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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^{1,2}. In infants, RSV is the leading cause of lower respiratory tract infections (LRTI) and is responsible for 80% of acute bronchiolitis cases³. 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^{4–7}. 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^{8,9}. 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 smoking¹⁰. 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^{11–14}. For RSV infections, this has supported the characterization of vaccine-induced skewed host responses upon infection^{15,16}. Meijas *et al.*¹⁷ recently used

¹Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands. ²Department of Viroscience, Erasmus Medical Center, Rotterdam, The Netherlands. ³Department of Pediatrics, Laboratory of Pediatric Infectious Diseases, Radboud Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, The Netherlands. ⁴Center for Biomics, Erasmus Medical Center, Rotterdam, The Netherlands. ⁵Department of Pediatrics, Erasmus Medical Center, Rotterdam, The Netherlands. ⁶Research Institute for Infectious Diseases and Zoonoses, Veterinary University Hannover, Germany. ^{*}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 (TempusTM, 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 described¹⁸. 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 3.1.2¹⁹ and Bioconductor²⁰. Upon initial quality control and VSN normalization (to render samples comparable), probeset (a combination of multiple probes) summarization was performed by median polish^{21,22}. 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*²³. Additionally, we assessed confounding effects of clinical parameters age and sex on gene expression–severity relationship using "biasograms"²⁴.

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 models²⁵ implemented in the R package *limma*²⁶. Details of the models are found in supplementary material. We controlled for multiple testing via false discovery rate (FDR) using a Benjamini and Hochberg procedure²⁷. 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 predictions²⁸. 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)³¹, shrunken centroids discriminant analysis (SCDA)³² and random forest (RF)³³.

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 ₂ (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*³⁴, *e1071*³⁵, *pamr*³⁶ and *randomForest*³⁷ 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 severity³⁸. 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.*¹⁷ 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

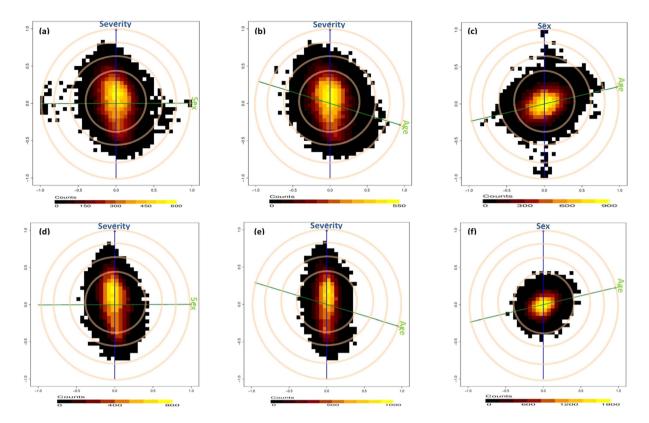
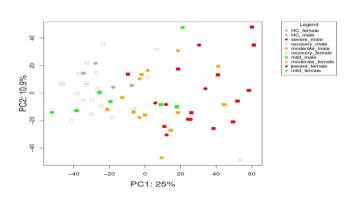
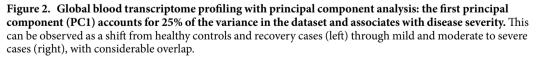


Figure 1. Confounding effect of Sex, Age and Age by Sex on gene expression-severity relationship, before. (**a**,**b**,**c**) and after: (**d**,**e**,**f**), an age by sex standardization. The blue and green lines represent the clinical variables, the cosine of the angle between the lines represents 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.

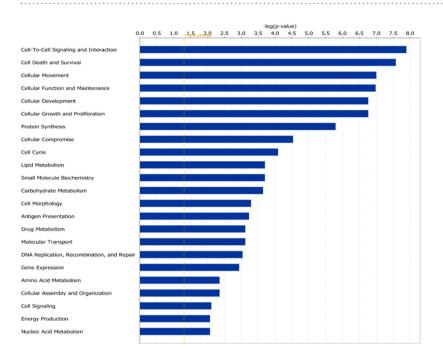


Figure 3. Ingenuity pathway analysis (IPA) Molecular and Cellular functions gene set analysis for severe vs healthy control contrast.

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^{29,30}. 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

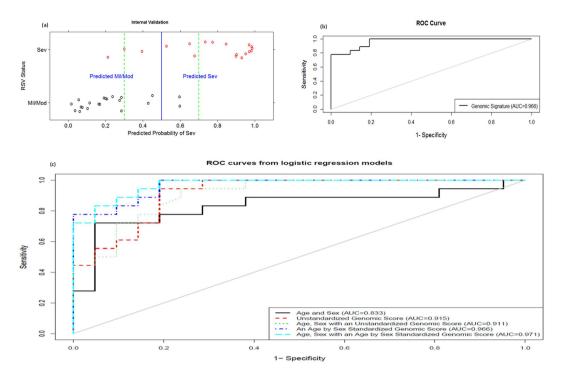


Figure 4. Internal validation of gene signature. (**a**) samples' predicted probabilities of being severe. (**b**) shows the ROC curve and the AUC for predicted probabilities. The AUC value of approximately 1 indicates how accurate our signature performs on this internal validation set. (**c**) shows 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.*¹⁷ 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 |
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| 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.

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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 observations³⁸ and observations of Mejias *et al.*¹⁷, 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 previously³⁹. 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^{39–43}. 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.

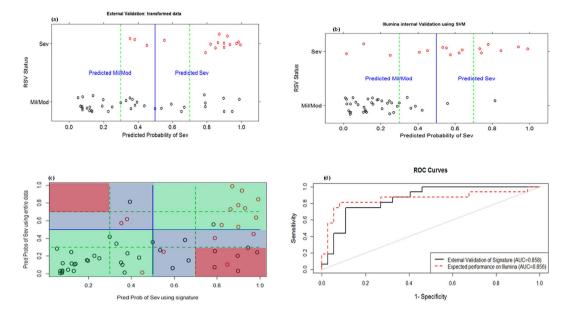


Figure 5. Predicted probabilities of being severe from the validation data against true RSV status using; our diagnostic signature (**a**) and LOOCV on unrestricted data (**b**). (**c**) illustrates the agreement of the predictions from both models, green regions are perfect agreement, blue are disagreements 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.

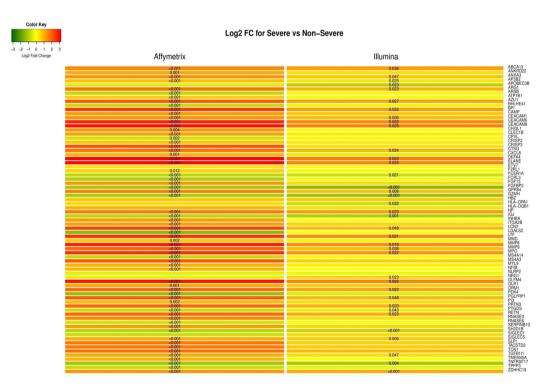


Figure 6. Log₂ Fold change between Severe vs Non-Severe infants for 75 common genes in Affymetrix and Illumina datasets. Red represent up-regulation while green represents a down-regulation and the significant FDR adjusted p-values are placed in the cells. As one can clearly see, there is a huge overlap 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 disease⁴⁴. ARG1 and CHI3L1 that have been linked to alternatively activated macrophages in a mouse model for vaccine enhanced RSV disease¹⁶ 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 by⁴⁵⁻⁴⁸ 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 bias⁴⁶ 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 error⁴⁹ 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 Spector⁵⁰. 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.

References

- 1. Simoes, E. a. Respiratory syncytial virus infection. Lancet 354, 847-852 (1999).
- Falsey, A. R. et al. Respiratory Syncytial Virus and Other Respiratory Viral Infections in Older Adults With Moderate to Severe Influenza-like Illness. J. Infect. Dis. 1–9 doi: 10.1093/infdis/jit839 (2014).
- 3. Bush, A. & Thomson, A. H. Acute bronchiolitis. BMJ 335, 1037-1041 (2007).
- 4. Nair, H. *et al.* Global and regional burden of hospital admissions for severe acute lower respiratory infections in young children in 2010: a systematic analysis. *Lancet* **381**, 1380–1390 (2013).
- 5. Hall, C. B. et al. The burden of respiratory syncytial virus infection in young children. N Engl J Med 360, 588-598 (2009).
- Stockman, L. J., Curns, A. T., Anderson, L. J. & Fischer-Langley, G. Respiratory Syncytial Virus-associated Hospitalizations Among Infants and Young Children in the United States, 1997–2006. *Pediatr. Infect. Dis. J.* 31, 5–9 (2012).
- 7. Jain, S. et al. Community-Acquired Pneumonia Requiring Hospitalization among US Children. N. Engl. J. Med. **372**, 835–845 (2015).
- 8. Adams, M. & Doull, I. Management of bronchiolitis. Paediatr. Child Health (Oxford). 19, 266-270 (2009).
- 9. Meissner, H. C. Viral Bronchiolitis in Children. N. Engl. J. Med. 374, 62–72 (2016).
- Tregoning, J. S. & Schwarze, J. Respiratory viral infections in infants: causes, clinical symptoms, virology, and immunology. *Clin. Microbiol. Rev.* 23, 74–98 (2010).
- Pulendran, B., Oh, J. Z., Nakaya, H. I., Ravindran, R. & Kazmin, D. a. Immunity to viruses: learning from successful human vaccines. Immunol. Rev. 255, 243–255 (2013).
- Sekaly, R. & Pulendran, B. Systems biology in understanding HIV pathogenesis and guiding vaccine development. Curr. Opin. HIV AIDS 1–3 doi: 10.1097/COH.0b013e32834e0667 (2011).
- van de Weg, C. a. M. et al. Time since Onset of Disease and Individual Clinical Markers Associate with Transcriptional Changes in Uncomplicated Dengue. PLoS Negl. Trop. Dis. 9, e0003522 (2015).
- Zhai, Y. et al. Host Transcriptional Response to Influenza and Other Acute Respiratory Viral Infections A Prospective Cohort Study. PLOS Pathog. 11, e1004869 (2015).
- 15. Schuurhof, A. *et al.* Gene expression differences in lungs of mice during secondary immune responses to respiratory syncytial virus infection. *J. Virol.* **84**, 9584–9594 (2010).
- van Diepen, A. *et al.* Host Proteome Correlates of Vaccine-Mediated Enhanced Disease in a Mouse Model of Respiratory Syncytial Virus Infection. J. Virol. JVI.03630–14 doi: 10.1128/JVI.03630-14 (2015).
- Mejias, A. *et al.* Whole Blood Gene Expression Profiles to Assess Pathogenesis and Disease Severity in Infants with Respiratory Syncytial Virus Infection. *PLoS Med.* 10, e1001549 (2013).
- Templeton, K. E., Scheltinga, S. a, Beersma, M. F. C., Kroes, A. C. M. & Claas, E. C. J. Rapid and sensitive method using multiplex real-time PCR for diagnosis of infections by influenza a and influenza B viruses, respiratory syncytial virus, and parainfluenza viruses 1, 2, 3, and 4. J Clin Microbiol 42, 1564–1569 (2004).

- 19. R. Core Team. R: A language and environment for statistical computing. http://www.R-project.org/ (2014).
- Gentleman, R. C. et al. Bioconductor: open software development for computational biology and bioinformatics. Genome Biol 5, R80 (2004).
- 21. Gautier, L., Cope, L., Bolstad, B. M. & Irizarry, R. A. Affy Analysis of Affymetrix GeneChip data at the probe level. *Bioinformatics* 20, 307–315 (2004).
- 22. Huber, W., von Heydebreck, A., Sültmann, H., Poustka, A. & Vingron, M. Variance stabilization applied to microarray data calibration and to the quantification of differential expression. *Bioinformatics* **18** Suppl 1, S96–S104 (2002).
- Johnson, W. E., Li, C. & Rabinovic, A. Adjusting batch effects in microarray expression data using empirical Bayes methods. Biostatistics, doi: 10.1093/biostatistics/kxj037 (2007).
- Krzystanek, M., Szallasi, Z. & Eklund, A. C. Biasogram: Visualization of Confounding Technical Bias in Gene Expression Data. PLoS One doi: 10.1371/journal.pone.0061872 (2013).
- 25. Smyth, G. K. Linear models and empirical bayes methods for assessing differential expression in microarray experiments. *Stat Appl Genet Mol Biol.* **3**, Article 3 (2004).
- Ritchie, M. E. et al. limma powers differential expression analyses for RNA-sequencing and microarray studies. 1–13 doi: 10.1093/ nar/gkv007 (2015).
- 27. Benjamini, Y. & Hochberg, Y. Controlling the false discovery rate: a practical and powerful approach to multiple testing. J. R. Stat. Soc. Ser. 57, 289–300 (1995).
- 28. Pepe, M. S. Evaluating technologies for classification and prediction in medicine. Stat. Med. 24, 3687–3696 (2005).
- Jong, V. L., Novianti, P. W., Roes, K. C. B. & Eijkemans, M. J. C. Exploring homogeneity of correlation structures of gene expression datasets within and between etiological disease categories. *Stat. Appl. Genet. Mol. Biol.* doi: 10.1515/sagmb-2014-0003 (2014).
- 30. Kim, K. I. & Simon, R. Probabilistic classifiers with high-dimensional data. *Biostatistics* doi: 10.1093/biostatistics/kxq069 (2011).
- 31. Bernhard Schölkopf & Alexander J. Smola. Learning with Kernels. (MIT Press, 2001).
- Tibshirani, R., Hastie, T., Narasimhan, B. & Chu, G. Diagnosis of multiple cancer types by shrunken centroids of gene expression. Proc. Natl. Acad. Sci. USA doi: 10.1073/pnas.082099299 (2002).
- 33. Breiman, L. Random forests. Mach. Learn. 5-32 doi: 10.1023/A:1010933404324 (2001).
- Slawski, M., Daumer, M. & Boulesteix, A.-L. CMA: a comprehensive Bioconductor package for supervised classification with high dimensional data. BMC Bioinformatics doi: 10.1186/1471-2105-9-439 (2008).
- 35. Meyer, D., Dimitriadou, E., Hornik, K., Weingessel, A. & Leisch, F. Misc Functions of the Department of Statistics (e1071). *R Packag. version 1.6-4* (2014).
- 36. Hastie, T., Tibshirani, R., Narasimhan, B. & Chu, G. pamr: Pam: prediction analysis for microarrays. R Packag. version 1.55 (2014).
- 37. Liaw, A. & Wiener, M. Classification and Regression by randomForest. *R News* 2, 18–22 (2002).
- Berger, T. M., Aebi, C., Duppenthaler, a. & Stocker, M. Prospective population-based study of rsv-related intermediate care and intensive care unit admissions in Switzerland over a 4-year period (2001–2005). *Infection* 37, 109–116 (2009).
- Brand, H. K. et al. Infection with multiple viruses is not associated with increased disease severity in children with bronchiolitis. Pediatr. Pulmonol. 47, 393–400 (2012).
- Hasegawa, K. *et al.* Multicenter study of viral etiology and relapse in hospitalized children with bronchiolitis. *Pediatr. Infect. Dis. J.* 33, 809–813 (2014).
- Mansbach, J. M. et al. Prospective multicenter study of the viral etiology of bronchiolitis in the emergency department. Acad. Emerg. Med. 15, 111–118 (2008).
- 42. Chorazy, M. L. et al. Polymicrobial acute respiratory infections in a hospital-based pediatric population. Pediatr. Infect. Dis. J. 32, 460–466 (2013).
- Martin, E. T., Kuypers, J., Wald, A.& Englund, J. A.Multiple versus single virus respiratory infections: viral load and clinical disease severity in hospitalized children. *Influenza Other Respi. Viruses* 6, 71–77 (2012).
- Brand, K. et al. Use of MMP-8 and MMP-9 to Assess Disease Severity in Children With Viral Lower Respiratory Tract Infections. J. Med. Virol. 84, 1471–1480 (2012).
- 45. Varma, S. & Simon, R. Bias in error estimation when using cross-validation for model selection. BMC Bioinformatics 7, 91 (2006).
- Tibshirani, R. J. & Tibshirani, R. A bias correction for the minimum error rate in cross-validation. *The Annals of Applied Statistics* 3, 822–829 (2009).
- Bernau, C., Augustin, T. & Boulesteix, A. L. Correcting the Optimal Resampling-Based Error Rate by Estimating the Error Rate of Wrapper Algorithms. *Biometrics* 69, 693–702 (2013).
- Ding, Y. et al. Bias correction for selecting the minimal-error classifier from many machine learning models. Bioinformatics btu520– (2014).
- 49. Hastie, T., Tibshirani, R. & Friedman, J. The Elements of Statistical Learning: Data Mining, Inference, and Prediction. (Springer, 2009).
- 50. Breiman, L. & Spector, P. Submodel Selection and Evaluation in Regression. The X-Random Case. Int. Stat. Rev. 60, 291-319 (1992).

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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

Supplementary information accompanies this paper at http://www.nature.com/srep

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