Key viral immune genes and pathways identify elite athletes with URS

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ABSTRACT

Purpose: *Habitual intense exercise may increase the incidence of upper respiratory symptoms (URS) in elite athletes. This study investigated whether immune gene expression could identify gene markers that discriminate athletes with a higher prevalence of URS.*
Methods: *This cross-sectional analysis of elite Australian athletes from various sports investigated whether athletes retrospectively reporting URS for two days or more in a month (n=38), had an altered immune gene expression profile compared with asymptomatic athletes (n=33). Peripheral blood samples were collected during Olympic selection events with corresponding URS data collected for the one-month period before sampling. Digital immune gene expression analysis was undertaken using the NanoString PanCancer Immune Profiling panel.*
Results: *Fifty immune genes were differentially expressed between the groups ($p<0.05$) and approximately 78% of these genes were more highly expressed in athletes reporting URS. Many of these genes were interferon-stimulated genes or genes involved in the Jak/Stat signalling pathway. Only interferon alpha inducible protein 27 (IFI27), an interferon stimulated gene involved in viral response, remained significantly higher in athletes reporting URS (log^2 fold-difference=2.49, odds ratio 1.02 per unit increase; $p<0.01$) post-adjustment and discriminated athletes reporting URS from asymptomatic athletes with 78% accuracy.*
Conclusion: *Expression of IFI27 could differentiate athletes reporting URS from asymptomatic athletes, a gene that is upregulated in the immune response to viral infection. Upregulation of viral signalling pathways provides novel information on the potential aetiology of URS in elite Olympic athletes.*

Key words: NanoString, elite athletes, digital immune gene expression, respiratory illness

INTRODUCTION

The chronic effects of habitual exercise on the immune system in elite athletes are well documented (43). Habitual, intense exercise can modulate various aspects of immune function associated with an increase in upper respiratory symptoms (URS), which can have a negative impact on sporting performance in elite athletes (14, 15, 32, 34). Preventing URS is a high priority for athletes and coaches underpinning extensive investigation for predictive biomarkers that indicate an increased risk of URS (7, 15, 17).

An increasingly common approach to enhance the understanding of immune regulation in disease is through multiparametric immune profiling, such as immune gene expression analysis (24, 36). Studying immune gene expression provides additional insight beyond simple phenotypic measurement of individual immune parameters as indicators of immune status. This approach accounts for the complex interaction between a diffuse biological network comprising a multitude of cells and molecules (23). Gene expression analysis has been utilised in exercise immunology to provide a deeper understanding of the immune-regulatory networks

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activated by acute exercise (29). Preliminary studies indicate changes in immune gene expression that might increase the risk of URS. In a study of marathon runners, increased expression of genes relating to a T-helper 2 (Th2) anti-inflammatory immune status was reported one week post-race (45). In endurance runners, a post-event reduction in toll-like receptor (TLR) transcripts from dendritic cell fractions isolated from whole blood has been reported (27). While these studies focus on the effects of acute exercise they provide evidence for exercise-induced immune regulation in support of the open-window theory that proposes a bout of intense exercise induces a transient period of immunosuppression lasting between three and 72 h (28). With regards to habitual exercise training, regular bouts of intense exercise likely act in a cumulative manner to induce a chronic anti-inflammatory immune phenotype (37, 42) that could compromise the ability of the immune system to prevent infection and viral re-activation (42).

URS are the most common illness in elite athletes and are the most common presentation to medical professionals during elite sporting events, such as the Olympic Games(11). While reports are mixed, illness during competition negatively impacts competitive performance (13, 33). Investigations of the etiology of URS in elite athletes during competition report a mix of viral, bacterial, allergic and airway irritation as key factors underpinning illness symptoms (15). Clearer identification of the basis of URS in athletes will inform strategies to reduce the risk of illness. To date, no study has examined the immune gene expression profiles of elite athletes reporting URS with reference to asymptomatic athletes. Characterising immune status in association with self-reported URS may provide key information on the inflammatory basis of disease and inform athlete management and treatment strategies to reduce illness negatively impacting athletic performance. A recognised limitation in elite athlete research is cohort size. We were able to compare URS data with immune gene expression in 71 athletes selected for a summer Olympic Games. The aim of this study was to determine whether immune gene expression profile of peripheral blood could differentiate athletes reporting URS for two days or more during the month prior to Olympic selection, from asymptomatic athletes.

METHODS

Design and participants

A cross-sectional design was employed to examine the prevalence of URS in Australian Olympic athletes and determine whether URS is associated with patterns of immune gene expression. Questionnaire and sample collection were undertaken during Olympic selection events that occurred over a three-month period, approximately six months (March – April 2016; Southern Hemisphere autumn) before the 2016 Rio Olympic Games. A total of 71 athletes provided a blood sample 24-48 hours following completion of their selection eventsand responded to the questionnaires, with enough detail specific to URS, for inclusion in this study. Some athletes had trained prior to sample collection. To account for the effects of training, three classifications were used as determined by the sports scientists on the research team: trained for fewer than 3 hours at moderate intensity pre-sampling; trained for fewer than 3 hours at light intensity pre-sampling; and had not trained in the 12 hours prior to sampling. Athletes were also asked to report whether they had used probiotic supplementation during the previous month and these responses were recorded simply as 'yes' or 'no' (Supplement 1). Athletes also provided self-reported training hours per week and described the number of hours spent undertaking endurance, strength and team-based training from which group mean values were calculated. Ethical approval for the study was granted by the Australian Institute of Sport Ethics Committee (Approval number 20160407) and the Griffith University Human Ethics Committee (HREC 2016/213). All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All participants provided written informed consent prior to data and sample collection as part of the Stay Healthy project and as described previously (11).

To determine the prevalence of URS, a self-reported, retrospective illness symptoms log was completed via an electronic athlete management system used regularly by the athletes, as previously described (44). The illness symptoms log gathered information regarding the number of days athletes experienced URS, such as a blocked or runny nose, sore throat or sneezing as well as symptoms of chest illness including coughing, sputum, chest congestion, wheezing or high temperature over the previous month (Supplement 1). Based on their responses, athletes were allocated to one of two groups; the URS group (n=38) and the asymptomatic group (n=33). Where athletes had reported URS for two or more days during the previous month, they were classified in the URS group. Athletes were classified as asymptomatic if they did not report URS in the previous month. Athletes who were experiencing symptoms at the time of sampling or who reported URS for a single day only in the previous month were not included in analyses.

Blood sample collection

A peripheral blood sample (2.5mL) was collected from an antecubital vein by a qualified phlebotomist, on a single occasion for the evaluation of messenger ribonucleic acid (mRNA). Samples were collected into an RNA PAXgene® tube (Pre-AnalytiX, Feldbachstrasse, Switzerland), kept at room temperature for two hours and stored at -80°C until analysis. Due to the limitations of samples being collected during an Olympic selection event the time of sampling and whether athletes were fasted could not be controlled.

RNA extraction and mRNA isolation

Total RNA was extracted using the commercially available Maxwell® RSC miRNA tissue kit (Promega, Wisconsin, USA) as per the manufacturer's protocol using the Maxwell® RSC Instrument (Promega, Wisconsin, USA). Extracted RNA was stored at -80°C until required for mRNA and micro RNA separation (miRNA). To separate mRNA and miRNA from total RNA the commercially available RNA Clean and Concentrator™ kit (Zymo Research, California, USA) was used as per manufacturer's instructions. Isolated mRNA was stored at -80°C. The LabChip GX Touch 24 (PerkinElmer®, Massachusetts, USA) was used to assess the concentration and quality of mRNA samples.

Gene expression analysis

Isolated mRNA was analysed for digital gene expression analysis of 730 immune genes and key inflammatory pathways [11, 12], using the nCounter® PanCancer Immune Profiling panel (NanoString Technologies, WA, USA) on the nCounter® Gene Expression Assay (NanoString Technologies, WA, USA) as per the manufacturer's instructions. The nCounter® PanCancer Immune Profiling panel (NanoString Technologies, WA, USA) includes 38 housekeeping genes, with full information available at nanostring.com. In brief, 100 ng of mRNA was hybridised with sequence-specific barcoded probes at 65 °C for 24 h before being placed into the NanoString Prep Station where the target-probe complex was immobilised on to the analysis cartridge. Cartridges were read by the nCounter Digital Analyser for digital counting of molecular barcodes corresponding to each target. Validation using polymerase chain reaction or other methods was not pursued due to the literature demonstrating the reproducibility and validity of digital gene expression analysis (1, 2, 10, 22).

Statistical analysis

Differences in group characteristics were evaluated in SPSS version 25 (IBM Computing, New York, USA). All data were evaluated for skewness and kurtosis (within the range of 0 ± 3) to confirm normal distribution. Continuous variables were assessed using a t-test and are presented as mean and standard variation (SD). Categorical variables are presented as count (n) and percent (%) and assessed using the Chi-square test for independence. The Yates' Continuity Correction was applied to compensate for two-by-two comparisons and Cramer's V was reported to show effect size (small 0.1; medium 0.3; large 0.5). The Phi correlation coefficient was used to indicate the degree of association between two variables. Adjustments for multiple comparisons were made using the Benjamini-Hochberg procedure and presented as a *q*-value. Statistical significance was indicated at the level of $p<0.05$ or $q<0.05$.

Immune gene expression data was evaluated using the Advanced Analysis Module in nSolver™ Analysis Software 4.0 (NanoString Technologies, WA, USA). The package includes modules enabling automated and optimised normalization using geNorm, differential gene expression analysis and Pathview plots analysis (5). Raw data was normalised using negative controls to account for systemic background noise and platform-associated sources of variation were normalised using positive controls. An optimized set of reference genes were used to adjust transcript counts relative to housekeeping genes included in the panel. Assessment of immune gene expression data was undertaken and confounding variables, sport and probiotic use, were adjusted for. Unsupervised hierarchical clustering was used to generate a heat map to visualize normalized data and view relationships between and within clusters of genes. Differential immune gene expression was determined between athletes reporting URS and asymptomatic athletes using multiple linear regression, and adjustment for multiple comparisons was performed using the Benjamini-Yekutieli false discovery rate (FDR). The Pathview Plots Module was used to map differential gene expression to known protein-based KEGG (Kyoto Encyclopaedia of Genes and Genomes) pathways.

RESULTS

Prevalence of URS in Olympic athletes

Responses to the URS log indicated that 53% of athletes reported URS and/or chest symptoms for two or more days in the month prior to sampling. Sixty-three percent of athletes reported URS for 2-5 days, 19% of athletes experienced URS for 6-9 days and 18% for more than 10 days, respectively. Thirty-three out of 71 athletes reported no URS and/or chest symptoms during the previous month. These results determined the two groups within this study for subsequent gene expression analysis: the URS group (n=38) and the asymptomatic group (n=33).

Group characteristics

The group characteristics are described in Supplement 2; groups did not differ significantly in age, gender distribution or self-reported training load. The URS and asymptomatic groups were significantly different with regards to the distribution of sports (p=0.04, Cramer's V = 0.01, small effect size). Benjamini-Hochberg adjusted post-hoc analysis revealed that, between the groups, the significantly different sport was water polo (p=0.02) with only one water polo player categorized in the asymptomatic group compared to 11 within the URS group. The URS group reported significantly higher probiotic use (p=0.007, Cramer's V = 0.03, small effect size) from which 53% of athletes indicated probiotic use in the previous month compared to 21% of athletes from the asymptomatic group.

Differential gene expression

A total of 305 immune genes within the Pan Cancer Immune Profiling Panel were expressed above background and unsupervised hierarchic clustering of these genes could not separate the groups (Supplement 3). Prior to adjustment, 50 immune genes were differentially expressed ($p<0.05$) between athletes reporting URS and asymptomatic athletes. Of these 50 genes, 36 were upregulated (72%) and 14 were downregulated (28%) in athletes reporting URS in comparison with athletes reporting no URS. Following Benjamini-Yekutieli adjustment only one gene, *IFI27*, remained significant ($p=6.7*10^{-04}$; 2.49 Log^2 fold-difference, confidence interval (CI) 1.67-3.31), see Supplement 4 for the full results table. The top 40 most significant genes can be viewed at Figure 1.

Results from the differential expression analysis were overlaid on various KEGG pathways to identify perturbed pathways and returned a plot for the JAK-STAT pathway (Figure 2). Multiple genes and gene families were over-expressed in the JAK-STAT pathway in the athletes reporting URS compared to asymptomatic athletes prior to Benjamini-Yekutieli adjustment. The Pathview module also returned plots for immune processes known to be involved in the response to influenza A (Supplement 5) and the Herpes Simplex Virus (Supplement 6). The genes common to all three Pathview plots are central to the JAK-STAT pathway and have primary roles in immune regulation.

Gene expression and self-reporting URS

Logistic regression was performed to assess the effects of probiotic use, sport of the athlete and *IFI27* expression on the

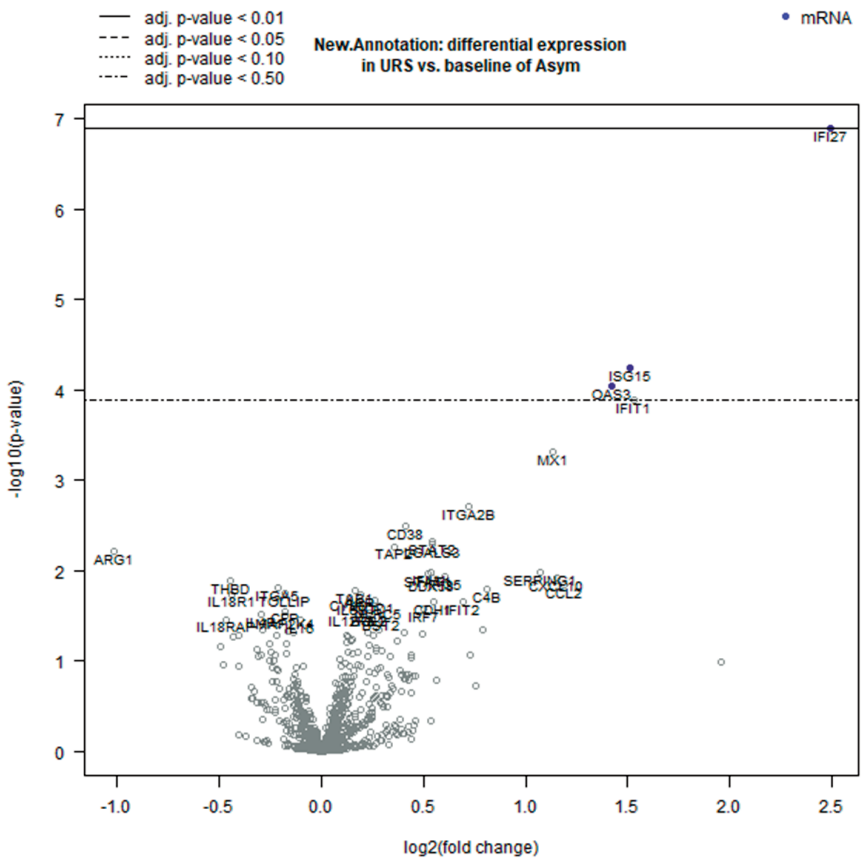

Figure 1: Volcano plot displaying the top 40 differentially expressed genes between athletes reporting URS compared to asymptomatic athletes. Highly differentially expressed genes, by (log^2) fold-difference fall to either side of the plot and highly significantly different genes fall at the top of the plot. *IFI27*, an interferon signalling gene, is shown in the top right corner with a log^2 fold-difference of 2.49, p=6.7*10^-4.

likelihood that athletes would report URS (Table 1). The logistic regression model was statistically significant $\chi^2(df=6, n=71) = 31.59$, p=<0.001 indicating that the model could distinguish between athletes reporting URS and asymptomatic athletes. The model explained between 35% (Cox and Snell R square) and 47% (Nagelkerke R square) of the variance in URS and correctly classified 78% of cases. The only variable within the model that achieved statistical significance was *IFI27* (Odds ratio (OR)=1.02, p=0.01, 95% CI, 1.004 to 1.03). For every unit increase in *IFI27* mRNA, athletes were 1.02 times more likely to report URS in the previous month.

DISCUSSION

Highly multi-parametric immune gene expression profiling in elite athletes during Olympic selection resulted in two novel discoveries. For the first time we have identified that athletes reporting URS could be differentiated from asymptomatic athletes with 78% accuracy by the expression of one gene, *IFI27*. The expression of this gene, an interferon-stimulated gene, is increased during the viral innate immune response via interferon signalling and increased mitochondrial activity (6). Secondly, in light of recent findings from Tang *et al.*, that *IFI27* is able to differentiate viral URS from other URS aetiologies (41) our results provide unique insight into the aetiology of URS in an elite athlete cohort in the lead up to an Olympic selection event. Furthermore, our observation of an increased expression of the immune anti-viral genes *MX1, OAS3, IFIT2* and I*SG15,* in the current study (prior to Benjamini-Yekutieli adjustment) were also reported as being related to viral infection by Tang et al. Our findings provide preliminary evidence for a viral basis of URS in highly trained athletes and indicates that inflammatory processes may still have been resolving.

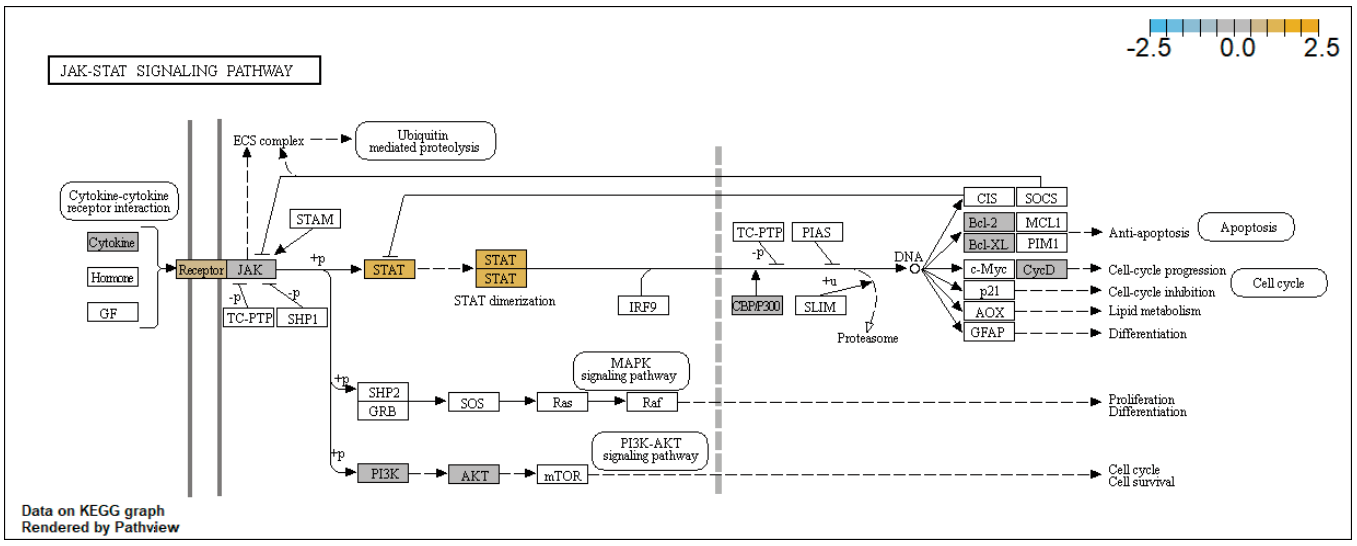

Figure 2: Genes from the STAT family and SOCS family are over expressed within the JAK-STAT pathway in athletes reporting URS compared to asymptomatic athletes. A KEGG diagram (Kyoto encyclopedia of genes and genomes) is a computerised representation of a biological pathway and its components. Genes and genes families within the plot and are represented within the Pan Cancer Immune Profiling Panel shown in colour or in grey. Genes and gene families known to be involved in the pathway but are not represented within the panel are shown in white. Genes and gene families that are over-expressed in the KEGG pathway are shown in shades of orange (log2 fold-difference 0 to 2.5).

Table 1 Logistic regression of probiotic supplementation, sport of the athlete and *IFI27* gene expression on the likelihood that athletes report URS (*indicates p<0.05)

							95% CI	
Variables	**B**	**SE**	**Wald**	**df**	***p*-value**	**Odds ratio**	**Lower**	**Upper**
***IFI27* gene expression**	0.18	0.007	6.27	1	0.01*	1.02	1.004	1.03
Probiotic supplementation	1.1	0.85	1.65	1	0.20	3.0	0.56	15.94
Sport *(Rowing as reference)*			2.73	4	0.60			
Rugby 7's	-0.06	1.09	0.003	1	0.96	0.94	0.11	8.01
Soccer	0.03	1.18	0.001	1	0.98	1.03	0.1	10.39
Triathlon	-20.12	2.84x10^4	5.0x10^-7	1	0.99	1.83x10^-9	0.0	0.0
Water polo	1.95	1.32	2.17	1	0.14	7.0	0.53	93.12
Constant	-1.56	1.25	1.57	1	0.21	0.21		

Other investigators have also pointed to a link between *IFI27* expression and infection with respiratory syncytial virus (12) and a number of other viruses (48), (31), (6). These associations indicate that *IFI27* expression is stimulated by a range of viruses and stressors and could explain, in part, why some of the athletes self-reported URS. To date, assessment of URS aetiology in athletes typically identify infective sources in approximately thirty percent of cases, which has prevented definitive recommendations for preventive interventions to reduce the risk of URS in athletic cohorts (38). Current paradigms in exercise immunology indicate that respiratory symptoms, particularly in athletes prone to recurrent illness, may be related to viral reactivation, although the role of viral reactivation in respiratory illness in athletes is conflicting (16, 18, 20). Our findings contribute to the evidence for a viral aetiology for URS in highly trained athletes. Future research could incorporate viral molecular profiling in conjunction with clinical investigation in longitudinal studies to inform diagnostic, treatment and prevention programs for URS in elite athlete cohorts.

The higher expression of immune genes in the JAK-STAT pathway and interferon-stimulated genes (ISG's) are also associated with viral infection (41, 47). The JAK-STAT pathway is central to multiple immune processes via cellular membrane signalling that leads to the induction of immune gene expression (36). Interferons, cytokines, interleukins and hormones are all able to activate the JAK-STAT pathway with widespread downstream effects (30). A key mechanism of JAK-STAT activation is via interferon signalling which leads to the expression of ISG's (21). JAK-STAT upregulation was observed in the URS group in addition to two other KEGG pathways outlining genes known to be involved in the immune response to influenza A and herpes simplex infection. Identification of upregulated gene expression across these two viral response pathways is important as both viruses have been identified as sources of URS in athletes either through primary, unresolved or reactivated infection (8, 20, 35, 39). Several other studies involving non-athletes have identified a strikingly similar set of core genes that are common to the immune gene expression response elicited following viral inoculation (3, 9, 19, 26, 40, 46, 47).

Evaluating other respiratory pathologies also provides insights into immune-regulatory mechanisms that may be relevant in the context of URS in athletes. In patients with asthma, peripheral blood immune gene expression was measured from 166 blood samples taken following asthma exacerbations and compared to 1149 samples representing quiescent asthma in the same patients. This study reported upregulation of the JAK-STAT pathway and for ISG's. Upregulated genes included *STAT1, STAT2, IFI27, JAK1, JAK2, IRF7, MX1, IFI35, ISG15, OAS2, IFIH1,* and *OASL* (4). Many of the same genes in this study were significantly upregulated in athletes reporting URS in our study, including *IFI27*. Although patients experiencing asthma exacerbations were excluded from the study if diagnosed by a physician with an active illness, an accurate URS diagnosis is difficult (39). In individuals with allergic inflammation, a recent study compared the gene expression of PBMCs with or without antigen challenge from four subjects with diagnosed allergic inflammation compared to the cells from four healthy controls (25). Although the study involved a very small cohort, gene activation of the JAK-STAT pathway within PBMC's was observed in patients with allergic inflammation (25). The studies described above had recruited patients with diagnosed URS caused by either asthma, allergic inflammation or infection and all reported involved upregulation of the JAK-STAT pathway and ISG immune expression. Our results indicating up-regulation of *IFI27* was reported in patients following asthma exacerbation but not following allergic inflammation. The current results provide cohort-specific evidence for *IFI27* as a potential viral biomarker in highly trained athletes although the involvement of *IFI27* in other inflammatory pathways should be examined further.

Limitations

The main limitation of this study was that sampling conditions were not standardized. The variables that were not controlled included sex, diet, sport, the time of day samples were collected, whether the athletes had trained or were rested, whether athletes were fasted/non-fasted, the location athletes were sampled and by whom they were sampled. Many of these factors can alter the circulation / mobilisation of immune cells and, where possible, the statistical approach adjusted for those variables that were statistically significant between the groups. The

current findings should be confirmed using a more structured study design, ideally within a prospective-longitudinal study using athletes from multiple centers, to determine whether *IFI27* is related to URS. An additional limitation of this study was that the number of days between sample collection and when URS were experienced was not recorded. A record of when URS was last experienced could be used to inform statistical evaluation and further interpretation of the results.

Conclusion

Athletes reporting URS were able to be differentiated from asymptomatic athletes for the first time by a higher expression of the *IFI27* immune gene involved in the response to viral infection and multiple genes within the JAK-STAT pathway. The results give important insight into the aetiology of URS in athletes. The results present an opportunity for further research aiming to refine diagnostic, treatment and URS prevention programs in elite athletes.

Contribution: The data presented were collected as part of the "Stay Healthy" project which was led by MKD in collaboration with AJC, DBP, NV, DH, GW, RA, LMB, BL, MT, DW, GL, SP, SH, MW, AWC and NPW. The study was undertaken by CC as part of her PhD research and she played a central role in all stages of the research and manuscript writing. AWC, NPW and AJC were her supervisors, they conceived the study design and guided all stages of the work. JV and AJC guided laboratory analyses. All authors contributed with the logistics of "Stay Healthy" project as well as the interpretation of the study results, the editorial process and the revision of the manuscript.

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Conflicts of Interest: Nil

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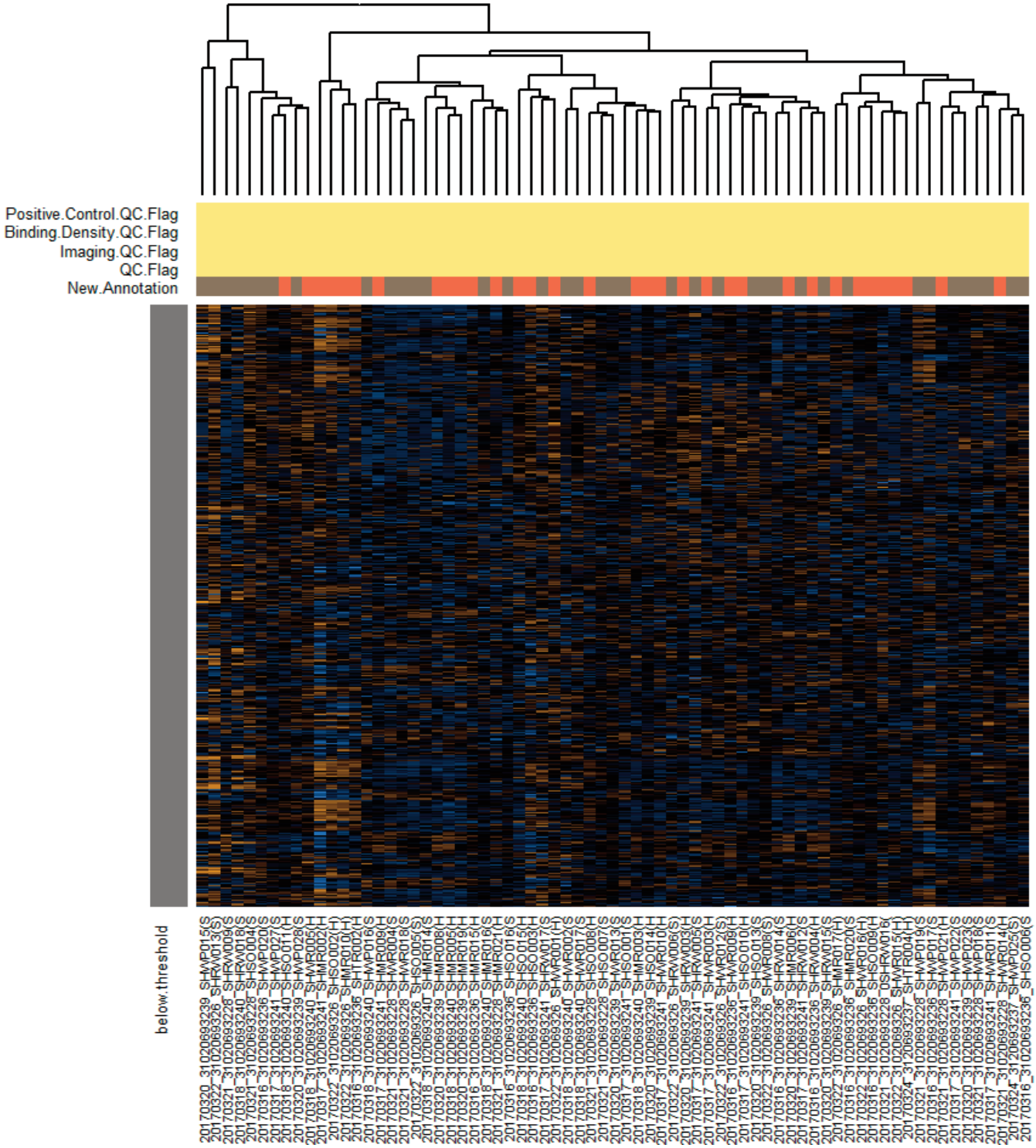
Supplement 1: Illness symptoms log and group characteristics questionnaire	**Answer**
Q1. In the last month, have you had upper respiratory symptoms such as blocked or runny nose, sore throat or sneezing?	Yes/No
Q1-1. How many days of FULL TRAINING with upper respiratory symptoms?	Number of days
Q1-2. How many days of MODIFIED TRAINING with upper respiratory symptoms?	Number of days
Q1-3. How many days were there where you COULD NOT TRAIN due to upper respiratory symptoms?	Number of days
Q2. In the last month, have you had chest infection symptoms such as coughing, sputum, chest congestion, wheezing or high temperature?	Yes/No
Q2-1. How many days of FULL TRAINING with chest infection symptoms?	Number of days
Q2-2. How many days of MODIFIED TRAINING with chest infection symptoms?	Number of days
Q2-3. How many days were there where you COULD NOT TRAIN due to chest infection symptoms?	Number of days
Q4. In the last month, have you taken probiotic supplements?	Yes/No
Q5. When was the last time you trained and at what intensity did you train?	Open question
Q6. Describe your normal amount of training in a week?	Open question

Supplement 2: Group characteristics; sex, the main sport of the athletes, the time and intensity of the training session immediately prior to sampling, age and self-reported training load (* indicates $p<0.05$)

	Asym (*n*=33) n (%)	**URS (*n*=38) n (%)**	**X^2**	**Adj. *p*-value**	**Yates' continuity correction**	**Phi coefficient**	***q*-value**
Sex							
Male	13 (39.4)	8 (21.1)	0.09		0.15	0.20	-
Female	20 (60.6)	30 (78.9)					
Sport							
Triathlon	2 (6.1)	0 (0)		0.17			
Rugby 7's	19 (57.6)	11 (28.9)		0.05			
Water polo	1 (3.0)	11 (28.9)	0.04*	0.02*	-	0.46	-
Rowing	3 (9.1)	9 (23.7)		0.17			
Soccer	8 (24.2)	7 (18.4)		0.55			
Time and intensity of the training session immediately prior to sampling							
>12 hrs; overnight rest	21 (64)	18 (47)					
<3 hrs; light session	8 (24)	7 (18)	0.09		-	0.26	-
<3 hrs; typical session	4 (12)	13 (34)					
Probiotic use							
Yes	7(21.2)	21(55.3)	0.003		0.007*	0.35	-
No	26(78.8)	17(44.7)					
	Asym mean(SD)	**URS mean(SD)**	**Mean difference**		**SE of difference**	***p*-value**	***q*-value**
Age	25.1 (4.4)	23.8 (3.5)	1.33		0.94	0.16	0.32
Self-reported training hrs/week							
Resistance	4.2 (1.3)	4.2(1.5)	0.1		0.48	0.90	0.9
Endurance	14.9 (10.8)	10.1 (9.6)	4.8		5.0	0.35	0.47
Team	8.4 (2.5)	9.6 (1.9)	1.2		0.74	0.11	0.32

Supplement 3: Unsupervised hierarchic clustering of 305 immune genes that were above background and differentiated URS (n=38, grey) and asymptomatic athletes (n=33, coral), within the horizontal row above the heat map. Each column within the heat map represents a sample and each row represents a gene. The horizontal yellow bar at the top of the map represents the quality control (QC) standards (positive control, binding density and imaging) the yellow colour indicates that all sample passed QC. The grey column to the left of the map represents the gene count threshold and the grey colour indicates that all genes met the minimum expression of 50 transcripts. Within the heat map, the data is plotted as a z-score - orange is indicative of high gene expression and blue is indicative of low gene expression. Despite some minor clustering of URS subjects to the right of the map no substantial differences in overall immune gene expression could separate the groups.



Supplement 4: Adjusted differential gene expression between the URS and Asym group. Most genes reaching $p<0.05$ were expressed at a higher frequency in the URS group. Only *IFI27* remained significant following adjustment for multiple comparisons BY.$p<0.05$.

Gene	Log^2 FC	Linear Fold-difference	Confident limit Log^2 Lower	Confident limit Log^2 Upper	P-value	BY.*p*.value
IFI27	2.49	5.62	1.67	3.31	1.28*10^-07	6.7*10-04
ISG15	1.51	2.85	0.83	2.20	5.71*10-05	0.15
OAS3	1.42	2.68	0.76	2.09	9.03*10-05	0.16
IFIT1	1.53	2.89	0.80	2.27	1.30*10-04	0.17
MX1	1.13	2.19	0.53	1.73	4.90*10-04	0.51
ITGA2B	0.72	1.65	0.28	1.16	1.93*10-03	1
CD38	0.41	1.33	0.15	0.68	3.18*10-03	1
STAT2	0.54	1.46	0.18	0.91	4.80*10-03	1
LGALS3	0.54	1.46	0.18	0.91	5.12*10-03	1
TAP2	0.36	1.28	0.12	0.61	5.41*10-03	1
ARG1	-1.02	0.49	-1.73	-0.32	6.13*10-03	1
SERPING1	1.07	2.10	0.28	1.87	0.010	1
IFIH1	0.53	1.45	0.14	0.93	0.011	1
STAT1	0.52	1.43	0.13	0.91	0.011	1
IFI35	0.60	1.52	0.15	1.06	0.012	1
DDX58	0.54	1.45	0.13	0.95	0.012	1
CXCL10	1.15	2.22	0.28	2.03	0.012	1
THBD	-0.45	0.73	-0.79	-0.10	0.013	1
CCL2	1.19	2.28	0.26	2.12	0.014	1
ITGA5	-0.21	0.86	-0.38	-0.05	0.015	1
C4B	0.81	1.75	0.17	1.45	0.016	1
TAB1	0.16	1.12	0.03	0.29	0.017	1
TOLLIP	-0.18	0.88	-0.33	-0.03	0.018	1
IL18R1	-0.44	0.74	-0.80	-0.08	0.018	1
APP	0.19	1.14	0.04	0.35	0.019	1
CYLD	0.14	1.10	0.03	0.25	0.020	1
NOD1	0.26	1.20	0.04	0.48	0.022	1
IFIT2	0.69	1.62	0.11	1.27	0.022	1
CDH1	0.55	1.46	0.09	1.01	0.022	1
IL6ST	0.18	1.13	0.03	0.32	0.023	1
NLRC5	0.28	1.22	0.04	0.52	0.025	1
IRF7	0.50	1.42	0.07	0.93	0.026	1
CFP	-0.18	0.88	-0.34	-0.02	0.028	1
BCL2	0.23	1.18	0.03	0.44	0.030	1
IL12RB1	0.18	1.13	0.02	0.34	0.030	1
IL4R	-0.30	0.81	-0.56	-0.03	0.031	1
MAP2K4	-0.18	0.89	-0.33	-0.02	0.032	1
BST2	0.30	1.23	0.03	0.57	0.034	1
IL18RAP	-0.47	0.72	-0.90	-0.04	0.035	1
IL16	-0.10	0.93	-0.20	-0.01	0.035	1
FLT3LG	0.16	1.12	0.01	0.31	0.037	1
CD83	0.24	1.18	0.02	0.46	0.038	1
CD97	-0.21	0.87	-0.40	-0.01	0.040	1
BID	-0.29	0.82	-0.56	-0.01	0.045	1
ISG20	0.28	1.21	0.01	0.55	0.046	1
SIGLEC1	0.79	1.73	0.03	1.55	0.046	1
SELPLG	-0.17	0.89	-0.33	-0.01	0.047	1
UBC	-0.14	0.91	-0.27	0.00	0.049	1
THBS1	0.40	1.32	0.01	0.79	0.049	1
IRF4	0.23	1.17	0.01	0.45	0.049	1
PBK	0.49	1.41	0.01	0.97	0.05	1
TNFSF14	-0.22	0.86	-0.44	0.00	0.05	1

HLADOB	0.25	1.19	0.00	0.50	0.05	1
IL1R2	-0.41	0.76	-0.81	0.00	0.05	1
TRAF3	0.12	1.09	0.00	0.24	0.05	1
ITGA4	0.13	1.09	0.00	0.26	0.05	1
S100A12	-0.44	0.74	-0.87	0.00	0.05	1
POU2F2	0.15	1.11	0.00	0.30	0.06	1
HLADMA	0.15	1.11	0.00	0.30	0.06	1
BCL2L1	0.37	1.29	-0.01	0.75	0.06	1
IL2RG	0.12	1.09	0.00	0.25	0.06	1
STAT5B	-0.17	0.89	-0.35	0.01	0.06	1
TNFRSF10C	-0.25	0.84	-0.52	0.01	0.07	1
LRP1	0.24	1.18	-0.01	0.48	0.07	1
IL17A	-0.50	0.71	-1.02	0.03	0.07	1
TAP1	0.27	1.20	-0.02	0.56	0.07	1
CXCR6	-0.32	0.80	-0.66	0.03	0.08	1
F13A1	0.27	1.20	-0.02	0.55	0.08	1
LCN2	0.29	1.23	-0.03	0.62	0.08	1
FOS	-0.25	0.84	-0.53	0.03	0.08	1
CD36	0.18	1.13	-0.02	0.38	0.08	1
SMAD3	0.13	1.09	-0.01	0.27	0.08	1
ICAM3	-0.17	0.89	-0.36	0.02	0.08	1
CD74	0.15	1.11	-0.02	0.32	0.08	1
SLC11A1	-0.30	0.82	-0.63	0.04	0.09	1
IDO1	0.73	1.66	-0.09	1.55	0.09	1
CEBPB	-0.23	0.86	-0.48	0.03	0.09	1
ROPN1	0.44	1.35	-0.06	0.93	0.09	1
MFGE8	0.22	1.17	-0.03	0.48	0.09	1
PRG2	0.34	1.26	-0.05	0.72	0.09	1
BCL6	-0.31	0.81	-0.67	0.04	0.09	1
ITGB3	0.44	1.36	-0.07	0.94	0.09	1
MAP4K2	0.09	1.06	-0.01	0.19	0.10	1
FUT7	-0.26	0.84	-0.55	0.04	0.10	1
CXCR1	-0.23	0.85	-0.51	0.04	0.10	1
HLADRB4	1.96	3.89	-0.37	4.28	0.10	1
IKBKE	0.11	1.08	-0.02	0.25	0.11	1
HAMP	-0.48	0.72	-1.06	0.10	0.11	1
CD40	0.18	1.13	-0.04	0.40	0.11	1
CD1E	-0.41	0.75	-0.90	0.09	0.11	1
PNMA1	0.14	1.10	-0.03	0.30	0.11	1
CYBB	0.19	1.14	-0.04	0.43	0.12	1
IKBKB	0.10	1.07	-0.02	0.22	0.12	1
TRAF6	-0.09	0.94	-0.20	0.02	0.12	1
TREM1	-0.24	0.85	-0.54	0.06	0.12	1
TFRC	0.29	1.22	-0.07	0.64	0.12	1
RELA	-0.13	0.92	-0.28	0.03	0.12	1
TNFSF10	0.28	1.21	-0.07	0.62	0.12	1
TLR4	-0.22	0.86	-0.50	0.06	0.12	1
LTA	0.16	1.11	-0.04	0.36	0.13	1
IL6	0.39	1.31	-0.11	0.88	0.13	1
CXCR2	-0.21	0.86	-0.48	0.06	0.13	1
IL15	0.24	1.18	-0.07	0.54	0.13	1
CCRL2	0.26	1.20	-0.08	0.60	0.14	1
IL13	0.41	1.33	-0.13	0.95	0.14	1
IL15RA	0.32	1.25	-0.10	0.74	0.14	1
MST1R	0.39	1.31	-0.12	0.91	0.14	1
IL2	0.42	1.34	-0.13	0.98	0.14	1
MAPK3	-0.13	0.91	-0.31	0.04	0.14	1
ICOS	0.16	1.11	-0.05	0.36	0.15	1
CCL14	0.45	1.36	-0.15	1.04	0.15	1
SELE	0.46	1.38	-0.16	1.08	0.15	1
ANP32B	0.12	1.08	-0.04	0.27	0.15	1

IL11RA	0.14	1.10	-0.05	0.34	0.15	1
CD209	0.33	1.26	-0.12	0.77	0.15	1
HLADMB	0.12	1.08	-0.04	0.28	0.15	1
CD99	0.10	1.07	-0.04	0.24	0.15	1
IFNGR1	-0.14	0.91	-0.33	0.05	0.16	1
SOCS1	0.41	1.33	-0.16	0.98	0.16	1
SAA1	0.41	1.32	-0.15	0.96	0.16	1
LAMP3	0.56	1.47	-0.22	1.34	0.16	1
IL17B	0.43	1.35	-0.17	1.03	0.17	1
FPR2	-0.22	0.86	-0.53	0.09	0.17	1
GNLY	-0.24	0.85	-0.57	0.10	0.17	1
CDKN1A	0.22	1.16	-0.09	0.52	0.17	1
CD244	-0.12	0.92	-0.28	0.05	0.17	1
CTLA4	0.15	1.11	-0.06	0.35	0.17	1
ILF3	0.07	1.05	-0.03	0.16	0.18	1
TAPBP	0.12	1.09	-0.05	0.29	0.18	1
TNFSF8	0.09	1.06	-0.04	0.21	0.18	1
TNFSF12	-0.11	0.92	-0.28	0.05	0.18	1
CD3G	0.12	1.09	-0.06	0.30	0.19	1
CD58	-0.13	0.92	-0.31	0.06	0.19	1
PSMB9	0.15	1.11	-0.07	0.37	0.19	1
TFEB	-0.12	0.92	-0.30	0.06	0.19	1
XCR1	0.35	1.27	-0.16	0.85	0.19	1
C2	0.76	1.69	-0.36	1.87	0.19	1
IFNAR1	-0.14	0.91	-0.34	0.07	0.19	1
PSMB10	0.12	1.09	-0.06	0.30	0.19	1
CD63	-0.12	0.92	-0.30	0.06	0.19	1
CRP	-0.35	0.79	-0.86	0.17	0.19	1
MASP1	-0.34	0.79	-0.86	0.17	0.19	1
TNFSF13B	0.27	1.20	-0.14	0.67	0.20	1
ICAM2	0.09	1.06	-0.04	0.22	0.20	1
C3AR1	-0.21	0.87	-0.52	0.11	0.20	1
IFITM2	-0.21	0.87	-0.52	0.11	0.20	1
CD40LG	0.10	1.07	-0.05	0.26	0.20	1
TLR1	-0.16	0.90	-0.39	0.08	0.21	1
CCL15	0.35	1.27	-0.19	0.88	0.21	1
PTGS2	-0.14	0.91	-0.34	0.07	0.21	1
PSEN1	-0.10	0.93	-0.26	0.06	0.22	1
CD180	0.14	1.10	-0.08	0.36	0.22	1
CTCFL	0.39	1.31	-0.23	1.00	0.22	1
HLADRB3	0.12	1.09	-0.07	0.31	0.22	1
THY1	-0.33	0.79	-0.86	0.20	0.22	1
CD274	0.44	1.35	-0.26	1.13	0.22	1
CFB	0.34	1.26	-0.20	0.88	0.22	1
ITK	0.10	1.07	-0.06	0.27	0.23	1
LILRB1	0.13	1.10	-0.08	0.34	0.23	1
TAL1	0.20	1.15	-0.12	0.51	0.23	1
TBK1	0.10	1.07	-0.06	0.26	0.23	1
TFE3	-0.17	0.89	-0.43	0.10	0.23	1
TRAF2	0.08	1.06	-0.05	0.21	0.23	1
CD33	-0.11	0.92	-0.30	0.07	0.24	1
TCF7	0.10	1.07	-0.06	0.26	0.24	1
NFKBIA	-0.10	0.93	-0.26	0.06	0.24	1
MAPK11	0.27	1.20	-0.17	0.70	0.24	1
MAPK14	-0.15	0.90	-0.39	0.09	0.24	1
LTF	0.30	1.23	-0.19	0.79	0.24	1
MAPKAPK2	-0.10	0.93	-0.28	0.07	0.24	1
CD276	0.31	1.24	-0.21	0.84	0.24	1
FCER1A	-0.17	0.89	-0.47	0.12	0.24	1
ADORA2A	0.09	1.06	-0.06	0.23	0.24	1
BTK	0.10	1.07	-0.06	0.26	0.25	1

CCL19	0.32	1.25	-0.22	0.86	0.25	1
ATG16L1	0.07	1.05	-0.05	0.18	0.25	1
CD28	0.12	1.09	-0.08	0.32	0.25	1
IFI16	0.19	1.14	-0.13	0.50	0.25	1
CLEC7A	0.14	1.10	-0.10	0.37	0.25	1
GTF3C1	0.10	1.07	-0.07	0.27	0.25	1
SPO11	0.33	1.25	-0.23	0.88	0.25	1
TNFRSF17	0.26	1.20	-0.18	0.71	0.25	1
CTSW	-0.16	0.90	-0.42	0.11	0.25	1
CASP8	-0.08	0.95	-0.21	0.06	0.25	1
IL18	-0.17	0.89	-0.45	0.12	0.26	1
PIN1	0.08	1.05	-0.05	0.21	0.26	1
IFNA8	-0.34	0.79	-0.91	0.24	0.26	1
CD96	0.09	1.06	-0.06	0.24	0.26	1
BCL10	-0.08	0.95	-0.21	0.06	0.26	1
CCL21	-0.34	0.79	-0.93	0.25	0.26	1
ELANE	0.25	1.19	-0.19	0.69	0.26	1
RUNX1	0.08	1.06	-0.06	0.22	0.26	1
TNFRSF11A	-0.23	0.86	-0.62	0.17	0.27	1
HLADPA1	0.11	1.08	-0.08	0.31	0.27	1
LILRA5	-0.19	0.88	-0.52	0.14	0.27	1
LILRB2	-0.12	0.92	-0.32	0.09	0.27	1
NFATC1	0.08	1.06	-0.07	0.23	0.27	1
TNFRSF8	-0.12	0.92	-0.32	0.09	0.28	1
IFNAR2	-0.08	0.95	-0.21	0.06	0.28	1
CD6	0.09	1.06	-0.07	0.25	0.28	1
IRF8	0.09	1.06	-0.07	0.25	0.28	1
IRAK2	-0.11	0.92	-0.32	0.09	0.29	1
CD34	0.29	1.22	-0.24	0.82	0.29	1
VCAM1	-0.32	0.80	-0.90	0.27	0.29	1
EPCAM	-0.29	0.82	-0.84	0.25	0.29	1
C9	-0.28	0.82	-0.80	0.24	0.29	1
CASP1	0.13	1.09	-0.11	0.36	0.30	1
IL2RA	0.13	1.10	-0.11	0.38	0.30	1
MAP2K2	0.07	1.05	-0.06	0.20	0.30	1
CSF3R	-0.13	0.91	-0.37	0.11	0.30	1
TNFRSF1A	-0.11	0.93	-0.31	0.10	0.30	1
C6	0.29	1.22	-0.26	0.84	0.30	1
STAT4	0.09	1.06	-0.08	0.25	0.30	1
CEACAM1	0.24	1.18	-0.21	0.68	0.30	1
HLADRA	0.09	1.06	-0.08	0.26	0.31	1
TLR8	-0.14	0.91	-0.41	0.13	0.31	1
DOCK9	0.10	1.07	-0.09	0.29	0.31	1
CD4	0.10	1.07	-0.09	0.28	0.31	1
LTBR	-0.11	0.93	-0.33	0.10	0.31	1
LY86	0.09	1.06	-0.08	0.26	0.32	1
NFATC4	-0.28	0.83	-0.81	0.26	0.32	1
MAGEC1	0.32	1.25	-0.31	0.96	0.32	1
NLRP3	-0.12	0.92	-0.35	0.11	0.32	1
NFKB2	0.08	1.05	-0.07	0.23	0.33	1
TNFAIP3	0.08	1.06	-0.08	0.24	0.33	1
PLA2G1B	0.31	1.24	-0.30	0.91	0.33	1
MR1	0.11	1.08	-0.11	0.33	0.33	1
PSMB8	0.10	1.07	-0.10	0.31	0.33	1
ZAP70	0.08	1.06	-0.08	0.23	0.33	1
CLEC4C	0.25	1.19	-0.25	0.74	0.33	1
TLR2	-0.13	0.92	-0.38	0.13	0.33	1
CD47	0.04	1.03	-0.04	0.12	0.34	1
S100A8	-0.18	0.88	-0.54	0.19	0.34	1
RELB	0.12	1.08	-0.12	0.35	0.34	1
MNX1	-0.26	0.84	-0.79	0.27	0.34	1

NRP1	0.19	1.14	-0.20	0.58	0.34	1
CD14	-0.12	0.92	-0.36	0.12	0.34	1
NUP107	0.07	1.05	-0.08	0.22	0.34	1
MPPED1	-0.23	0.85	-0.70	0.24	0.35	1
BATF	-0.10	0.93	-0.32	0.11	0.35	1
CD3E	0.07	1.05	-0.08	0.22	0.35	1
CCL3L1	-0.27	0.83	-0.82	0.29	0.35	1
CCL5	0.10	1.07	-0.11	0.32	0.35	1
C1QBP	0.06	1.05	-0.07	0.20	0.36	1
CCND3	-0.06	0.96	-0.20	0.07	0.36	1
IL6R	-0.09	0.94	-0.30	0.11	0.36	1
MEF2C	0.10	1.07	-0.12	0.31	0.37	1
CCL3	-0.23	0.86	-0.72	0.27	0.37	1
LAMP2	-0.09	0.94	-0.27	0.10	0.37	1
PYCARD	-0.09	0.94	-0.29	0.11	0.37	1
CX3CL1	0.25	1.19	-0.29	0.79	0.37	1
FYN	0.06	1.04	-0.07	0.18	0.37	1
ATG10	-0.08	0.94	-0.27	0.10	0.38	1
TLR6	-0.11	0.93	-0.36	0.14	0.38	1
ENTPD1	-0.13	0.92	-0.40	0.15	0.38	1
CD3D	0.08	1.05	-0.09	0.24	0.38	1
PECAM1	-0.08	0.95	-0.26	0.10	0.38	1
NOD2	0.13	1.09	-0.16	0.42	0.38	1
EWSR1	0.04	1.03	-0.05	0.12	0.38	1
IFITM1	0.16	1.12	-0.20	0.52	0.38	1
CARD9	0.09	1.06	-0.11	0.29	0.39	1
IL1RAP	-0.12	0.92	-0.40	0.15	0.39	1
PPARG	0.23	1.18	-0.29	0.76	0.39	1
PIK3CD	-0.06	0.96	-0.21	0.08	0.39	1
ANXA1	-0.06	0.96	-0.19	0.07	0.39	1
REL	0.06	1.04	-0.08	0.19	0.40	1
TLR10	-0.08	0.95	-0.27	0.11	0.40	1
TANK	0.09	1.06	-0.12	0.30	0.41	1
IFNL2	0.24	1.18	-0.32	0.79	0.41	1
NCF4	-0.11	0.93	-0.35	0.14	0.41	1
CD8B	-0.11	0.93	-0.36	0.14	0.41	1
IL17F	0.24	1.18	-0.32	0.80	0.41	1
IL8	0.16	1.12	-0.23	0.55	0.42	1
FCER1G	-0.14	0.91	-0.47	0.19	0.42	1
HCK	-0.09	0.94	-0.31	0.13	0.42	1
IRF5	0.09	1.06	-0.12	0.30	0.42	1
LIF	0.25	1.19	-0.35	0.84	0.42	1
JAK2	0.10	1.07	-0.14	0.33	0.42	1
CR1	-0.12	0.92	-0.43	0.18	0.42	1
IFNB1	0.22	1.17	-0.32	0.77	0.43	1
TICAM1	-0.07	0.95	-0.25	0.10	0.43	1
SPANXB1	0.25	1.19	-0.36	0.85	0.43	1
NOTCH1	-0.09	0.94	-0.30	0.13	0.43	1
BLK	0.14	1.10	-0.21	0.49	0.43	1
IRAK4	-0.05	0.96	-0.19	0.08	0.43	1
PTPRC	-0.11	0.93	-0.37	0.16	0.44	1
PDCD1LG2	0.39	1.31	-0.59	1.36	0.44	1
ALCAM	0.08	1.05	-0.12	0.27	0.44	1
CD27	0.07	1.05	-0.10	0.24	0.44	1
IRAK1	-0.05	0.97	-0.16	0.07	0.44	1
CXCL13	0.23	1.17	-0.36	0.81	0.45	1
LILRA1	-0.07	0.95	-0.27	0.12	0.45	1
KLRK1	-0.08	0.94	-0.30	0.13	0.45	1
CXCR4	-0.06	0.96	-0.20	0.09	0.45	1
TXNIP	-0.05	0.96	-0.20	0.09	0.45	1
CD5	0.07	1.05	-0.11	0.24	0.45	1

USP9Y	-0.29	0.82	-1.03	0.45	0.45	1
SH2B2	-0.09	0.94	-0.33	0.15	0.45	1
ETS1	0.06	1.04	-0.10	0.23	0.45	1
C7	0.24	1.18	-0.38	0.85	0.45	1
CCL11	-0.21	0.87	-0.75	0.33	0.45	1
ITGB1	0.06	1.04	-0.10	0.23	0.46	1
MSR1	0.46	1.38	-0.76	1.68	0.46	1
AICDA	-0.17	0.89	-0.62	0.28	0.46	1
EP300	0.04	1.03	-0.07	0.15	0.46	1
CXCL11	0.54	1.45	-0.89	1.96	0.47	1
LTB	0.05	1.04	-0.09	0.19	0.47	1
CXCL16	-0.09	0.94	-0.33	0.15	0.47	1
ECSIT	0.08	1.06	-0.14	0.29	0.47	1
IGF2R	-0.09	0.94	-0.33	0.16	0.47	1
TNFSF11	-0.19	0.88	-0.69	0.32	0.48	1
MAP3K5	0.06	1.04	-0.11	0.24	0.48	1
PASD1	0.21	1.15	-0.36	0.77	0.48	1
FUT5	0.21	1.15	-0.36	0.78	0.48	1
ULBP2	0.17	1.13	-0.30	0.64	0.48	1
LRRN3	0.13	1.09	-0.23	0.49	0.48	1
TIGIT	0.10	1.07	-0.17	0.36	0.48	1
CCR1	0.13	1.10	-0.24	0.50	0.48	1
HSD11B1	-0.17	0.89	-0.65	0.31	0.49	1
SYT17	-0.17	0.89	-0.65	0.31	0.49	1
SBNO2	-0.09	0.94	-0.36	0.17	0.49	1
IL26	-0.16	0.90	-0.61	0.29	0.49	1
CD22	0.08	1.06	-0.16	0.32	0.50	1
TLR5	-0.16	0.90	-0.61	0.29	0.50	1
CCR7	0.08	1.05	-0.14	0.29	0.50	1
CCL22	0.21	1.16	-0.40	0.82	0.50	1
MAF	0.06	1.04	-0.12	0.24	0.51	1
KIR3DL1	0.35	1.28	-0.69	1.40	0.51	1
IL13RA1	-0.08	0.95	-0.32	0.16	0.51	1
TNFRSF11B	0.21	1.16	-0.42	0.85	0.51	1
KLRB1	-0.10	0.94	-0.38	0.19	0.51	1
CD24	0.07	1.05	-0.15	0.30	0.51	1
CCR6	0.08	1.06	-0.17	0.34	0.51	1
KIR Activating Subgroup 2	0.31	1.24	-0.62	1.24	0.51	1
C8G	0.14	1.10	-0.27	0.54	0.51	1
IL22	0.20	1.15	-0.40	0.80	0.52	1
IL1RN	0.12	1.09	-0.25	0.49	0.52	1
TNFSF4	0.09	1.06	-0.18	0.36	0.52	1
KLRC1	0.12	1.09	-0.25	0.49	0.52	1
KIR Inhibiting Subgroup 1	0.45	1.37	-0.92	1.82	0.52	1
BTLA	0.06	1.04	-0.12	0.24	0.52	1
MAGEA12	0.18	1.13	-0.37	0.73	0.52	1
FCGR2B	0.10	1.07	-0.21	0.41	0.52	1
C1QB	0.36	1.29	-0.76	1.48	0.53	1
PRM1	0.18	1.13	-0.37	0.73	0.53	1
KIR_ Inhibiting Subgroup 2	0.43	1.34	-0.91	1.76	0.53	1
CD207	0.17	1.13	-0.37	0.72	0.54	1
CCR2	0.06	1.04	-0.13	0.25	0.54	1
ITGAL	0.03	1.02	-0.07	0.14	0.54	1
FCGR2A	-0.09	0.94	-0.37	0.19	0.54	1
CXCR5	0.08	1.06	-0.17	0.33	0.54	1
RORA	0.06	1.04	-0.12	0.24	0.54	1
MRC1	-0.12	0.92	-0.52	0.27	0.54	1
CD84	0.05	1.04	-0.12	0.23	0.54	1

HMGB1	0.02	1.02	-0.05	0.09	0.54	1
ICAM1	-0.08	0.95	-0.34	0.18	0.54	1
TBX21	-0.08	0.95	-0.33	0.17	0.55	1
YTHDF2	0.03	1.02	-0.07	0.14	0.55	1
VEGFA	-0.08	0.95	-0.34	0.18	0.55	1
IL3	0.19	1.14	-0.42	0.80	0.55	1
LCP1	-0.06	0.96	-0.24	0.13	0.55	1
PIK3CG	-0.04	0.97	-0.16	0.09	0.55	1
CD86	0.06	1.04	-0.14	0.26	0.56	1
IL24	-0.13	0.91	-0.58	0.31	0.56	1
IGLL1	0.17	1.12	-0.40	0.73	0.57	1
MEFV	-0.07	0.95	-0.31	0.17	0.57	1
SMPD3	0.32	1.25	-0.78	1.43	0.57	1
MME	-0.10	0.93	-0.44	0.24	0.57	1
CCR5	-0.07	0.95	-0.32	0.18	0.57	1
CFI	0.17	1.12	-0.40	0.73	0.57	1
IFNA7	0.14	1.10	-0.33	0.60	0.57	1
MARCO	0.39	1.31	-0.96	1.74	0.57	1
IL7R	0.05	1.04	-0.12	0.22	0.57	1
NFKB1	-0.05	0.97	-0.21	0.12	0.58	1
CSF2RB	-0.07	0.96	-0.30	0.17	0.58	1
CFD	0.15	1.11	-0.39	0.70	0.58	1
CTSL	0.44	1.36	-1.15	2.04	0.59	1
CD19	0.07	1.05	-0.19	0.34	0.59	1
SLAMF7	0.08	1.05	-0.20	0.35	0.59	1
APOE	0.15	1.11	-0.39	0.69	0.59	1
MAGEA1	-0.17	0.89	-0.79	0.45	0.59	1
LAMP1	-0.03	0.98	-0.15	0.09	0.59	1
IL25	-0.15	0.90	-0.70	0.40	0.59	1
CD53	-0.04	0.97	-0.21	0.12	0.59	1
TREM2	0.14	1.10	-0.37	0.65	0.59	1
IFNA17	0.14	1.10	-0.36	0.63	0.60	1
MAPK8	-0.03	0.98	-0.16	0.09	0.60	1
ATF1	-0.03	0.98	-0.12	0.07	0.60	1
IL1RL2	0.14	1.10	-0.39	0.68	0.60	1
MAVS	-0.03	0.98	-0.15	0.09	0.61	1
IL23A	0.07	1.05	-0.19	0.33	0.61	1
ITGA1	0.43	1.35	-1.20	2.06	0.61	1
CYFIP2	-0.02	0.99	-0.11	0.06	0.61	1
LYN	-0.06	0.96	-0.28	0.17	0.61	1
CMA1	0.14	1.10	-0.40	0.67	0.61	1
SPP1	0.24	1.18	-0.69	1.18	0.61	1
TYK2	-0.03	0.98	-0.17	0.10	0.62	1
IL22RA1	0.16	1.11	-0.45	0.76	0.62	1
C8B	0.14	1.10	-0.40	0.68	0.62	1
CCR3	-0.09	0.94	-0.46	0.27	0.62	1
CD1C	-0.06	0.96	-0.30	0.18	0.62	1
VEGFC	0.32	1.25	-0.93	1.56	0.62	1
CDH5	0.12	1.09	-0.36	0.61	0.62	1
CCL8	0.35	1.27	-1.04	1.74	0.62	1
KLRD1	-0.07	0.96	-0.33	0.20	0.63	1
CKLF	-0.07	0.96	-0.33	0.19	0.63	1
NFATC2	0.04	1.03	-0.13	0.21	0.63	1
LILRB3	-0.06	0.96	-0.31	0.19	0.63	1
PRAME	0.14	1.11	-0.44	0.73	0.63	1
SYCP1	-0.15	0.90	-0.78	0.47	0.63	1
RIPK2	0.05	1.04	-0.16	0.26	0.63	1
PDGFRB	0.41	1.32	-1.25	2.06	0.63	1
TARP	-0.08	0.95	-0.39	0.24	0.64	1
ITGAE	0.04	1.03	-0.13	0.21	0.64	1
SIGIRR	0.04	1.02	-0.11	0.18	0.64	1

CX3CR1	0.06	1.04	-0.19	0.31	0.64	1
BST1	-0.06	0.96	-0.32	0.19	0.64	1
PDCD1	0.36	1.29	-1.15	1.88	0.64	1
C1S	0.10	1.08	-0.33	0.54	0.64	1
IL17RB	-0.11	0.93	-0.55	0.34	0.64	1
MICA	0.07	1.05	-0.22	0.36	0.64	1
ARG2	0.40	1.32	-1.29	2.09	0.65	1
IL34	-0.10	0.93	-0.52	0.32	0.65	1
CARD11	0.04	1.03	-0.15	0.23	0.65	1
CLEC6A	0.37	1.29	-1.22	1.96	0.65	1
CCL28	-0.14	0.91	-0.73	0.46	0.65	1
FLT3	-0.41	0.76	-2.18	1.37	0.66	1
ABCB1	-0.05	0.97	-0.26	0.16	0.66	1
SELL	0.06	1.04	-0.21	0.33	0.66	1
MYD88	-0.04	0.97	-0.24	0.15	0.66	1
ITGA6	0.04	1.03	-0.14	0.23	0.66	1
CTSG	0.30	1.23	-1.02	1.62	0.66	1
TNFRSF13C	0.06	1.04	-0.21	0.33	0.66	1
SMAD2	-0.02	0.99	-0.12	0.08	0.66	1
GZMM	0.05	1.03	-0.17	0.26	0.66	1
CAMP	-0.08	0.95	-0.45	0.29	0.67	1
CD48	0.04	1.03	-0.13	0.21	0.67	1
IRF1	0.05	1.04	-0.19	0.30	0.67	1
EBI3	-0.11	0.93	-0.63	0.40	0.67	1
MERTK	-0.37	0.77	-2.08	1.34	0.67	1
MAP2K1	-0.03	0.98	-0.14	0.09	0.67	1
CDK1	0.33	1.26	-1.22	1.88	0.68	1
CD160	-0.08	0.95	-0.45	0.29	0.68	1
CD2	0.03	1.02	-0.13	0.20	0.68	1
SH2D1B	-0.06	0.96	-0.34	0.22	0.68	1
CD1B	0.12	1.08	-0.44	0.67	0.69	1
CEACAM8	0.27	1.21	-1.04	1.58	0.69	1
EGR1	0.10	1.07	-0.37	0.56	0.69	1
CXCL1	-0.06	0.96	-0.34	0.22	0.69	1
JAM3	0.09	1.06	-0.34	0.52	0.69	1
IFNA2	0.12	1.09	-0.48	0.72	0.69	1
PSMB7	0.02	1.01	-0.08	0.13	0.70	1
GZMK	0.05	1.03	-0.20	0.30	0.70	1
CD46	0.03	1.02	-0.13	0.19	0.70	1
MASP2	0.12	1.09	-0.49	0.73	0.70	1
NEFL	0.24	1.18	-0.97	1.44	0.70	1
MCAM	0.10	1.07	-0.42	0.62	0.70	1
HLADPB1	0.03	1.02	-0.14	0.20	0.71	1
IL3RA	0.08	1.06	-0.34	0.50	0.71	1
CHUK	-0.03	0.98	-0.17	0.12	0.71	1
MBL2	-0.11	0.93	-0.70	0.47	0.71	1
LCK	0.03	1.02	-0.12	0.18	0.71	1
CXCL14	-0.11	0.93	-0.69	0.47	0.71	1
GPI	-0.03	0.98	-0.16	0.11	0.71	1
IL1RAPL2	0.08	1.05	-0.33	0.48	0.71	1
ITGAM	-0.04	0.97	-0.25	0.18	0.72	1
ATF2	0.02	1.01	-0.08	0.11	0.72	1
TPSAB1	-0.19	0.88	-1.25	0.88	0.73	1
BMI1	0.03	1.02	-0.12	0.17	0.73	1
CCL26	0.11	1.08	-0.49	0.70	0.73	1
SLAMF1	0.04	1.03	-0.18	0.25	0.74	1
MAP3K1	-0.02	0.98	-0.16	0.11	0.74	1
CD247	0.03	1.02	-0.13	0.19	0.74	1
LBP	0.10	1.07	-0.50	0.71	0.74	1
KIR3DL2	0.44	1.36	-2.16	3.04	0.74	1
JAK3	0.04	1.02	-0.18	0.25	0.74	1

DUSP4	0.08	1.06	-0.41	0.58	0.74	1
A2M	0.09	1.06	-0.45	0.62	0.74	1
CD37	-0.02	0.98	-0.17	0.12	0.75	1
HLAC	-0.06	0.96	-0.41	0.30	0.75	1
BIRC5	0.22	1.16	-1.12	1.55	0.75	1
IL1R1	-0.32	0.80	-2.26	1.63	0.75	1
IL17RA	-0.04	0.98	-0.25	0.18	0.75	1
CXCL6	-0.27	0.83	-1.96	1.42	0.75	1
PPBP	0.06	1.05	-0.35	0.47	0.76	1
STAT6	-0.02	0.98	-0.17	0.12	0.76	1
HLAG	-0.06	0.96	-0.46	0.33	0.76	1
CD9	0.04	1.03	-0.23	0.31	0.76	1
PVR	-0.04	0.97	-0.29	0.22	0.76	1
AKT3	-0.02	0.99	-0.17	0.12	0.77	1
C5	0.29	1.22	-1.62	2.19	0.77	1
TLR7	0.30	1.23	-1.70	2.30	0.77	1
CXCR3	0.04	1.03	-0.21	0.28	0.77	1
IL12B	0.08	1.06	-0.46	0.63	0.77	1
CD79B	-0.03	0.98	-0.25	0.19	0.78	1
PRF1	-0.03	0.98	-0.28	0.21	0.79	1
KIR3DL3	-0.09	0.94	-0.74	0.56	0.79	1
ATG5	0.02	1.01	-0.11	0.14	0.79	1
MS4A1	0.04	1.03	-0.23	0.30	0.79	1
IFNA1	-0.08	0.94	-0.69	0.52	0.79	1
MAGEC2	0.08	1.06	-0.50	0.66	0.79	1
CD1D	-0.02	0.98	-0.19	0.14	0.79	1
TNFRSF9	-0.28	0.82	-2.36	1.79	0.79	1
MUC1	0.23	1.17	-1.45	1.91	0.79	1
IL13RA2	0.09	1.06	-0.56	0.74	0.79	1
FOXJ1	-0.28	0.83	-2.31	1.76	0.79	1
CCL18	0.07	1.05	-0.42	0.55	0.79	1
PMCH	-0.08	0.95	-0.64	0.49	0.79	1
CTSS	0.02	1.02	-0.16	0.21	0.79	1
C1QA	0.14	1.10	-0.91	1.19	0.80	1
KLRC2	-0.05	0.97	-0.40	0.30	0.80	1
CCL25	-0.06	0.96	-0.54	0.42	0.80	1
TGFB1	-0.02	0.99	-0.13	0.10	0.80	1
KLRF1	-0.04	0.97	-0.33	0.25	0.80	1
CCL27	-0.06	0.96	-0.53	0.41	0.80	1
ZNF205	0.07	1.05	-0.48	0.62	0.80	1
LAG3	0.04	1.03	-0.28	0.36	0.81	1
RRAD	0.07	1.05	-0.47	0.60	0.81	1
IL5	0.08	1.06	-0.55	0.71	0.81	1
STAT3	-0.02	0.98	-0.22	0.17	0.81	1
IL2RB	-0.03	0.98	-0.26	0.20	0.81	1
S100B	0.08	1.06	-0.56	0.72	0.81	1
CD80	0.20	1.15	-1.42	1.82	0.81	1
IRF2	0.02	1.02	-0.17	0.22	0.81	1
TNFRSF1B	-0.02	0.99	-0.18	0.14	0.81	1
ADA	0.02	1.01	-0.15	0.19	0.81	1
DUSP6	-0.02	0.98	-0.23	0.18	0.82	1
TNFSF13	-0.02	0.98	-0.22	0.17	0.82	1
ATG7	0.02	1.01	-0.15	0.18	0.82	1
TNFRSF4	0.27	1.20	-2.04	2.57	0.82	1
HLADQA1	-0.26	0.83	-2.51	1.99	0.82	1
SLAMF6	-0.02	0.99	-0.22	0.17	0.82	1
CXCL5	0.06	1.04	-0.47	0.59	0.82	1
RUNX3	-0.02	0.99	-0.18	0.14	0.83	1
MS4A2	-0.17	0.89	-1.63	1.30	0.83	1
CCL7	-0.07	0.95	-0.67	0.53	0.83	1
LY9	0.02	1.01	-0.14	0.18	0.83	1

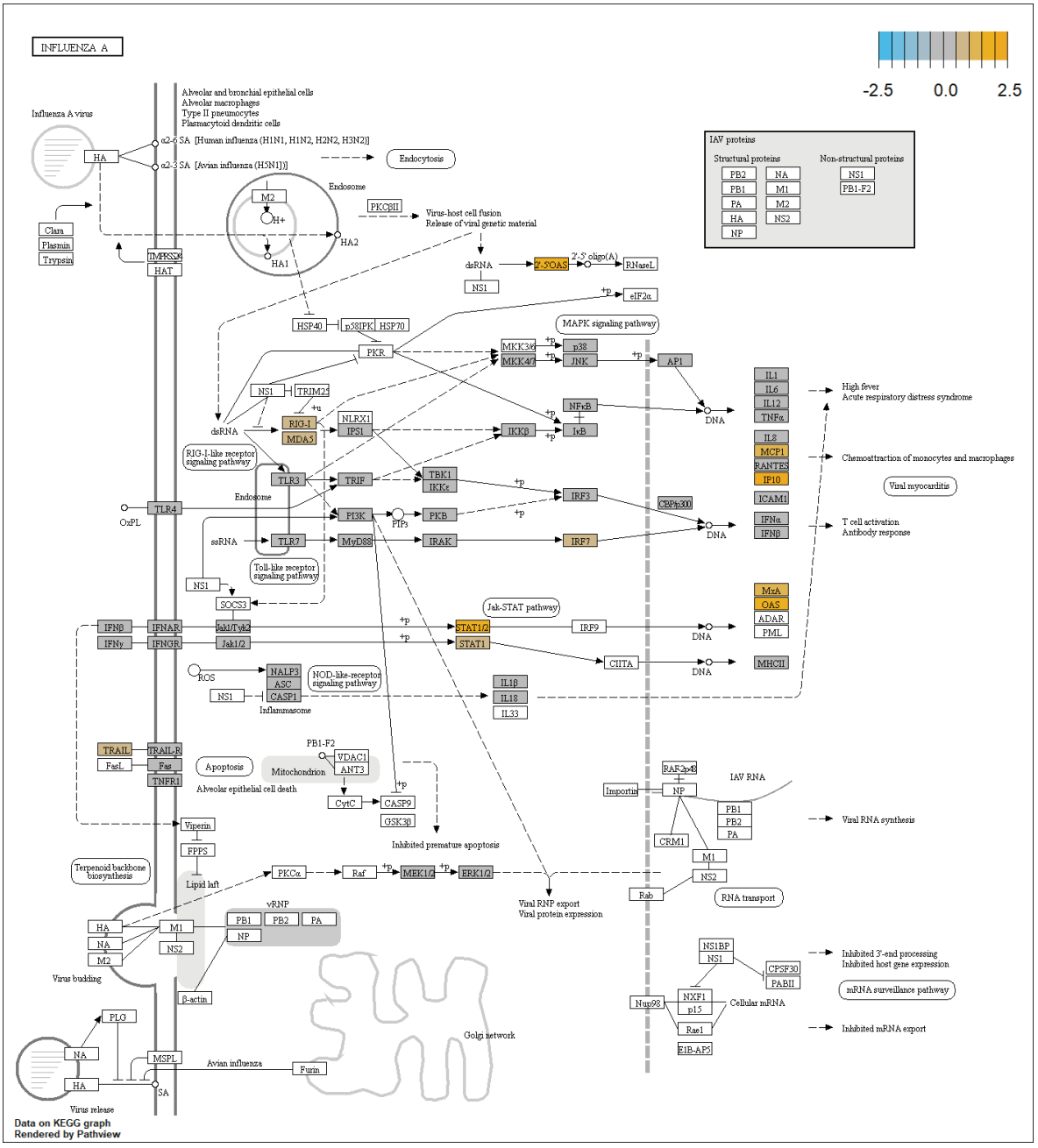
CCL4	0.03	1.02	-0.22	0.28	0.83	1
SYK	-0.02	0.99	-0.19	0.15	0.83	1
CCL20	0.33	1.25	-2.76	3.42	0.84	1
NOS2A	0.06	1.05	-0.55	0.68	0.84	1
TICAM2	-0.03	0.98	-0.27	0.22	0.84	1
ITGAX	-0.02	0.98	-0.25	0.20	0.84	1
IL27	0.17	1.12	-1.42	1.75	0.84	1
GZMA	-0.02	0.98	-0.26	0.21	0.84	1
CXCL9	0.20	1.15	-1.72	2.12	0.84	1
LILRA4	0.16	1.12	-1.37	1.69	0.84	1
TNFSF18	0.06	1.04	-0.51	0.62	0.84	1
CLEC4A	0.02	1.02	-0.20	0.24	0.84	1
IL7	0.22	1.16	-1.90	2.33	0.84	1
ITGB2	0.02	1.01	-0.14	0.17	0.84	1
CEACAM6	0.12	1.09	-1.08	1.33	0.84	1
CHIT1	-0.17	0.89	-1.84	1.51	0.84	1
IL32	-0.02	0.99	-0.23	0.19	0.85	1
PTGDR2	-0.04	0.97	-0.47	0.38	0.85	1
PLA2G6	0.01	1.01	-0.12	0.15	0.85	1
MAGEA4	0.05	1.04	-0.50	0.61	0.85	1
IGF1R	-0.02	0.99	-0.21	0.18	0.86	1
FN1	0.05	1.04	-0.54	0.65	0.86	1
IL19	-0.05	0.97	-0.61	0.51	0.86	1
CSF3	0.04	1.03	-0.44	0.53	0.86	1
SPINK5	-0.05	0.96	-0.64	0.53	0.86	1
CMKLR1	-0.03	0.98	-0.36	0.30	0.86	1
HAVCR2	0.02	1.01	-0.17	0.21	0.86	1
CASP10	0.20	1.15	-1.98	2.38	0.86	1
GATA3	0.18	1.14	-1.87	2.24	0.86	1
IL9	0.05	1.04	-0.55	0.66	0.86	1
CXCL3	-0.18	0.88	-2.19	1.84	0.86	1
TP53	-0.01	0.99	-0.14	0.12	0.86	1
C3	0.25	1.19	-2.63	3.13	0.87	1
CD200	0.03	1.02	-0.28	0.33	0.87	1
DDX43	-0.12	0.92	-1.47	1.23	0.87	1
MAPK1	0.02	1.01	-0.19	0.23	0.87	1
TTK	0.13	1.09	-1.38	1.63	0.87	1
REPS1	0.02	1.01	-0.19	0.23	0.87	1
IL1RL1	-0.09	0.94	-1.24	1.05	0.87	1
FEZ1	-0.17	0.89	-2.18	1.85	0.87	1
GZMB	-0.02	0.98	-0.33	0.28	0.87	1
MAP3K7	0.01	1.00	-0.08	0.10	0.88	1
CREB5	-0.02	0.99	-0.29	0.25	0.88	1
TIRAP	-0.02	0.99	-0.21	0.18	0.88	1
EOMES	-0.14	0.91	-1.84	1.57	0.88	1
F2RL1	-0.03	0.98	-0.37	0.32	0.88	1
SPACA3	-0.04	0.97	-0.62	0.53	0.88	1
CD163	0.02	1.02	-0.29	0.34	0.88	1
MAGEB2	0.04	1.03	-0.46	0.54	0.88	1
IL21R	0.02	1.01	-0.21	0.25	0.88	1
CSF2	-0.05	0.97	-0.64	0.55	0.88	1
TNFRSF18	0.16	1.12	-1.91	2.23	0.88	1
TNFRSF12A	0.20	1.15	-2.42	2.81	0.88	1
IL23R	0.10	1.07	-1.18	1.37	0.88	1
IRF3	-0.01	0.99	-0.20	0.17	0.88	1
ELK1	0.13	1.09	-1.55	1.80	0.88	1
BAGE	-0.04	0.98	-0.51	0.44	0.88	1
SPA17	0.20	1.15	-2.43	2.83	0.88	1
SPN	0.01	1.01	-0.16	0.18	0.89	1
TLR3	-0.11	0.92	-1.67	1.44	0.89	1
AMICA1	-0.01	0.99	-0.20	0.18	0.89	1

TNFRSF13B	-0.13	0.92	-1.91	1.65	0.89	1
C8A	0.04	1.03	-0.54	0.62	0.89	1
PSEN2	0.23	1.17	-2.98	3.44	0.89	1
PRKCE	0.17	1.13	-2.23	2.58	0.89	1
GAGE1	0.19	1.14	-2.44	2.82	0.89	1
S100A7	0.04	1.03	-0.52	0.60	0.89	1
LTK	-0.11	0.93	-1.68	1.46	0.89	1
IKBKG	-0.01	0.99	-0.16	0.14	0.89	1
DMBT1	0.17	1.13	-2.36	2.70	0.90	1
PRKCD	-0.01	0.99	-0.20	0.18	0.90	1
BAX	-0.01	1.00	-0.10	0.09	0.90	1
CD79A	0.02	1.01	-0.24	0.27	0.90	1
CD59	-0.02	0.99	-0.30	0.27	0.90	1
RPS6	0.01	1.01	-0.19	0.21	0.90	1
XCL2	0.02	1.01	-0.31	0.35	0.91	1
IL5RA	-0.07	0.95	-1.33	1.18	0.91	1
OSM	0.08	1.06	-1.32	1.48	0.91	1
IFNG	0.09	1.06	-1.43	1.60	0.91	1
MIF	0.01	1.01	-0.14	0.16	0.91	1
CR2	0.16	1.12	-2.69	3.02	0.91	1
ITGB4	-0.10	0.93	-1.89	1.69	0.91	1
CD1A	0.12	1.08	-1.92	2.16	0.91	1
CLEC5A	0.09	1.06	-1.48	1.66	0.91	1
HLAA	-0.01	0.99	-0.19	0.17	0.91	1
CCL13	0.16	1.12	-2.65	2.96	0.91	1
SH2D1A	-0.01	0.99	-0.21	0.19	0.91	1
IL11	-0.03	0.98	-0.64	0.58	0.92	1
RAG1	0.03	1.02	-0.44	0.49	0.92	1
ITCH	-0.01	1.00	-0.10	0.09	0.92	1
FADD	-0.13	0.91	-2.56	2.30	0.92	1
TPTE	-0.02	0.99	-0.43	0.39	0.92	1
CD44	-0.01	1.00	-0.11	0.10	0.92	1
CTAG1B	-0.10	0.93	-1.93	1.74	0.92	1
IL22RA2	0.03	1.02	-0.51	0.57	0.92	1
CD70	0.09	1.06	-1.61	1.79	0.92	1
RORC	0.02	1.01	-0.32	0.35	0.92	1
KIT	-0.11	0.93	-2.30	2.08	0.92	1
TNFRSF10B	-0.01	0.99	-0.20	0.18	0.92	1
JAK1	0.00	1.00	-0.10	0.09	0.92	1
CD164	-0.01	1.00	-0.16	0.15	0.93	1
CCR4	0.12	1.09	-2.44	2.68	0.93	1
PLAUR	-0.01	0.99	-0.27	0.25	0.93	1
MAGEA3	-0.03	0.98	-0.61	0.55	0.93	1
SEMG1	0.11	1.08	-2.26	2.48	0.93	1
TNF	0.01	1.01	-0.16	0.17	0.93	1
COLEC12	0.03	1.02	-0.52	0.57	0.93	1
IL12RB2	-0.09	0.94	-2.08	1.90	0.93	1
KLRG1	-0.02	0.99	-0.36	0.33	0.93	1
CREB1	0.01	1.01	-0.16	0.18	0.93	1
COL3A1	-0.13	0.92	-2.98	2.73	0.93	1
CD68	-0.01	0.99	-0.21	0.19	0.93	1
HLAB	-0.01	1.00	-0.18	0.16	0.93	1
CD81	-0.01	1.00	-0.18	0.16	0.94	1
IL4	0.05	1.04	-1.32	1.43	0.94	1
CCR9	0.06	1.04	-1.37	1.48	0.94	1
TMEFF2	-0.02	0.99	-0.56	0.52	0.94	1
IRGM	-0.06	0.96	-1.82	1.69	0.94	1
CREBBP	-0.10	0.93	-2.93	2.73	0.95	1
CTSH	-0.01	1.00	-0.17	0.16	0.95	1
EGR2	-0.09	0.94	-2.64	2.46	0.95	1
ATG12	0.10	1.07	-2.76	2.96	0.95	1

POU2AF1	0.07	1.05	-2.06	2.20	0.95	1
AXL	0.02	1.01	-0.44	0.47	0.95	1
GZMH	0.01	1.01	-0.39	0.42	0.95	1
FAS	0.01	1.01	-0.30	0.32	0.95	1
FCER2	0.01	1.01	-0.29	0.31	0.95	1
ENG	0.09	1.06	-2.61	2.79	0.95	1
PDGFC	0.09	1.06	-2.53	2.71	0.95	1
AMBP	0.02	1.01	-0.62	0.66	0.95	1
HLADQB1	-0.06	0.96	-1.82	1.71	0.95	1
CXCL12	0.02	1.01	-0.60	0.64	0.95	1
CD55	0.12	1.09	-3.65	3.90	0.95	1
DPP4	-0.11	0.93	-3.65	3.42	0.95	1
IL21	-0.02	0.99	-0.55	0.52	0.95	1
TNFRSF14	0.00	1.00	-0.15	0.16	0.95	1
IL1B	-0.01	0.99	-0.39	0.36	0.95	1
IL10RA	0.00	1.00	-0.11	0.11	0.95	1
PSMD7	0.00	1.00	-0.08	0.08	0.96	1
C1R	0.08	1.06	-2.99	3.15	0.96	1
TXK	0.00	1.00	-0.18	0.19	0.96	1
NFATC3	0.00	1.00	-0.10	0.09	0.96	1
F12	-0.04	0.97	-1.72	1.63	0.96	1
C4BPA	0.03	1.02	-1.05	1.10	0.96	1
DEFB1	0.01	1.01	-0.54	0.57	0.96	1
BLNK	0.06	1.04	-2.57	2.68	0.97	1
PLAU	-0.05	0.97	-2.17	2.08	0.97	1
IL12A	-0.04	0.97	-1.85	1.78	0.97	1
SERPINB2	0.04	1.03	-2.09	2.18	0.97	1
TGFB2	-0.01	1.00	-0.45	0.44	0.97	1
CSF1	0.04	1.02	-2.20	2.27	0.98	1
CXCL2	-0.03	0.98	-1.89	1.83	0.98	1
CCL1	0.04	1.03	-2.50	2.58	0.98	1
TNFSF15	0.10	1.07	-6.98	7.17	0.98	1
TLR9	-0.07	0.96	-5.19	5.06	0.98	1
CTAGE1	-0.01	0.99	-0.65	0.63	0.98	1
FCGR1A	0.01	1.01	-0.64	0.65	0.98	1
CD3EAP	0.04	1.03	-3.28	3.36	0.98	1
INPP5D	0.00	1.00	-0.12	0.13	0.98	1
CSF1R	-0.02	0.98	-2.30	2.25	0.98	1
SSX1	-0.01	1.00	-0.57	0.55	0.98	1
ICAM4	-0.02	0.98	-2.40	2.35	0.98	1
NCR1	0.00	1.00	-0.29	0.28	0.99	1
CCL24	-0.01	1.00	-0.70	0.68	0.99	1
ATM	0.03	1.02	-2.77	2.82	0.99	1
HRAS	0.03	1.02	-2.94	2.99	0.99	1
ST6GAL1	0.00	1.00	-0.15	0.15	0.99	1
LY96	0.00	1.00	-0.36	0.36	0.99	1
MICB	0.00	1.00	-0.21	0.21	0.99	1
HLAE	0.00	1.00	-0.15	0.15	0.99	1
CCL16	0.00	1.00	-0.60	0.59	0.99	1
IL1A	0.00	1.00	-0.56	0.57	0.99	1
CD8A	0.00	1.00	-0.28	0.27	0.99	1
CASP3	0.00	1.00	-0.10	0.10	0.99	1
AIRE	0.01	1.01	-2.02	2.05	0.99	1
KIR_Activating Subgroup_1	-0.01	1.00	-0.91	0.89	0.99	1
NT5E	-0.01	0.99	-2.00	1.98	0.99	1
FOXP3	0.01	1.01	-1.78	1.80	0.99	1
CLU	0.00	1.00	-0.57	0.56	0.99	1
FCGR3A	0.00	1.00	-0.28	0.28	0.99	1
ICOSLG	0.01	1.01	-2.38	2.40	0.99	1
NCAM1	-0.01	0.99	-2.10	2.08	0.99	1

ITGA2	-0.02	0.99	-3.84	3.81	0.99	1
LAIR2	0.00	1.00	-0.18	0.18	0.99	1
CCL17	0.00	1.00	-0.58	0.59	0.99	1
IL10	0.01	1.01	-2.99	3.01	1.00	1
CCL23	0.00	1.00	-1.36	1.37	1.00	1
CD7	0.00	1.00	-0.19	0.19	1.00	1
PAX5	0.00	1.00	-1.87	1.87	1.00	1
CT45A1	0.00	1.00	-1.74	1.75	1.00	1
ABL1	0.00	1.00	-5.41	5.40	1.00	1
SSX4	0.00	1.00	-5.40	5.40	1.00	1

Supplement 5: A KEGG pathway of the genes involved in the immune response to influenza A. Genes shown in white are known to be involved in the pathway however, but not represented within the Pan Cancer Immune Profiling Panel. Genes and gene families that are over-expressed in the KEGG pathway are shown in shades of orange (log2 fold-difference 0 to 2.5). The genes upregulated in athletes reported URS are as follow: *RIG1* (retinoic acid inducible gene 1) and *MDA5* (melanoma differentiation associated protein 5) translation yields proteins involved in the pattern recognition of viruses, the *OAS* genes (oligoadenylate synthase) leads to synthesis of protein capable of degrading viral RNA, *IRF3* (interferon regulatory factor 3) genes products stimulates transcription of interferon genes while the product of the *MCP1* (monocyte chemotactic protein 1) and *IP10* genes (interferon-inducible cytokine10) are involved in T cell activation and migration of monocytes. *TRAIL* (TNF-related apoptosis-inducing ligand), a gene whose protein is involved in initiation of apoptosis was also upregulated.



Supplement 6: A KEGG pathway of the genes involved in the immune response to herpes simplex virus. Genes shown in white are known to be involved in the pathway however, are not represented within the Pan Cancer Immune Profiling Panel. Genes and gene families that are over-expressed in the KEGG pathway are shown in shades of orange (log2 fold-difference 0 to 2.5). The genes upregulated in athletes who reported URS are as follow: *RIG1* (retinoic acid inducible gene 1) and *MDA5* (melanoma differentiation associated protein 5) translation yields proteins involved in the pattern recognition of viruses, the *2'-5'OAS* (oligoadenylate synthase 1) gene leads to synthesis of protein capable of degrading viral RNA, *IRF3* (interferon regulatory factor 3) gene products stimulates transcription of interferon genes while the product of the *MCP1* (monocyte chemotactic protein 1) and *ISG56* genes (interferon stimulated gene 56) are involved in T cell activation, monocytes activation and migration. *ISG56* is also involved in sensing single stranded (viral) RNA.