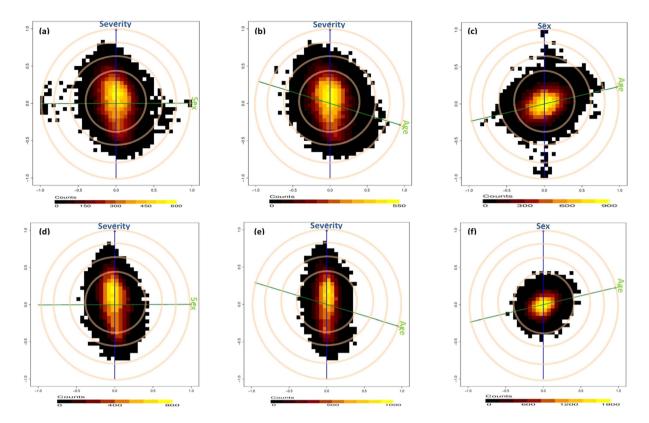
**Validation of biomarkers.** For an independent validation, a subset of the Illumina RSV data of Meijas *et al.*<sup>17</sup> was used. Since the experimental data and validation data were obtained using different platforms, we linked the data using gene symbols and applied cross-platform transformation (to render gene expression comparable across datasets) as described in supplementary material. The transformed data was supplied to our prognostic model for predictions of probabilities of severity. For a confirmatory analysis of how well our prognostic model performs, we built and evaluated a prediction model with the chosen function (same function used to build our prognostic model) on the entire Illumina data and compared our validation performance to the performance from this (unrestricted) data.

#### Results

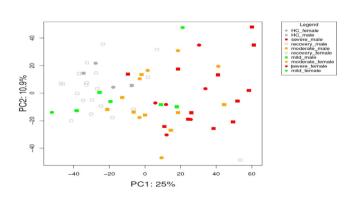
**Study subjects and sampling.** Thirty-nine infants hospitalized with acute RSV bronchiolitis were included in the study. Nasopharyngeal wash and whole blood samples for mRNA profiling were collected within 24 hours upon hospital admittance. Table 1 presents the characteristics of the study subjects. As expected, patients with the most severe course of RSV bronchiolitis were significantly younger than those with a relative mild or moderate course of this disease. The variables related to disease severity; duration of oxygen, and length of stay in the hospital were highest in the severe group, with ventilation indicating the method by which oxygen was supplied. The proportion of co-infections was lower in severe patients as compared to the other severity categories. There were no differences in the occurrence of other known risk factors.

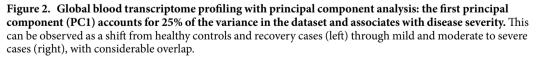
**Age and sex as confounders of gene expression–severity relationship.** Figure 1a,b respectively illustrate the confounding effects of sex and age on the gene expression-disease severity relationship. These figures show that whereas age is negatively correlated to severity, sex is uncorrelated to severity. Nevertheless, the high positive/negative correlations of a considerable number of transcripts to sex and age, as well as severity, indicate a confounding effect of these variables on the expression-severity relationship of these transcripts, thus warrant adjustment. Figure 1d,e illustrate the "biasograms" after an age by sex standardization. These figures show that standardization has no effect on severity correlated transcripts but as expected, transcripts that were originally correlated to age and sex become uncorrelated. A positive correlation of age to sex which signifies an age by sex interaction as a potential confounder on the gene expression-severity relationship was also observed (Fig. 1c) and eliminated after standardization (Fig. 1f).

**Global blood transcriptome profiles associate with RSV disease severity.** Figure 2 illustrate a PCA on the whole transcriptome and the first principal component accounts for 25% of the variance in the



**Figure 1.** Confounding effect of Sex, Age and Age by Sex on gene expression-severity relationship, before. (**a**,**b**,**c**) and after: (**d**,**e**,**f**), an age by sex standardization. The blue and green lines represent the clinical variables, the cosine of the angle between the lines represents its correlation to the blue line (Sex is not correlated to Severity, Age is negatively correlated to Severity i.e. younger kids become severe and Age is positively correlated to sex i.e. females are older). The cloud of points represent the transcripts and their correlations to both variables with most transcripts uncorrelated to the variables (yellow cloud) while a considerable number (black cloud) are correlated to Severity, Sex, Age and Age \*Sex. The associations between the transcripts and Sex, Age or Age \*Sex are significantly eliminated after standardization while retaining that of Severity.





transcriptomes and associates with disease severity. Transcriptome profiles of HC and recovery samples group together on the first principal component and are located opposite to profiles of severe infants. The distinct groups do not form discrete clusters in the PCA but gradually shift from mild through moderate to severe, with considerable overlap. This shows that the blood mRNA profiles substantially capture the severity of lower respiratory tract RSV infection.

	Mil-HC	Mod-HC	Sev-HC	Mod-Mil	Sev-Mil	Sev-Mod	RC-HC	Sev-(Mil+Mod)/2
UP	0	15	194	0	164	42	0	82
Down	0	2	27	0	14	7	1	13
Total	0	17	221	0	178	49	1	95

Table 2. Number of differentially expressed transcripts for each contrast at FDR of 5% and absolute foldchange cutoff of 2. Where Mil: Mild, Mod: Moderate, Sev: Severe, HC: Healthy controls (<2years) and RC:</td>Recovery samples.

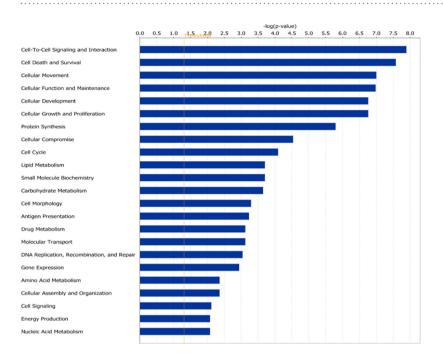
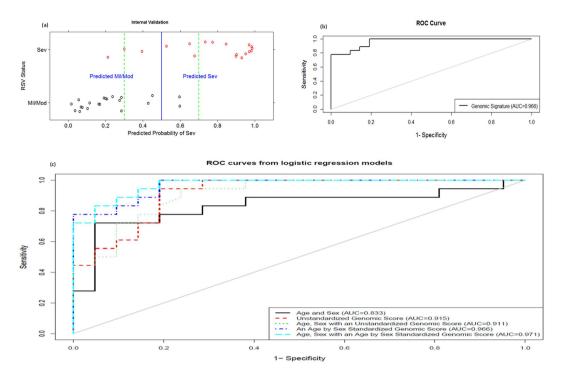


Figure 3. Ingenuity pathway analysis (IPA) Molecular and Cellular functions gene set analysis for severe vs healthy control contrast.

**Number of differential gene expression relates to RSV disease severity.** Table 2 presents results of differential gene expression analysis and reveals that the number of DE transcripts increases with disease severity. No DE transcript was identified between mild versus HC samples when applying a FDR of 5% and absolute fold change (FC) threshold of 2. However, 17 and 221 transcripts were DE between moderate and severe versus HC respectively. Interestingly, all transcripts that are DE in moderate class are also DE in severe class with larger FC. About 90% of these DE transcripts are up-regulated. Comparison of HC with recovery samples revealed a single down-regulated transcript while moderate versus mild yielded no DE transcript, severe versus mild or moderate yielded 178 and 49 DE transcripts respectively. Lastly, 95 transcripts were DE between severe versus combined mild/moderate samples.

**RSV induced blood transcriptome profiles reveal an inflammatory response.** Figure 3 shows that multiple relevant categories of molecular and cellular functions are significantly enriched when comparing severe to HC samples. With "Cell-to-Cell Signaling and Interaction" top category, gene sets related to activation of several types of immune cells including lymphocytes, granulocytes and specifically neutrophils are most significantly enriched. In addition, gene sets that are involved in migration and tissue infiltration of these same activated cell types are most significantly enriched within the category "Cellular Movement" that ranks third on this figure. Finally, several high ranking molecular and cellular function categories and their underlying gene sets indicate the immune cells involved are strongly proliferating. A list of genes involved in each of these pathways is presented in supplementary Table S1. Taken together, blood transcriptome changes in RSV disease reveal a typical inflammatory response to a viral infection.

**Early blood transcriptome changes to predict a severe outcome of RSV infection.** To construct a predictive model, we combined mild and moderate cases as a single group and three probabilistic classification functions were chosen based on supplementary Fig. S2 and results of Jong *et al.* and Kim and Simon<sup>29,30</sup>. Using these functions, classifiers were built and evaluated using LOOCV on the experimental data. SVM was chosen as the best calibrated and refined as shown on supplementary Fig. S3 and henceforth considered for all analyses. The LOOCV predicted probabilities from SVM were used to evaluate its performance and are plotted on Fig. 4a against the true RSV status as retrospectively determined. This figure shows that 5 samples out of 39 were



**Figure 4. Internal validation of gene signature.** (**a**) samples' predicted probabilities of being severe. (**b**) shows the ROC curve and the AUC for predicted probabilities. The AUC value of approximately 1 indicates how accurate our signature performs on this internal validation set. (**c**) shows that a genomic model from the age by sex standardized data out performs that from the unstandardized data. In addition, there is a significant difference between a model with clinical parameters and that with a genomic score and just a slight improvement when both parameters are included in a model.

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misclassified at a 50% cutoff and when applying a proposed uncertainty band of 30–70% just one false negative is witnessed. Evaluation of the clinical characteristics of the single false negative patient as well as those patients with uncertain predictions (plotted within the proposed uncertainty band) did not reveal any recognizable pattern. The false negative patient had uniquely RSV and only a single patient plotted within the uncertainty band had RSV+ other virus(es). Figure 4b presents the corresponding ROC curve from the LOOCV predicted probabilities and AUC of 0.966 demonstrates the high discriminative power of our prognostic model.

**Genomic biomarkers outperform clinical parameters age and sex.** Figure 4c presents the ROC curves from logistic models of clinical parameters and/or genomic scores. The genomic score model from the standardized data (AUC = 0.966) outperforms that from the unstandardized data (AUC = 0.915). In addition, there is a significant difference between a model with age and sex only (AUC = 0.833) and that with a standardized (AUC = 0.966) or unstandardized genomic score (AUC = 0.915). Whereas there is a slight improvement from clinical parameters and standardized genomic score model (AUC = 0.971), there is no improvement from the clinical parameters and unstandardized genomic score (AUC = 0.911), indicating that indeed standardization completely removed an age-by-sex effect on the gene expression data.

**An 84 gene expression signature predicts absence of disease progression.** To extract the prognostic signature, we selected top transcripts maximizing the binomial log-likelihood function using LOOCV predicted probabilities as illustrated on supplementary Fig. S4. This figure depicts a 1-SE maximum of 95 transcripts corresponding to 84 unique genes, which are displayed on Table 3. Of the 95 transcripts constituting the prognostic signature, 81 (85.26%) were found to be significantly DE between severe and non-severe patients (FDR cutoff of 5%, supplementary Table S2). The inclusion of non-DE transcripts in the classification model is expected, since not only DE genes are instrumental in class discrimination as illustrated by the two-dimensional scenario in supplementary Fig. S5.

**Performance of the genomic signature retained on an independent dataset.** For an independent validation, a subset of the Illumina RSV data of Meijas *et al.*<sup>17</sup> was used. Since the experimental data and validation data were obtained using different platforms, we linked the data using gene symbols and applied cross-platform transformation (to render gene expression comparable across datasets) as shown on supplementary Fig. S6 and extensive described in the supplementary material. Figure 5a presents predicted probabilities of severe on the validation data using 75 of our 84 prognostic gene signature that were common in both experimental and validation datasets, while Fig. 5b presents the LOOCV predicted probabilities from SVM on the entire Illumina data. Both figures show that using the unrestricted data leads to more certain probabilities and slightly improves specificity

1         55005.g., at         APC.A13         6pf.OBe-betW.anD/XRQ           2         2849.g. 2919.6., at         ANKRD22         6xd.g.gbkh/YEMCCTo.xnWSex/GaP_LINCHO.HIL_(7)qUB.g]IPF860           4         20578.g.         APB2         9sc.F54UDm47n/M           5         20652.g., at         APB2         9sc.F54UDm47n/M           6         20677.g., at         ARG1         0FMTmod_gbhAnFE           7         22197.x.at         ARG1         0FMTmod_gbhAnFE           8         2012.d.g., at         APB1         umaiNNSUSGacEg.spU20PBMTDM264 DFM.TUBe64 FORD.m.E.B1.110           10         21575.g., at         BPI         Eq.RaX/VAG12.g.G/GBHANTDM264 DFM.TUBe64 FORD.m.E.B1.110           11         20557.g., at         BPI         Eq.RaX/VAG12.g.G/GBHANTDM264 DFM.TUBe64 FORD.m.E.B1.110           12         20214.g.         CAXAM         KpCTUMSRUBQB         FLARAVCHARTDM274 BBLA           13         20956.g.         CH11         X	Nº	Affymetrix IDs	Gene Symbol	Illumina IDs
3         29369_att         ANXA3         orojh4PCCMN1ArUY6k           4         20578_att         AP382         956674UDm77_mVM           5         20632_att         AP382         956674UDm77_mVM           6         206177_s_mt         ARG1         0UVMTIood_g0AnFE           7         20197_s_mt         ARG1         0UVMTIood_g0AnFE           8         201425_s_mt         ATU1         QBaHY05Creaky4CDe cMm17195NdYNUqeo BIIKm4Feq01E3e1b4           10         21353_s_mt         ATU1         QBaHY05Creaky4CDe cMm17195NdYNUqeo BIIKm4Feq01E3e1b4           11         20557_aft         AZU1         QBaHY05Creaky4CDe cMm17195NdYNUqeo BIIKm4Feq01E3e1b4           12         210244_aft         CAMP         rhcm74v64K6fp3A           13         20998_ar211889_x_mt         CAAAM         KpCYUma3RLKQeILdQU rhcFeaHaTH9XTU54xXXKB1Uosba6L3ce0           14         20457_aft         CEACAMB         ubSAS01LUVDo           15         20656_aft         CEACAMB         ubSAS001LUVDo           16         20995_aft20996_aft         CHI51.M         Zh_0578/aft           17         201465_aft         CFECH         uSCDm6c6jt20AN0gp1ZetAC6eFe1pCaH1N1           18         20496_aft         CTECH         uSCDm6c6jt20AN0gp1           20145	1	1553605_a_at	ABCA13	0pf.QRwb4sWsn7jQKQ
4         26578_at         AP382         99acFS4fUDm67_nVM           5         26652_st         APOBECM         9F619hjLUTm6x40hAnFE           7         232197_x,at         ARS1         0/WTM0sd_pMAnFE           7         232197_x,at         ARS1         0/WTM0sd_pMAnFE           8         20142_x,at         ATP1B1         um3NNSUGecage 9p120[PBMdTLBee4 frofs_Dm_E38_11o           9         21457_x,at         AZU         QBuTlerVib/XZVBac5           10         22557_at         BF1         EqueXVVKg120FBac6           11         20557_at         BF1         EqueXVKg120FBac6           12         21024_at         CAACAM         9cri2FUucDeaE1B4           13         20496a_x1211880_x,at         CEACAM         9cri2FUucDeaE1B4           14         20757_x21216CACAM         9cri2FUucDeaE1B4         12           15         20667_act         CEACAM         9cri2FUucDeaE1B4           16         20935_a1209396_act         CEIC1B         0caCDirCoScip2rNg           17         20816a_xat         CHIS1         XacLams           18         20496_xat         CHIS1         Na           19         20456_xat         CYFL         cdjGreegKNLMAQGIZekeaCe1FGCuHINI           10 <td>2</td> <td>238439_at 239196_at</td> <td>ANKRD22</td> <td>oXed_glbkhVEMCDCTo xnW5awXa6P_EbICH0s HIf_t7qU.BejlFP86o</td>	2	238439_at 239196_at	ANKRD22	oXed_glbkhVEMCDCTo xnW5awXa6P_EbICH0s HIf_t7qU.BejlFP86o
9         20632_s_st         APOBEC3B         9f619hplDXIPnOK6I           6         20177_s_st         ARG1         0IVMTIsod_globAnEE           7         252197_s_st         ARGB         0IVMTIsod_globAnEE           8         20124_st         ARBB         0IVMTIsod_globAnEE           9         214575_s_st         AZU1         QBaHuFVINS72VBBs5           10         21530_s_st         BPI         EpäKe2VVKg13yBl0g           11         20537_st         BPI         EpäKe2VVKg13yBl0g           12         210244_st         CAAPI         rice/TcV64KFp1A           13         20998_st21809_st_st         CEACAMI         KPCYUm4381kQNIAQU fcrelelaInT19XTU54 xKXCRD0x08x612x00           14         20375_st_201507_st         CEACAMI         VMEVA-8001.LUVDo           15         206676_st         CEACAMI         VMEVA-8001.LUVDo           16         209395_st209396_st         CHIS1L         Zn_st/antWrHVHodF1U           17         20164_st         CECIEB         upCIAROSERIBMODA           18         20496_st         CECIEIB         upCIAROSERIBMODA           17         21052_st         CERIE         WICHVASSNEgNBNQ4           12         20553_st         CRISP         upCIAROSERIBMODA <td>3</td> <td>209369_at</td> <td>ANXA3</td> <td>orojh4FCCMN1ArUY6k</td>	3	209369_at	ANXA3	orojh4FCCMN1ArUY6k
6         206175_s_at         ARG1         0!VMTload_globAnFE           7         23197_x_at         ARSB         31DbPVCxeAqVdCDc Mm1/1795N4TNUqce BJRKm4FqJ01E3cHp4           8         201242_s_at         ATP1B1         um3N0RSU06cu5c9.0p1201RBM4TL0e64 fv06s_DnLE3H_110           9         21457_s_at         ATP1B1         um3N0RSU06cu5c9.0p1201RBM4TL0e64 fv06s_DnLE3H_110           10         22550_at         BHLHE41         EUN3CXU07p3ptxedvU           11         20557_at         CEACAM         KpCYUn43RIkQFdIdQU fr_eFeEAfuTH9XTU54 sKXCKBUooshn6J.cx0           12         2044_at         CEACAM         KpCYUn43RIkQFdIdQU fr_eFeEAfuTH9XTU54 sKXCKBUooshn6J.cx0           12         20456_at         CEACAM         KpCYUn43RIkQFdIdQU fr_eFeEAfuTH9XTU54 sKXCKBUooshn6J.cx0           13         20456_at         CHTI         NA           20456_at         CHTI         NA           20456_at         CHTI         NA           20456_at         CRTI         upXiAqQSFEHuwb0A           21         20452_at         CRTI         upXiAqQSFEHuwb0A           21         20562_at         CTSC         0KXD1XQSSFEMbw0A           21         20563_at         CTSC         0KXD1XQSSFEMbw0A           21         20563_at         CTSC <td< td=""><td>4</td><td>205678_at</td><td>AP3B2</td><td>9SneFS4fUDnuF7_nVM</td></td<>	4	205678_at	AP3B2	9SneFS4fUDnuF7_nVM
7         232197_x_ati         ARSB         30DiPUC_vkqViCDz MatryU195MdYUUqeo BIIKm4IFq01E3EHp4           8         201242_s_ati         ATP1B1         um3iNNSU0fscuEqc 9pU20]PBMdTL@e64 frOfs_Dm_E31_110           9         14757_s_ati         AZUI         QBuHurViNSZVBBu5E           10         205357_ati         BPI         EqRex2VVkg13UjBQg           11         205357_ati         BPI         EqRex2VVkg13UjBQg           12         10244_ati         CAMP         rttcn7kvd6kfep3iA           13         20696_ati         CEACAMB         eprivationEntitA           14         203757_s_at211657_ati         CEACAMB         eprivationEntitA           15         20666_ati         CEACAMB         eprivationEntitA           16         20955_atitA         CEACAMB         eprivationEntitA           17         208168_s_at         CHTI1         NA           18         20496_atit         CHTI1         NA           19         208164_s_atit         CPV1         edigToegKNUMQg1ZeEaC6evE1pCauH1N1           20         20653_atit         CTSG         GRKUnUS7SBIDAbUS         20657           20         20571_atit         ELNE         NiFoniRFRH4STeAAVAKe4         20671           20         20571_atit	5	206632_s_at	APOBEC3B	9Ff619hplIXH7nOK6I
1         21373_2.41         ARSB         0001M70QUU_GOLO34           2         214573at         AZU1         QBuItuPVibS7ZVBBa5E           10         21535s.41         AZU1         QBuItuPVibS7ZVBBa5E           11         20557at         BH1.HEI         EUN35CXUD3p.insek/U           12         21024at         CAMP         rikewIV/gi10jf0Q           13         20998at211867at         CEACAMB         wHBVA.SbO1LUVD0           14         20375s.at211867at         CEACAMB         wHBVA.SbO1LUVD0           15         20667at         CEACAMB         wHBVA.SbO1LUVD0           16         20935at.20936at         CHTI         NA           17         20816sat         CHCIB         uSC2Din6C6ip2vN0g           18         20466at         CHECIB         uSC2Din6C6ip2vN0g           19         20816sat         CHSP         ucDinfWNNShgSPMPGQ4           10         20156at         CRISP         ucDinfWNShgSPMPGQ4           11         20563at         CRISP         ucDinfWNShgSPMPGQ4           12         20454at         ELAHE         NFoinEWNShgSPMPQ4           12         20456at         CECIB         USCDin5MegUINFNCA          121	6	206177_s_at	ARG1	0lVMTIuod_g0ohAnFE
8         201242_s_at         ATP1B1         umu3NNNSU06cuEqc 9pU20JEBMdTLBe64 FrOfs_Dmt_EMI_110           9         21475_s_at         AZU1         QuFuTrVINSTX7Bma5E           10         21530_sat         BHLHEAL         ENNSCXUP3puscedvU           11         20557_at         BPI         EqRacX9VKg13UjBQg           12         10024L_at         CAMP         rftca7k/6KdKep3iA           13         20998_gat211889_x_at         CEACAMB         epRiVCVUn43RtKoPIdUQ ftcrEdEaHaTH9XTU54 stXXCKD40o8n6L3cd           14         20575_s_at211657_at         CEACAMB         epRiVCVUn43RtKoPIdUQ ftcrEdEaHaTH9XTU54 stXXCKD40o8n6L3cd           15         20667_at         CEACAMB         ebRVA.8001LUVDo           16         20939_s_at         CEACAMB         ebRVA.8001LUVDo           17         208168_s_at         CHI11         NA           18         20496_at         CHI31         Zn_jrdnvHVHvdFIU           10         20456_s_at         CHI31         Zn_jrdnvHVHvdFIU           11         20456_at         CHI31         NA           21         20553_at         CRISP2         ukOTdVSNNEQNHQP1ZEEaCaevElpCauHINI           21         20565_at         CRISP3         ugDXAQQSPEEhwohQ4           210352_at         CRISP3	7	232197_x_at	ARSB	
102130	8	201242_s_at	ATP1B1	
11         20557_at         BPI         EqRacXVKg13UjfBQg           12         210244_at         CAMP         ritco7k/06Kkp3A           13         20949_at 211892_xa1         CEACAMI         KpCVUm45RlkpGLdQU fr.cFeEaHnTH9XTU54 xKXCKBUoo8n6L5x01           14         203757_sat 21657_at         CEACAMI         wbBVA AbO1LUVDo           16         209395_at 209396_sa1         CHACAMI         wbBVA AbO1LUVDo           17         208166_sat         CHITI         NA           18         220496_at         CERCAMI         wbCDacCeijp2N0g           19         201632_at         CRISP2         ukCDMCceip2NN9Q           21         20263_at         CRISP3         uqDXiAQ05FHwohO4           22         20259_xat         CRISP2         ukOTMVSNRigNPAQ           23         20259_xat         CRISP3         uqDXiAQ05FHwohO4           24         207269_at         DEFA4         653079KdBCqTred_SM           25         206871_at         ELANE         NtFONIRFRH3TkekyeE           26         24225_xat         FTY7         9KCUP5JKVFXbDM           27         21306a_at         FGRIA         WgUcCoM94FRNQCPU           213083_at         FGRIA         MgUcOn934TkHCNQE           213093_at	9	214575_s_at	AZU1	QBuHuFVihS7ZVBBu5E
12         21024_at         CAMP         rhcu7kV64Kip3IA           13         209495_at 211889_x.at         CBACAMI         KpCTUn43RIkQRL4QU fr.ePeEaHuTH9XTU54 xKXCK3Uoo8n6L3ce0           14         20375_s_at 211657_at         CEACAMI         kpCTUn43RIkQRL4QU fr.ePeEaHuTH9XTU54 xKXCK3Uoo8n6L3ce0           15         20667_at         CEACAMI         ubIRVa.8b01LUVDo           16         209395_at 209396_s_at         CHITI         NA           17         208168_s_at         CHCI         NaC2Dir6Colip2vN0g           18         20496_s_at         CERCI         usC2Dir6Colip2vN0g           19         208146_s_at         CHCI         usC2Dir6Colip2vN0g           10         20362_at         CRISP3         upDIAQ0SFEMwoh04           21         207580_at         CISG         0RKUnIX7SSDDAbUS1           22         20555_at         CISG         0RKUnIX7SDDAbUS1           23         202859_x_at         CXCAB         3Vy3nj0UQr/UcSfo EVLftPIJ7vrLnn_Dxo           24         207269_at         DEFA4         65309KBICqTrd_SM           25         206871_at         ELANE         NtroInFRHASTKeW2           26         20425_s_at         FCR1A         KV7kDSLOAuggulXHZ ZUGXNUGFVEAUGPU           21300_at         FCR1A </td <td>10</td> <td>221530_s_at</td> <td>BHLHE41</td> <td>EUN35CXUp3p.txedvU</td>	10	221530_s_at	BHLHE41	EUN35CXUp3p.txedvU
13         209498_at 211889_x_att         CEACAM1         KPCTUm43RRQFdL4QU fr.FeEaHuTH9XTU54 xKXCKf3Uoo8n6L3ca           14         203757_s_at 21657_att         CEACAM6         9crIZPUmcDnEx1B4           15         20667_s_att         CEACAM6         9crIZPUmcDnEx1B4           16         20957_s_at 20196_s_att         CHI3L1         X_n_stand           17         208168_s_att         CHI3L1         X_n_stand         X_n           18         20496_att         CHI3L1         X_n_stand         X_n           19         208168_s_att         CHI3L1         X_n_stand         X_n           10         20496_att         CHI3L1         X_n_stand         X_n           10         20486_s_att         CHI3L1         X_n_stand         CHI3L1         X_n_stand           10         20486_s_att         CHI3L1         X_n_stand         CHI3L1         X_n_stand           11         20835_att         CRISP         VX/SIGMAQQFIZeEuCevE1pCauHINI           12         20487_att         CRISP         VX/SIGMAQQFIZEUCeVE1pCauHINI           12         20487_att         DEFA         6530*KdBCqTred_SN         SN <sigmactacsn< th="">           12         20367_att         ELANE         NEPIORISNATSNEWE         SN</sigmactacsn<>	11	205557_at	BPI	EqRaeX9VKg13UjfBQg
14         203757_s_at 211657_at         CEACAM6         VertZPUUucDnEx1B4           15         206676_at         CEACAM8         whBVA.ABOUIL.UVDo           16         209395_at 209396_s_at         CHI3L1         Zn_tzfam/VHIVHodF1U           17         208168_s_at         CHITI         NA           18         20496_at         CECIB         uSCDIEGGENDEAQD2 ElecGevE1pCauH1N1           19         208146_s_at         CRISP2         ukOTRVSNNEgNI9RQ4           21         207802_at         CRISP2         ukOTRVSNNEgNI9RQ4           22         205535_at         CRCL8         3Vy3nJSUQtiVu5/6 EV1fi/DHJVrInu_Dxo           23         202859_x_at         CRCL8         3Vy3nJSUQtiVu5/6 EV1fi/DHJVrInu_Dxo           24         20720_at         DEFA4         65309KdRC1/red_SM           25         206871_at         ELANE         NF0nIRFRHdSTeQWE           26         24225_s_at         FUT         9KUpfi/UVFSDM           27         21306_at         FQE11         BH5HQSt30xAKS4Z4940UTIaAykE           28         21734_s_at         FCER1A         WgUoCa0H94FRNcjQFU           29         231093_at         FCR13         H7/SIA7ISQ_3qhS-tHVA037CE0HugeT7c TmCOYpTscJV7AXE           210321_at         GZM4         H	12	210244_at	CAMP	rItcu7lcV6dKfep3iA
1         20676_at         CEACAMS         ubf8VA.8bOII.LUVDo           16         20395_st 20936_s_at         CHILI         Zn_tzfamVHIVHodFIU           17         208168_s_at         CHITI         NA           18         220496_st         CLECIB         usC2Dit6C6ijp2vN0g           19         208146_s_at         CLECIB         usC2Dit6C6ijp2vN0g           20         20563_st         CRISP2         ukDTMVSNNEgN198Q4           21         207802_at         CRISP3         uqDXiAQ0SFE4bwohO4           21         205653_at         CTSG         ORKUUC57SDIDAUSI           23         202859_x_at         CXCL8         3Vy3nJSUQtfvUc56 FVLfiPJ[VrLnu_Dxo           24         207269_at         DEFA         65309KdBCqTred_SM           25         206871_at         ELANE         NtPonIRFRHdSteRQwE           26         224225_s_at         FCRI         WgUcOnth/HRNQPU           27         215506_at         FCRIA         WgUcOnth/HRNQPU           28         20110_s_at         FCFIA         WgUcOnth/HRNQPU           29         21010_s_at         FCFIA         WgUcOnth/HRNQPU           20         21510_s_at         FCFIA         WgUcOnth/HRNQPU           225767_at	13	209498_at 211889_x_at	CEACAM1	KpCYUm43RIkQFdLdQU fr.cFeEaHuTH9XTU54 xKXCKf3Uoo8n6L3cx0
16         209395_st 209396_s_att         CHI3L1         Zn_tzfam/HIVHodF1U           17         208168_s_att         CHI3L         NA           18         20496_at         CLEC1B         uSC2DiteGcip2xN0g           19         208146_s_at         CLEC1B         uSC2DiteGcip2xN0gAQgP1ZeEaC6evE1pCauH1NI           20         20262_at         CKISP3         uqDXIAQQSFE4iwohO4           21         207802_at         CKISP3         uqDXIAQQSFE4iwohO4           22         205653_at         CTGG         RKUnUS7SifDAbUSI           23         20289_x_at         CXCL8         3Vy3nJSUQivUc5fo FVLÅPIJ7vrLnu_Dxo           24         202269_at         DEFA4         6530PdRdECfTred_SM           25         206871_at         ELANE         NF0nIRFRHASTe&QvE           26         224225_st         FTV7         9KCUpFiJV/PKSADM           27         21506_at         FCR1A         WgUoCab94FRNcQFU           28         211734_s_at         FCR1A         WgUoCab94FRNcQFU           29         21093_at         FCF1A         Hd751ATSQ_a3yhScHuna7SCEbHug477c TmCOYpTxejV7aXpE           21         223767_at         GPR4         okb7653OU4FIDI1CQ         223767_at           210321_at         ICAPA1         HF0ANCSb3	14	203757_s_at 211657_at	CEACAM6	9criZPiUuucDnEx1B4
17       208168_s_at       CHIT1       NA         18       220496_at       CLECIB       uSC2Dir6C6jp2vN0g         19       208146_s_at       CPVL       cdjqTogEKNUoMQgpI ZEuG6vE1pCauH1NI         10       208146_s_at       CRISP3       ukDTdiVSNFgpN19KQ4         21       207802_at       CRISP3       uqDXiAQ0SFE4hwohO4         22       208553_at       CTSG       ORKUNUS7S5jD3kDUSI         23       202859_x_at       CXCL8       3Vy3nJSJQ1fvUe5fo EVLfPIJ7vrLnu_Dxo         24       207209_at       DEFA4       6530v6MEG7Ted_SM         25       206871_at       ELANE       NtFonIRFRHdSTekQwE         26       224225_s_at       ETV7       9KCUEpFIKVIVFXsDoM         27       213506_at       FCRL3       KV7kDSLO4uggquLX84 ZUdXuEVE         28       21173_s_at       FCRL3       KV7kDSLO4uggquLX84 ZUdXuEVE         29       231093_at       FCRL3       KV7kDSLO4uggquLX84 ZUdXuEVEA         21       22386_at       FGFB2       xmX900031ithKCFE         21       223836_at       FGFB1       Hdr5tA/XSQ34phE1Hu1GQ         21       22357_at       GZMH       rgmXcEkpOLF9d6l4U         32       20321_at       HGF       FQCCKSNUHD1UMBQ	15	206676_at	CEACAM8	ubtBVA.8bOI1.LUVDo
Instruct         CLEC1B         uSC2Dit6C6ijp2vN0g           19         208146_s_at         CPVL         cdjGTocgKNUoMGpl ZeEuC6evE1pCauH1NI           20         210262_at         CRISP2         udpXIAQ02FEdwohO4           21         20780_at         CRISP3         udpXIAQ02FEdwohO4           22         205653_at         CTSG         0RKUnUS75SjfDAbUSI           23         202859_x_at         CXCI8         3Vy3nJSUQfr/Uc56 EVLf/PI/TvrLnu_Dxo           24         207269_at         DEEA4         6530r9KdBCqTred_SM           25         206871_at         ELANE         NF0nIRFHAISTcQvE           26         224225_s_at         ETV7         9KCUpFJIKVJVFXsDoM           27         213506_at         F2RL1         BSHqBKISgaiosAXKe4 ZAJ9Iq.oUTd.oAy.KE           28         211734_s_at         FCRI3         Hd751A7ISQ_3qhScHwu37s/CEoHuge477c TmCOYpTxeJV7aAXpE           21         223767_at         GPB42         xmS900a31irhK/CFXE           21         223767_at         GPR44         ok0F23OSU4FDDICQ           31         210321_at         GZMH         rgmXcEbyDE9d4U           32         120320_at         HLA-DQA1         NA           33         210321_at         IGLN         NA	16	209395_at 209396_s_at	CHI3L1	Zn_tzf4mVHIVHodF1U
18         20496_at         CLEC1B         uSC2Dit6C6ijp2vN0g           19         208146_s_at         CPU         cdfGToegKNUoMQpI ZeEuC6evE1pCauH1NI           20         210262_at         CRISP2         ukDXIAQpSPEHuwbO4           21         20780g_at         CRISP3         uqDXIAQpSEHuwbO4           22         205653_at         CTSG         0RKUnUS755jfDAbUSI           23         202859_x_at         CXCI8         3/3jallyUQfWC56 EVLfPIJrvrLnu_Dxo           24         207269_at         DEFA4         65309KdBCqTred_SM           25         208671_at         ELANE         NfbnIRFRHASTEKQvE           26         224225_s_at         ETV7         9KCUpFJIkVJVFXsDoM           27         213506_at         FCRIA         WgUocn0b94FRNcJQFU           28         211734_s_at         FCRIA         WgUocn0b94FRNcJQFU           2003_at         FCRIA         KV7bSIS-D04uggpuLXB4ZUCXxU6VE0BJeRT8 67unrLPPijv_uzOeZU           30         2033_at         FGF13         Hd751A7ISQ_3qhSc Hvun37sCEoHuge477c TmCOYpTxejV7AAXpE           31         22386_at         GZMH         rgmXcEbpO1eP3d4U           34         20361_at         HEA         NA           35         20537_at         HLA-DQAI         NA	17		CHIT1	
19         208146_s_at         CPVL         cdigToegKNUoAQgp1ZeEuC6evE1pCauH1NI           20         210262_at         CRISP2         ukOTRIVSNNEgNH9KQ4           21         207802_at         CRISP3         uqDXiAQ0SFE4IwohO4           22         205633_at         CTSG         0RKUU57SFDAbUSI           23         20289_x_at         CXCL8         3Vy3nJSUQtfvUe5fo EVLftPIJTvrLnu_Dxo           24         207269_at         DEFA4         6530r9KdECqTred_SM           25         206871_at         ELANE         NFbnIRFRHdSTekQwE           26         224225_s_at         ETV7         9KCUpFjIkVIVFXsDoM           27         215306_at         F2RL1         BSHq8Klsgbu6xAXkd4 ZAJ9Iq.oUTd.oAy.kE           28         211734_s_at         FCERIA         WgUoCn0h94FRNcJQFU           29         231093_at         FGFB3         Hd751A7ISQ_3qhScHwu37cEoHuge477c TmCOYpTxejV7aAXpE3           31         20321_at         GZMH         rgmxCEpOlF9d6l4U         102133           32         20327_at         HBZ         hei/VSVR&WbDmUMBQ         10321           33         20329_at         HLA-DQA1         NA         10321           34         20647_at         HBZ         NA         10414           35 <td>18</td> <td></td> <td>CLEC1B</td> <td>uSC2Dit6C6ijp2vN0g</td>	18		CLEC1B	uSC2Dit6C6ijp2vN0g
2         21026_at         CRISP2         ukOTIGNSNNEgNII9KQ4           21         207802_at         CRISP3         uqDXiAQ0SFE4hwohO4           22         205653_at         CTSG         0RKUnUS7SSJ[DAbUSI           23         202859_x_at         CXCL8         3Vy3nJSJUQtfvUe5fo EVLftPIJ7vrLnu_Dxo           24         207269_at         DEFA4         65309r5MEQTerd_SMA         65309r5MEQTerd_SMA           26         224225_s_at         ETV7         9KCUpFJIkVJVFXsDoM           27         213506_at         FCRL1         BSHgRKigAGAKAK4ZAJ9Iq.oUTd.oAy.KE           28         211734_s_at         FCRL3         KV7kDSLO4uggquLX84 ZUClXXU6VE0BJRT8 67unrLPPnjv_uzOezU           20         205110_s.at         FCRL3         KV7kDSLO4uggquLX84 ZUClXXU6VE0BJRT8 67unrLPPnjv_uzOezU           21         223767_at         GPR4         ok0Fe3OSU4FIDICQ         223767_at           22         23767_at         GZR44         RgmX2k0bCPSd4U         231           32         20321_at         GZM4         RhZ-DPA1           34         20667_s_at         HBZ         IkivSVR8WbDmUMBQ           35         213537_at         HLA-DQA1         NA           36         203290_at         HLA-DQA1         NA				<i>A</i> 0
21         207802_att         CRISP3         uqDXiAQ0SPE4hwohO4           22         206653_at         CTSG         0RKUnUS7SSJfDAbUSI           23         202859_x_at         CXCL8         3Vy3nJSUQtifvE56 EVLfiPIJ7vrLnu_Dxo           24         207269_at         DEFA4         6530r9KdBCqTrd_SM           26         204225_s_at         ETV7         9KCUpFJIkVJVFXsDoM           27         213506_at         F2RL1         BSHqBKISgu6xAXk64 ZAJ94q.oUTId.oAy.kE           28         211734_s_at         FCEL3         Ky0con60494FRNcJQFU           29         231093_at         FCRI3         KV7bNDCAuggquLXAE4ZUCXxUi6VE0BJeRT8 67unrLpPnjv_ucOe2U           20         23103_s_at         FGF13         Hd751A7ISQ_3qyhScHvun37sCE0Huge477c TmCOYpTxsjV7aAXpE           31         22336_c_at         GZM4         egmXsEbQ1bHQU         egmXsEbQ1bHQU           32         20321_at         GZM4         pgmXsEbQ1bHQU         egmXsEbQ1bHQU           34         20647_at         HBZ         hetvVSVR8WbDmUMBQ         egmXsEbQ1bHQU           35         213537_at         HLA-DQ41         NA         egmXsE10Si0gKnU         egmXsE10Si0gKnU           36         20590_s_at         HP         fpOCKSWIRWAIRVIE         egmXsE10Si0gKnU         egmXsE10Si0gKnU <td></td> <td></td> <td></td> <td></td>				
22         2565_att         CTSG         0RKUnUS7SSJDAbUSI           23         202859_x_at         CXCL8         3Vy3nJSjUQt/vUe56 EVLftPJJ7vrLnu_Dxo           24         207269_at         DEFA4         6530*9KdBCqTred_SM           25         206871_at         ELANE         NtF0nIRFRHdSTeQwE           26         224225_s_at         ETV7         9KCUpFjIK/VFXsDoM           27         21356_at         F2RL1         BSHqBKISg3u6AXK64 ZAI9Iq.oUTd.oAy.kE           28         211734_s_at         FCERIA         WgUoCn0h94FRNcJQFU           29         231093_at         FCR13         Hd7t51A7SQ_3qyhSc Hvu37SCEoHuge477c TmCOYpTxe_jV7aXEPE           31         22336_at         FGFB2         xmX900n31inhK4CFXE           32         20321_at         GZMH         rgmXcEkpOlcF9d6l4U           34         206647_at         HBZ         ItevVSVR8WbDmUMBQ           35         213537_at         HLA-DQA1         NA           36         20329_at         HLA-DQA1         NA           37         20480_at         IGH         NA           38         215837_at         IGH         NA           39         215118_s_at         IGH         NA           40         212592_at				
23         202859_x_at         CXCL8         3Vy3nJSJUQtrVLeSio EVLftPIJ7vrLnu_Dxo           24         207269_at         DEFA4         6530r9KdBCqTred_SM           25         206871_at         ELANE         NtF0nIRFRH4STERQvE           26         224225_s_at         ETV7         9KCUpFJIkVJVFXsDoM           27         213506_at         F2RL1         BSHqRKSgaucAXK64ZAJ9Iq.oUTd.oAy.kE           28         211754_s_at         FCER1A         WgUoConb94FRNG/QFU           29         231093_at         FCR13         KV7kDSLO4uggquLXB4ZUdIXUi6VEoBJeRT8 67un1.pPnjv_uzOezU           30         205110_s_at         FGFB2         xmX900n31irhK4CFXE           22         23767_at         GPR84         ok0F53OSU4FIDIICQ           31         20321_at         GZM4         rgmxCEbpOIcP9d6l4U           34         206647_at         HBZ         licvVSVR8WbDmUMBQ           35         213537_at         HLA-DQ11         NA           36         20329_at         HLA-DQ11         NA           37         209480_at         IGJ         HhecR84SAQucR/7rVE           41         21748_x.at         IGI         HhecR84SAQucR/7rVE           42         234764_x.at         IGLC1         NA				* -
24         207269_at         DEFA4         6530r9KdBCqTred_SM           25         206871_at         ELANE         NtF0nIRFRHdSTekQwE           26         224225_s_at         ETV7         9KCUpFjik/VIPXsDoM           27         213506_at         EZRL1         BSHqBKISg3v6xAk64 ZAJ9Iq.oUTd.oAy.kE           28         211734_s_at         FCERIA         WgUoCn0b94FRNcjQFU           29         231093_at         FCFI3         Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxe;JV7aAXpE           31         223836_at         FGFB2         xmX900n31irhK4CFXE           32         223767_at         GPR84         ok0Fe53OSU4FID1ICQ           33         210321_at         GZMH         rgmXcEkp0IcF9d6l4U           34         206647_at         HBZ         IteivVSR8WbDmUMBQ           35         213537_at         HLA-DPA1         NFdNMC3eb3pThVaIQ           36         203290_at         HLA-DQ81         TXanqXzTU0Si0gKnU           37         209480_at         IGJ         HhecR84SAQucRJ7vE           41         21718_s_at         IGLC1         NA           42         24764_x_at         IGLV1-44         NA           43         227140_at         IGLC1         NA           44				
25         20687_at         ELANE         NtF0nIRFRHSTeQwE           26         224225_s_at         ETV7         9KCUpFjlkVJVFXsDoM           27         213506_at         F2RL1         BSHqBKISg3u6xAXk64ZAl9Iq.oUTd.oAy.kE           28         211734_s_at         FCERIA         WgUoCn0b94FNNcJQFU           29         231093_at         FCRL3         KV7kDSLO4uggquLXB4ZUclXxUi6VEoBJeRT8 67unrLpPniv_uzOezU           30         205110_s_at         FGF13         Hd7t51A7SQ_3qyhSc Hvun37sCEoFluge477c TmCOYpTxe.jV7aAXpE           31         22336_at         FGF82         xmX900n31irhK4CFXE           32         20321_at         GZMH         rgmXcEkpOlcF9d6l4U           34         206647_at         HBZ         lieivVSVR8WDDmUMBQ           35         213537_at         HLA-DQA1         NFdnMC3eb3pThValQ           36         203290_at         HLA-DQA1         NA           37         209480_at         HLA-DQA1         NA           38         206697_s_at         HP         fpPOCk\$S1WAIIRYIIc           39         215118_s_at         IGH         NA           40         21259_at         IGJ         HhccR84SAQucRJ7rVE           41         217148_s_at         IGIC1         NA				
26         22422.s_at         ETV7         9KCUpFjikVJVFXsDoM           27         213506_at         F2RL1         BSHqBKISg3u6xAXk64 ZAJ9Iq.oUTd.oAy.kE           28         211734_s_at         FCER1A         WgUoCn0b94FRNc/QFU           29         231093_at         FCR13         KV7kDSL04uggquLXB4 ZUCIXuli6VEoBJeRT8 67unrLpPnjv_uzOezU           30         205110_s_at         FGF13         Hd7t51A7ISQ_3qyh5c Hvun37SCEoHuge477c TmCOYpTxe.jV7aAXpE           31         223383_at         FCFP2         xmX900m31trhK4CFXE           32         223767_at         GPR4         ok0Fe53OSU4FDICQ           33         210321_at         GZMH         rgmXcEkpOlcF9d6l4U           34         206647_at         HBZ         lievVSVR8WbDmUMBQ           35         21357_at         HLA-DA1         NFdMMC3eb3ThValQ           36         203290_at         HLA-DQA1         NA           37         20480_at         HLA-DQA1         NA           38         206697_s_at         HP         fpPOCk51WAIRYILc           39         215118_s_at         IGJ         HhecR84SAQucR)7vFE           41         217148_s_at         IGLC1         NA           42         234764_s_at         IGLC1         NA				
27213506_atF2R.I.1B5HqEKISg3u6xAXk64 ZAI9Iq.oUTd.oAy,kE28211734_s_atFCER1AWgUoCn0h94FRNcJQFU29231093_atFCR13KV7kDSLO4uggquLXb4 ZUclXxU6VEoBJeRT8 67unrLpPnjy_uzOczU30205110_s_atFGF13Hd7t51A7ISQ_3qyh5c Hvun37sCEoHuge477c TmCOYpTxejV7aAXpE31223836_atFGFB2xmX900n31inhK4CFXE32223767_atGPR84ok0Fe33OSU4FID1ICQ33210321_atGZMHrgmXcEkpOlcF9d6IdU34206647_atHBZIteivVSVR8WbDmUMBQ35213537_atHLA-DQA1NA37209480_atHLA-DQ31NA38206697_s_atHPfpPOCkkS1WAIIRYIIc39215118_s_atIGHNA40212592_atIGIHhccR84SAQucRJ7rVE41217148_x_atIGLC1NA42234764_x_atIGLV1-44NA43227140_atINHBAcp0iOCS4CISg_oqAqI44216956_s_atITGA2BH3o0v7nktkZOvQbtdU4521231_atLCN2WUTbfV7DTUuzYacLk46208450_atLGA152WT6GkHqpCBBqCNF7k4722196_atLOC78613NA48238717_atLOC441528NA49156910_x_atITG7AQ412018_s_atMMD6p_X8jaueM_XV1yw6k51244523_atMMPfgrvFUrFTg7iffrKk BelTsr_hSKG0oopKI5320396_s_atMMPfn3Hpm4v0uL4FK6FA5420394_s_atMMPfn3Hpm4v0uL4FK6F				
28         211734_s_at         FCER1A         WgUoCn0h94FRNcJQFU           29         231093_at         FCR13         KV7kDSLO4uggquLXB4 ZUclXxUi6VEoBJeRT8 67unrLpPnjv_uzOczU           30         205110_s_at         FGF13         Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxejV7aAXpE           31         223836_at         FGFB22         xmX900n31irhK4CFXE           32         223767_at         GPR84         ok0Fe530SU4FID1ICQ           33         210321_at         GZMH         rgmXcEkp0IcF9d6l4U           34         206647_at         HBZ         IteivVSVR8WbDmUMBQ           35         213537_at         HLA-DQA1         NA           37         209480_at         HLA-DQA1         NA           38         206697_s_at         HP         fpPOCkS1WAIIRYIIc           39         215118_s_at         IGH         NA           40         212592_at         IGIV1-44         NA           41         217148_x_at         IGLC1         NA           42         234764_x_at         IGIV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at         ITGA2B         H300v7nktkZOvQbtdU           45				
29         231093_att         FCR1.3         KV7kDSLO4uggquLXB4 ZUclXxUi6VEoBJeRT8 67unrLpPnjv_uCOezU           30         205110_s_att         FGF13         Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxejV7aAXpE           31         223836_at         FGFB2         xmX900n31irhK4CFXE           32         223767_at         GPR84         ok0Fe53OSU4FID1ICQ           33         210321_at         GZMH         rgmXcEkpOlcPdeldU           34         206647_at         HBZ         lteivVSVR8WbDmUMBQ           35         213537_at         HLA-DQA1         NA           37         209480_at         HLA-DQA1         NA           38         206697_s_at         HP         fpPOCkS1WAIIRYIIc           39         215118_s_at         IGJ         HhecR84SAQucRJ7rVE           41         21748_x_at         IGL1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INBA         cp0iOCS4CISg_oqAqI           44         206697_s_at         ITGA2B         H300v7nklkZOvQbldU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGC12803         NA           47	-			
Image: Construct of Construction         Construction           30         205110_s_at         FGF13         Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxe,jV7aAXpE           31         223836_at         FGFB2         xmX900n31irhK4CFXE           32         223767_at         GPR84         ok0Fe53OSU4FID1ICQ           33         210321_at         GZMH         rgmXcEkpOlcF9d6l4U           34         206647_at         HBZ         IteivVSVR8WbDmUMBQ           35         213537_at         HLA-DPA1         NFuhMC3eb3pThValQ           36         203290_at         HLA-DQA1         NA           37         209480_at         HLA-DQB1         TXanqXzTU0si0gKnU           38         206697_s_at         HP         fpPOCkkS1WAIIRYIIc           39         215118_s_at         IGJ         HhecR84SAQucRJ7rVE           41         217148_xat         IGLC1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at/206493_at         ITGA2B         H300v7nktkZOvQbtdU           45         212531_at         LON2         WUTbfV7DYUuzYacLk           46         208450_at		211734_s_at	FCER1A	
31         223836_at         FGFBP2         xmX900n31irhK4CFXE           32         223767_at         GPR84         ok0Fe53OSU4FID1ICQ           33         210321_at         GZMH         rgmXcEkpOlcP9d6l4U           34         206647_at         HBZ         IteivVSVR8WbDmUMBQ           35         213537_at         HLA-DPA1         NFtdNMC3eb3pThValQ           36         203290_at         HLA-DQA1         NA           37         209480_at         HLA-DQB1         TfXanqXzTU0Si0gKnU           38         206697_s_at         IGH         NA           39         215118_s_at         IGH         NA           40         212592_at         IGIC1         NA           41         217148_x_at         IGLV1-44         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at         ITGA2B         H300v7nktkZOvQbtdU           45         212531_at         ICN2         WUTbfV7VDYUzYaeLk           46         208450_at         IGA1S2         WT66KHqpCBBqCNF7k           47         222196_at         ICOC34905         NA	29	231093_at	FCRL3	KV7kDSLO4uggquLXB4 ZUclXxUi6VEoBJeRT8 67unrLpPnjv_uzOezU
32       223767_at       GPR84       ok0Fe53OSU4FID1ICQ         33       210321_at       GZMH       rgmXcEkpOIcF9d6l4U         34       206647_at       HBZ       lteivVSVR8WbDmUMBQ         35       213537_at       HLA-DPA1       NFtdNMC3eb3pThValQ         36       203290_at       HLA-DQA1       NA         37       209480_at       HLA-DQB1       TfXanqXzTU0Si0gKnU         38       206697_s_at       HP       fpPOCkkS1WAIIRYIIc         39       215118_s_at       IGH       NA         40       212592_at       IGJ       HhcR84SAQucRJ7rVE         41       217148_x_at       IGLC1       NA         42       234764_x_at       IGLV1-44       NA         43       227140_at       INHBA       cp0ioCS4CISg_oqAqI         44       216956_s_at       ITGA2B       H300v7nktkZ0vQbtdU         45       212531_at       LCN2       WUTbfV7VDYUuzYaeLk         46       208450_at       LGALS2       WT6GkHqpCBBqCNF7k         47       22196_at       LOC28613       NA         48       238717_at       LOC41528       NA         50       202018_s_at       LTF       cQ05fddUoFsfScd65c <tr< td=""><td>30</td><td>205110_s_at</td><td>FGF13</td><td>Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxe.jV7aAXpE</td></tr<>	30	205110_s_at	FGF13	Hd7t51A7ISQ_3qyhSc Hvun37sCEoHuge477c TmCOYpTxe.jV7aAXpE
33210321_atGZMHrgmXcEkpOlcF9d6l4U34206647_atHBZlicivVSVR8WbDmUMBQ35213537_atHLA-DPA1NFtdNMC3eb3pThValQ36203290_atHLA-DQA1NA37209480_atHLA-DQB1TfXanqXzTU0Si0gKnU38206697_s_atHPfpPOCkkS1WAIIRYIIc39215118_s_atIGHNA40212592_atIGJHhecR84SAQucRJ7rVE41217148_x_atIGLC1NA42234764_x_atIGLV1-44NA43227140_atINHBAcp0iOCS4CISg_oqAqI44206494_s_at206493_at 216956_s_atITGA2BH300v7nktkZOvQbtdU45212531_atLCN2WUTbfV7VDYUuzYaeLk46208450_atLGALS2WT6GkkHqpCBBqCNF7k4722216_atLOC289906NA48238717_atLOC728613NA5020018_s_atLTFcQO5fddUoFsfScd65c51244523_atMMD6p_X8jaueM_Xv1yw6k52207329_at231688_atMMP9fi3Hpm4vVouL4FK6FA54203949_at203948_s_atMPOKXq9Q16d7p_cnO4×4k55229510_atMS4A14QqQF0qheQghuCkj.Q0JYKEKJ0rogLIAHvOU	31	223836_at	FGFBP2	xmX900n31irhK4CFXE
A         20647_at         HBZ         licivVSVR8WbDmUMBQ           35         213537_at         HLA-DPA1         NFtdNMC3eb3pThValQ           36         203290_at         HLA-DQA1         NA           37         209480_at         HLA-DQA1         NA           38         206697_s_at         HP         fpPOCkkS1WAIIRYIIc           39         215118_s_at         IGH         NA           40         212592_at         IGJ         HhecR84SAQucRJ7rVE           41         217148_x_at         IGLV1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at 216956_s_at         ITGA2B         H3o0v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGA152         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC28613         NA           48         238717_at         LOC728613         NA           50         202018_s_at         LTF         cQ05fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k	32	223767_at	GPR84	ok0Fe53OSU4FlD1lCQ
35       21357_at       HLA-DPA1       NFtdNMC3eb3pThValQ         36       203290_at       HLA-DQA1       NA         37       209480_at       HLA-DQA1       NA         38       206697_s_at       HP       fpPOCkkS1WAIIRYIIc         39       215118_s_at       IGH       NA         40       212592_at       IGJ       HhecR84SAQucRJ7rVE         41       217148_x_at       IGL1       NA         42       234764_x_at       IGL1       NA         43       227140_at       IGV1-44       NA         44       206494_s_at206493_at 216956_s_at       ITGA2B       H3o0v7nktkZOvQbtdU         45       212531_at       LCN2       WUTbfV7VDYUuzYaeLk         46       208450_at       LGALS2       WT6GkHqpCBBqCNF7k         47       22196_at       LOC389906       NA         48       238717_at       LOC728613       NA         50       202018_s_at       LTF       cQ05fdUoFsfScd65c         51       244523_at       MMD       6p_X8jaueM_XV1yw6k         52       207329_at231688_at       MMP8       fgvcFUrFg7ifFKLk BelT8r_h3KliQoopKI         53       203936_s_at       MMP0       KXq9Q16d7p_cnO4×4k	33	210321_at	GZMH	rgmXcEkpOIcF9d6l4U
And         And           37         209480_at         HLA-DQA1         NA           37         209480_at         HLA-DQB1         TfXanqXzTU0Si0gKnU           38         206697_s_at         HP         fpPOCkkS1WAIIRYIIc           39         215118_s_at         IGH         NA           40         212592_at         IGJ         HhecR84SAQucRJ7rVE           41         217148_x_at         IGLC1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at         ITGA2B         H300v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7DYUuzYaeLk           46         208450_at         LOC481528         NA           47         222196_at         LOC481528         NA           48         238717_at         LOC41528         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at231688_at         MMP8         fgvcFUrFTg7ifFkLk BelT8r_h3KIiQoopKI           53 <t< td=""><td>34</td><td>206647_at</td><td>HBZ</td><td>lteivVSVR8WbDmUMBQ</td></t<>	34	206647_at	HBZ	lteivVSVR8WbDmUMBQ
37         209480_at         HLA-DBI         TIXanqXzTU0Si0gKnU           38         206697_s_at         HP         fpPOCkkS1WAIIRYIIc           39         215118_s_at         IGH         NA           40         212592_at         IGJ         HhecR84SAQucRJ7rVE           41         217148_x_at         IGLC1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at206493_at         ITGA2B         H300v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC41528         NA           48         238717_at         LOC41528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         MD         6p_X8jaueM_Xv1yw6k           51         244523_at         MMP8         fgvcFUrFTg7ifFKLk BdT8r_h3KliQoopKI           52         207329_at231688_at         MMP9         fn3Hpm4vVouL4FK6FA           54         203949_at203948_s_at         MPO <td>35</td> <td>213537_at</td> <td>HLA-DPA1</td> <td>NFtdNMC3eb3pThValQ</td>	35	213537_at	HLA-DPA1	NFtdNMC3eb3pThValQ
38         206697_s_at         HP         fpPOckkS1WAIIRYIIc           39         215118_s_at         IGH         NA           40         212592_at         IGJ         HhecR4SAQucRJ7rVE           41         217148_x_at         IGL0         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at         ITGA2B         H300v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC441528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fdUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP9         fn3Hpm4vVouL4FK6FA           53         20394_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghu	36	203290_at	HLA-DQA1	NA
39         215118_s_att         IGH         NA           40         212592_at         IGJ         HhecR84SAQucRJ7rVE           41         21748_x_at         IGLC1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at206493_at 216956_s_at         ITGA2B         H3o0v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC441528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         ITF         cQ05fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KliQoopKI           53         20394_s_at         MPO         KXq9Q16d7p_cnO4×4k           54         20394_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A	37	209480_at	HLA-DQB1	TfXanqXzTU0Si0gKnU
40         212592_at         IGJ         HhecR84SAQucRJ7rVE           41         217148_x_at         IGLC1         NA           42         234764_x_at         IGLV1-44         NA           43         227140_at         INHBA         cp0iOCS4CISg_oqAqI           44         206494_s_at 206493_at 216956_s_at         ITGA2B         H3o0v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUu2YaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC441528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         ITF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFg7ifFKt.k BelT8r_h3KIiQoopKI           53         20394_s_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLIAHvOU <td>38</td> <td>206697_s_at</td> <td>HP</td> <td>fpPOCkkS1WAIIRYIIc</td>	38	206697_s_at	HP	fpPOCkkS1WAIIRYIIc
41       217148_x_at       IGLC1       NA         42       234764_x_at       IGLV1-44       NA         43       227140_at       INHBA       cp0iOCS4CISg_oqAqI         44       206494_s_at 206493_at 216956_s_at       ITGA2B       H3o0v7nktkZOvQbtdU         45       212531_at       LCN2       WUTbfV7VDYUuzYaeLk         46       208450_at       LGALS2       WT6GkkHqpCBBqCNF7k         47       222196_at       LOC4389906       NA         48       238717_at       LOC41528       NA         49       1569110_x_at       LOC728613       NA         50       202018_s_at       LTF       cQO5fddUoFsfScd65c         51       244523_at       MMD       6p_X8jaueM_Xv1yw6k         52       207329_at 231688_at       MMP8       fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI         53       203936_s_at       MMP       fn3Hpm4vVouL4FK6FA         54       203949_at 203948_s_at       MPO       KXq9Q16d7p_cnO4×4k         55       229510_at       MS4A14       QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU	39	215118_s_at	IGH	NA
42       234764_x_at       IGLV1-44       NA         43       227140_at       INHBA       cp0iOCS4CISg_oqAqI         44       206494_s_at 206493_at 216956_s_at       ITGA2B       H300v7nktkZOvQbtdU         45       212531_at       ICN2       WUTbfV7VDYUuzYaeLk         46       208450_at       IGALS2       WT6GkkHqpCBBqCNF7k         47       222196_at       LOC389906       NA         48       238717_at       LOC41528       NA         49       1569110_x_at       LOC728613       NA         50       202018_s_at       ITF       cQO5fddUoFsfScd65c         51       244523_at       MMD       6p_X8jaueM_Xv1yw6k         52       207329_at 231688_at       MMP8       fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI         53       203946_s_at       MPO       KXq9Q16d7p_cnO4×4k         54       203948_s_at       MPO       KXq9Q16d7p_cnQ4×4k	40	212592_at	IGJ	HhecR84SAQucRJ7rVE
42234764_x_atIGLV1-44NA43227140_atINHBAcp0iOCS4CISg_oqAqI44206494_s_at 206493_at 216956_s_atITGA2BH300v7nktkZOvQbtdU45212531_atLCN2WUTbfV7VDYUuzYaeLk46208450_atLGALS2WT6GkkHqpCBBqCNF7k47222196_atLOC389906NA48238717_atLOC441528NA491569110_x_atLOC728613NA50202018_s_atLTFcQO5fddUoFsfScd65c51244523_atMMD6p_X8jaueM_Xv1yw6k52207329_at 231688_atMMP8fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI53203936_s_atMPOKXq9Q16d7p_cnO4×4k55229510_atMS4A14QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU	41	217148_x_at	IGLC1	NA
43227140_atINHBAcp0iOCS4CISg_oqAqI44206494_s_at 206493_atITGA2BH300v7nktkZOvQbtdU45212531_atLCN2WUTbfV7VDYUu2YaeLk46208450_atLGALS2WT6GkkHqpCBBqCNF7k47222196_atLOC389906NA48238717_atLOC441528NA491569110_x_atLOC728613NA50202018_s_atLTFcQO5fddUoFsfScd65c51244523_atMMD6p_X8jaueM_Xv1yw6k52207329_at 231688_atMMP8fgvcFUrFrg7ifFKt.k BelT8r_h3KIiQoopKI54203946_s_atMPOKXq9Q16d7p_cnO4×4k55229510_atMS4A14QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				NA
44         206494_s_at 206493_at 216956_s_at         ITGA2B         H3o0v7nktkZOvQbtdU           45         212531_at         LCN2         WUTbfV7VDYUuzYaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC41528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI           53         203946_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
45         212531_at         LCN2         WUTbfV7VDYUu2YaeLk           46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC441528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI           53         203946_s_at         MPO         KXq9Q16d7p_cnO4×4k           54         202510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU		206494_s_at 206493_at		
46         208450_at         LGALS2         WT6GkkHqpCBBqCNF7k           47         222196_at         LOC389906         NA           48         238717_at         LOC41528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFg7ifFKt.k BelT8r_h3KIiQoopKI           53         203936_s_at         MMP         fn3Hpm4vVouL4FK6FA           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU	45		LCN2	WUTbfV7VDYUuzYaeLk
47       222196_at       LOC389906       NA         48       238717_at       LOC441528       NA         49       1569110_x_at       LOC728613       NA         50       202018_s_at       LTF       cQO5fddUoFsfScd65c         51       244523_at       MMD       6p_X8jaueM_Xv1yw6k         52       207329_at 231688_at       MMP8       fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI         53       203936_s_at       MMP       fn3Hpm4vVouL4FK6FA         54       203949_at 203948_s_at       MPO       KXq9Q16d7p_cnO4×4k         55       229510_at       MS4A14       QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
48         238717_at         LOC441528         NA           49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI           53         203936_s_at         MMP9         fn3Hpm4vVouL4FK6FA           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
49         1569110_x_at         LOC728613         NA           50         202018_s_at         LTF         cQO5fddUoFsfScd65c           51         244523_at         MMD         6p_X8jaueM_Xv1yw6k           52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI           53         203936_s_at         MMP9         fn3Hpm4vVouL4FK6FA           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
Image: Second				
51       244523_at       MMD       6p_X8jaueM_Xv1yw6k         52       207329_at 231688_at       MMP8       fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI         53       203936_s_at       MMP9       fn3Hpm4vVouL4FK6FA         54       203949_at 203948_s_at       MPO       KXq9Q16d7p_cnO4×4k         55       229510_at       MS4A14       QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
52         207329_at 231688_at         MMP8         fgvcFUrFTg7ifFKt.k BelT8r_h3KIiQoopKI           53         203936_s_at         MMP9         fn3Hpm4vVouL4FK6FA           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
53         203936_s_at         MMP9         fn3Hpm4vVouL4FK6FA           54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
54         203949_at 203948_s_at         MPO         KXq9Q16d7p_cnO4×4k           55         229510_at         MS4A14         QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
55 229510_at MS4A14 QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU				
Continued			MS4A14	QqQF0qheQ0ghuCkj.Q 0JYKEkJ0rogLlAHvOU
	Con	tinued		

Nº	Affymetrix IDs	Gene Symbol	Illumina IDs	
56	210254_at 1554892_a_at	MS4A3	lKdKj.P0uB56B0ROV4 Qen_rt.er1_QxUxR9Q B3q9A94B7R88Xs4E6k	
57	201058_s_at	MYL9	Tbs1URA5CdFCtV3S1U 3CBVEhgxeipOOJilWo	
58	209290_s_at	NFIB	BNHPXrzdFBgpyimm0g QUlzHnJJ50×5LQ8egk	
59	221690_s_at	NLRP2	EFIl20d6F6tINX6rcs	
60	206343_s_at	NRG1	ruNF5QODCEECIJIKkI EX0VFaBXiuIGVC0kHQ rcTUUeoQlN_ wDuaIKI 9QpESNQOTkjUnNJB00 uX15cu4f_VUIuXoST0 ZZImuuNioCuRWSaaSQ	
61	212768_s_at	OLFM4	rgjyBSHxwUPUVVFBVc c70LXLcyj6S.A5.HVU	
62	210004_at	OLR1	9V0C7RDnXXjh11UgBQ	
63	205040_at	ORM1	fG6ilCJP2dH5410qEU	
64	227474_at	PAX8-AS1	NA	
65	225207_at	PDK4	ESC1yEuE.fDrqLUnTk	
66	207384_at	PGLYRP1	3mxHd1KQUncUXTUg_k	
67	41469_at 203691_at	PI3	NeHlSg0ILnuCnfmo6U	
68	207341_at	PRTN3	EX243qjuUVl.1eH30Y	
69	211748_x_at 212187_x_at	PTGDS	HXlUBYwuThoEModVKk	
70	220570_at	RETN	Qz8qQwkk_l6LlIm0XU	
71	206851_at	RNASE3	9aLI9auX8dR7hdMDUo	
72	213566_at	RNASE6	Te4VV0giY1VcQvr17E	
73	214539_at	SERPINB10	f0LQV4ks6o4uOX0lAk	
74	1553177_at	SH2D1B	0TlE1O9_rTf.5×9Oi0	
75	219519_s_at	SIGLEC1	iiFGSdPjXjklE7iF0E	
76	220000_at	SIGLEC5	Q13VUdxtx69ahqiNUw oJC4o.lSL0tenoolEk	
77	203021_at	SLPI	No174RVAVBCigl6guU	
78	202286_s_at	TACSTD2	WihIT5WgHS3Pz30n5U	
79	205513_at	TCN1	i4uimBR4lCiesvG_1k	
80	209651_at	TGFB1I1	EJXHIJXn14J32nhJWc iJVfHqoq1_Q9SYNopQ	
81	219410_at	TMEM45A	6qievf0j6P7Xs1VS6I r_iBJ6cKOHcLse.k.U	
82	206641_at	TNFRSF17	iWCth3hT5.UdUnOigo	
83	218876_at	TPPP3	ENZUufqUJFe6TUJ1Xo QLe5eyXThVBUlUpOnA	
84	231122_x_at	ZDHHC19	69eJXi6CX97l_V.IR0	

#### Table 3. Gene signature of 95 transcripts (probesets) corresponding to 84 genes.

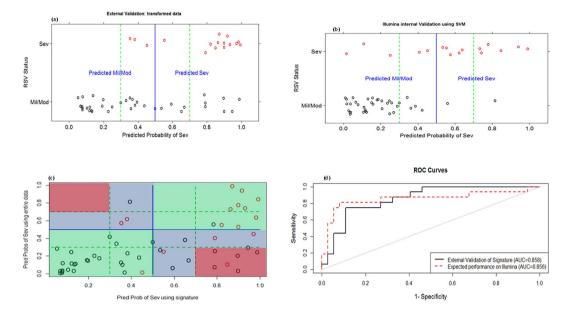
.....

compared to our signature. Nonetheless, Fig. 5c illustrates a large agreement between the predicted probabilities of the two models, while Fig. 5d clearly reveals that both models are alike as demonstrated by the AUCs of 0.858 and 0.856 for our signature and the unrestricted model respectively. To assess the concordance of the expression patterns of our signature on both datasets (Affymetrix and Illumina), we plotted the  $log_2$  fold changes of the common 75 genes as shown on Fig. 6. From this figure, one clearly sees that there is a huge concordance in the direction of expressions across datasets. Where there are slight differences, these differences are not significant as shown by a non-significant p-value in at least one of the datasets.

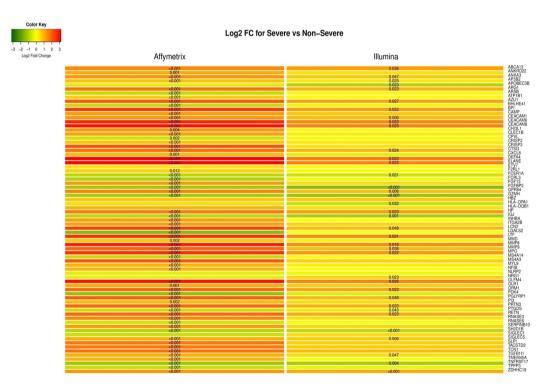
#### Discussion

RSV infection in infants may cause life-threatening disease. No vaccine is yet available and triage of patients is challenging since RSV infections may rapidly progress to severe disease. No reliable prognostic model to predict which RSV patient will not progress to severe disease and could be safely send home is available either. Thus, clinical care is symptom-based and a significant proportion of RSV infected infants is hospitalized for observation purposes. We have provided an 84 gene signature that discriminates hospitalized infants with less severe RSV infection from those infants with severe RSV disease. The identified signature yielded a LOOCV AUC of 0.966 on the experimental data and was independently validated with an AUC of 0.858 and might serve as a basis to develop a prognostic test for clinical management of RSV disease.

In line with epidemiological observations<sup>38</sup> and observations of Mejias *et al.*<sup>17</sup>, we showed the confounding effects of age and sex on gene expression-severity relationship for RSV disease. Studies in any RSV patient cohort with a naturally occurring "skewed" distribution of age and sex can be standardized for these parameters. By adjusting for an age-by-sex effect in our analyses, we obtained age-by-sex independent results which can be effectively applied to any patient(s). The high performance of our signature on the age and sex matched validation data signifies age-by-sex independence and robustness of this signature. Fewer co-infections were observed in severe patients (Table 1). A similar trend has been described previously<sup>39</sup>. In our cohort study we did not take into account co-infections since no consistent association between the occurrence or absence of co-infections with RSV disease severity have been reported<sup>39–43</sup>. Furthermore, we aimed at the identification of a gene signature in a natural "real-life" cohort of patients not stratified according to age or occurrence of co-infections.



**Figure 5.** Predicted probabilities of being severe from the validation data against true RSV status using; our diagnostic signature (**a**) and LOOCV on unrestricted data (**b**). (**c**) illustrates the agreement of the predictions from both models, green regions are perfect agreement, blue are disagreements at a 50% cutoff and red are disagreements at a 30–70% uncertainty band. Finally, (**d**) presents the ROC curves and AUC from both models illustrating similar AUC values.



**Figure 6.** Log<sub>2</sub> Fold change between Severe vs Non-Severe infants for 75 common genes in Affymetrix and Illumina datasets. Red represent up-regulation while green represents a down-regulation and the significant FDR adjusted p-values are placed in the cells. As one can clearly see, there is a huge overlap in the direction expressions across datasets. Where there are slight differences, these differences are not significant as shown by a non-significant p-value in at least one of the datasets.

We hypothesized that changes in blood cell type distribution and/or mRNA expression changes of the circulating cells collected from peripheral blood reflect local lung host response characteristics that associate with disease severity. PCA and DE analysis indeed revealed significant changes in the transcriptome profile of whole blood. Gene set analysis further shows that relevant processes are monitored including the activation, migration and tissue infiltration of lymphocytes, granulocytes and neutrophils. Individual DE genes in severe RSV disease revealed overexpression of the neutrophil associated genes MMP8 and MMP9, which have previously been related to severe RSV disease<sup>44</sup>. ARG1 and CHI3L1 that have been linked to alternatively activated macrophages in a mouse model for vaccine enhanced RSV disease<sup>16</sup> were also found to be strongly up-regulated. This suggests that the collected blood transcriptome profiles indeed reflect local lung host response.

In our class prediction analysis, three functions were evaluated and the best was chosen. While it has been pointed by<sup>45-48</sup> that selecting a minimal-error classifier leads to selection bias that should be corrected, the literature does not stipulate a selection bias when using calibration and refinement scores as evaluation measures. Nevertheless, we employed the nested cross-validation correction of selection bias<sup>46</sup> in our model building procedure by splitting our experimental data into learning and test sets with an inner loop split on the learning set for parameter(s) optimization. Though found to contain high variance, we utilized leave-one-out cross-validation for the test set because it yields approximately an unbiased estimate of the true (expected) prediction error<sup>49</sup> and because we were interested in the individual sample predicted probability of severe and not entirely on the expected predicted error. Nevertheless, where we were interested in the expected predicted error, as in the optimization of parameters, we utilized five-fold cross-validation as recommended by Breiman and Spector<sup>50</sup>. To validate the identified signature, an independent dataset generated on a different platform was used. Despite (i) the several sources of variability between our experimental data and the validation data that stem from - but not limited to - array platforms and different clinical cutoffs of RSV severity statuses, (ii) different time of profiling, 1-3 days after hospitalization and (iii) loss of information due to a reduction in signature because of no corresponding transcripts on Illumina platform and the aggregation of multiple transcripts to genes, our signature yielded an AUC of 0.858 that was comparable to accuracy (AUC of 0.856) when using the Illumina data (validation set) as experimental set. Cross-platform validation is rare due to lack of guidance on how this can be done reliably. We presented a cross-platform validation procedure.

The RSV patients enrolled in the study displayed varying disease severities but were all hospitalized thus representing a severe disease enriched subset of RSV infected infants. The patients enrolled however also represent a natural cohort of patients including a significant number of patients that eventually did not require extensive medical care and could have been discharged home. Since the blood samples were collected soon after hospital admission, the generated blood transcriptomes and the derived gene signature may serve as a basis for the development of a novel genomic tool to support clinical management of RSV disease including triage of patients presenting at the hospital provided that a rapid (real time) gene test can be developed. Larger transcriptome data sets are however required to construct predictive models that may also allow for discriminating mild from moderate and moderate from severe cases. Ultimately, one would like to extend the RSV biomarker program to earlier time point samples (e.g. obtained when visiting a general practitioner) and to samples collected from patients infected by other (respiratory) infectious agents or pathological conditions (comorbidities) in order to identify specific respiratory viral prognostic biomarkers. To this end a novel gene signature have to be developed using a much larger early blood sample cohort. The current results support the development of diagnostic tests for personalized medicine that not only provide information on the causative infectious agent, but also about the disease severity that may be expected.

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#### **Author Contributions**

V.L.J. performed data analysis and wrote the manuscript, I.M.L.A. collected the data and contributed in writing the manuscript, H.J.v.d.H. contributed in data analysis and writing the manuscript, J.J. contributed in data collection, F.Z. performed gene expression profiling, A.Z. contributed in data analysis, E.S. contributed in data collection, M.A.B. contributed in data analysis, H.K.B. contributed in data collection, W.F.J.v.I.J. performed gene expression profiling, M.I.d.J. contributed in data collection, P.L.F. contributed in data collection, R.d.G. designed the study and contributed in data collection, A.D.M.E.O. designed the study and contributed in data analysis, M.J.E. performed data analysis and contributed in writing the manuscript, G.F. collected the data and contributed in writing the manuscript, and A.C.A. designed the study, performed gene expression profiling, contributed in data analysis and wrote the manuscript.

#### Additional Information

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