Differential expression of heterogenous nuclear ribonucleoproteins in viral co-infections.

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Co-infection is a phenomena by which a host or cell is infected by at least two pathogens^{1,2}. The severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, has resulted in the death of greater than 200,000 people in the United States in less than one year, with an impending influenza season, raising the prospect of co-infection-related complications^{3,4,5}. We mined a published microarray dataset⁶ to discover genes associated with viral co-infection in the blood of human patients, including co-infections involving human rhinovirus, enterovirus, respiratory syncytial virus A, human coronavirus HKU1 and influenza B. We found significant differential expression of heterogenous nuclear ribonucleoproteins including hnRNP K in the blood of patients with viral co-infections. These data suggest hnRNPs may be of relevance to immunity against viral co-infections or utilized by viruses during completion of the viral life cycle in the context of co-infection.

Keywords: viral co-infection, coronavirus, HCoV HKU1, SARS-CoV-2, systems biology of viral infection.

1 The most basic relationship between host and pathogen is a simple infection between one
2 pathogen and one host or cell. Re-infection, or a second infection of a host with the same
3 pathogen despite an initial immune response can occur⁷. Super-infection, a process by which a
4 bacterial infection complicates an existing viral infection, such as those found in the respiratory
5 tract, can occur^{8,9}. A third type of complex infection setting is known as co-infection, a process
6 by which a cell or organism already infected with a virus is then infected with a second, different
7 virus^{1,2}. The novel coronavirus SARS-CoV-2 has resulted in the death of over 200,000
8 Americans in less than one year^{3,4}. The upcoming influenza season raises the prospect of
9 complications resulting from Influenza and SARS-CoV-2 co-infection. A recent study of patients
10 in Northern California found that of 116 patients testing positive for SARS-CoV-2, 24 (20.7%)
11 possessed a co-infection⁵. Little is known about the transcriptional changes that accompany
12 coronavirus co-infection. We mined published microarray data⁶ to understand in an unbiased
13 fashion and at the systems-level the most significant gene expression changes in the blood of
14 patients with viral co-infections, including viral co-infections involving a human coronavirus.
15 We observed significant transcriptional changes in expression of multiple heterogenous nuclear
16 ribonucleoproteins (hnRNPs), including hnRNP K, representing some of the largest gene
17 expression changes transcriptome-wide in the blood of patients with viral co-infection.
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25 **Methods**

26 We used dataset GSE68310⁶ for this differential gene expression analysis of the blood of
27 patients with viral co-infections. GSE68310 was generated using Illumina HumanHT-12 V4.0
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expression beadchip technology; analysis was performed with platform GPL10558. In the study from which this microarray data was obtained, investigators collected peripheral blood from patients at baseline, day 0 of infection, correlating with a visit to the clinic upon infection with a respiratory illness; day 2, day 4, day 6, and day 21 of infection following the clinic visit, as well as in the season following infection (“Spring”). We compared the blood of $n=2$ patients with HCoV HKU1 and human rhinovirus co-infection (IDs: JR0207 and JR1702) at baseline, day 0, day 2, day 4, day 6, and day 21. We compared the blood of $n=1$ patient with respiratory syncytial virus A (RSVA) virus infection (ID: JR0547) to the blood of $n=1$ patient with RSVA and rhinovirus co-infection (ID: JR1145). We compared the blood of $n=1$ patient with enterovirus infection (ID: JR0471) to the blood of $n=1$ patient with enterovirus and rhinovirus infection (ID: JR0209). We compared the blood of $n=4$ patients with influenza A infection only (JR0021, JR0023, JR0025 and JR0053) to the blood of $n=4$ patients with co-infection of influenza A and human rhinovirus (IDs: JR0033, JR0147, JR0174, JR0199). We compared the blood of $n=3$ patients with influenza B infection only (IDs: JR1412, JR1491, and JR1939) to the blood of $n=3$ patients with co-infection of influenza B and human rhinovirus (IDs: JR1053, JR1120 and JR1275). We compared the blood of patients with $n=6$ patients with rhinovirus infection only (IDs: JR0148, JR0154, JR0223, JR0228, JR0276, JR0287) at baseline, day 0, day 2, day 4, day 6, day 21 and Spring. We compared the blood of $n=3$ patients with influenza B infection only (IDs: JR1412, JR1491, JR1939) at baseline, day 0, day 2, day 4, day 6, day 21 and Spring.

The Benjamini and Hochberg method of p -value adjustment was used for ranking of differential expression but raw p -values were used for assessment of statistical significance of global differential expression. Log-transformation of data was auto-detected, and the NCBI generated category of platform annotation was used. A statistical test was used to evaluate the significance of difference in hnRNP gene expression between the blood of a patient with a single infection and the blood of a patient or patient(s) with co-infection, or between the blood of patients with co-infection over time, using either a two-tailed, unpaired t-test with Welch's correction, or a one-way ANOVA with Dunnett's multiple comparisons test. All statistical tests were performed with PRISM 8.4.0 (455).

Results

We mined published microarray data⁶ to discover genes associated with viral co-infection in the blood of humans during the course of *bona fide* infections in the clinic.

Co-infection of human coronavirus HKU1 and human rhinovirus is associated with differential expression of hnRNP K, hnRNP A0, and hnRNP A3.

By comparing the blood of two patients with infection of both HCoV HKU1 and human rhinovirus at baseline, day 0, day 2, day 4, day 6, and day 21, we identified significant differential expression of hnRNP K and hnRNP A0 over the course of co-infection in patient blood (Table 1). When sorting each transcript measured by microarray based on significance of change in expression across time, hnRNP A0 ranked 201 out of 47254 total transcripts (99.6% differential expression) while hnRNP K ranked 47 out of 47254 total transcripts (99.9%

differential expression) (Table 1). Differential expression of hnRNP K and hnRNP A0 was statistically significant (Table 1; $p=0.0016619$ and $p=0.0066584$, respectively).

We obtained exact mRNA expression levels for each hnRNP to directly compare hnRNP expression over the course of co-infection. At day 2 and day 4, expression of hnRNP K was significantly decreased as compared to baseline, with a mean fold change of 0.9707 ± 0.0021 and 0.9763 ± 0.0054 , respectively (Figure 1; $p=0.0041$ at day 2 and $p=0.0117$ at day 4, respectively). At day 0 and day 4, expression of hnRNP A0 was also significantly decreased as compared to baseline, with a mean fold change of 0.9684 ± 0.0002 and 0.9692 ± 0.0028 , respectively (Table 1; $p=0.0091$ for at day 0 and $p=0.0104$ at day 4).

To a lesser extent, hnRNP A3 was also significantly differentially expressed over time in the blood of two patients with co-infection of HCoV HKU1 and human rhinovirus. When sorting each transcript measured by microarray based on significance of change in expression across time, hnRNP A3 ranked 1321 out of 47254 total transcripts (97.2% differential expression) (Table 1). Differential expression of hnRNP A3 was statistically significant (Table 1; $p=0.0424469$).

Co-infection of respiratory syncytial virus A (RSVA) and human rhinovirus is associated with differential expression of hnRNP L and hnRNP A2B1.

Next, we compared total gene expression in the blood of a patient with infection of RSVA with that of a patient with co-infection of RSVA and human rhinovirus and found significant differential expression of hnRNP L and hnRNP A2B1 (Figure 2). When sorting each

transcript measured by microarray based on significance of change in expression between single infection and co-infection, hnRNP L ranked 63 out of 47254 total transcripts (99.9% differential expression) while hnRNP A2B1 ranked 4095 out of 47254 total transcripts (91.3% differential expression) (Table 2). Differential expression of hnRNP L and hnRNP A2B1 was statistically significant (Table 2; $p=6.52E-07$ and $p=1.98E-02$, respectively).

We obtained exact hnRNP L mRNA expression levels to directly compare hnRNP L expression in RSVA infection to that of RSVA and human rhinovirus co-infection. hnRNP L was expressed at significantly lower levels in the blood of a patient with co-infection of RSVA and human rhinovirus as compared to RSVA infection only; this difference was statistically significant (Figure 2; $p<0.0001$). We calculated a mean fold change of 0.9398 ± 0.0149 in hnRNP L expression in RSVA and human rhinovirus co-infected patient blood relative to that of patient with RSVA infection only (Table 2).

Co-infection of enterovirus and human rhinovirus is associated with differential expression of hnRNP K, hnRNP R, hnRNP L, hnRNP M, and hnRNP UL1.

Next, we compared total gene expression in the blood of a patient with infection of enterovirus only with that of a patient with co-infection of enterovirus and human rhinovirus and found significant differential expression of hnRNP K, hnRNP R, hnRNP L, hnRNP M, and hnRNP UL1 (Table 3). When sorting each transcript measured by microarray based on significance of change in expression between single infection and co-infection, hnRNP K ranked 99 out of 47254 total transcripts (99.8% differential expression), hnRNP R ranked 1661 out of

47254 total transcripts (96.5% differential expression), hnRNP L ranked 1866 out of 47254 total transcripts (96.1% differential expression), hnRNP M ranked 2412 out of 47254 total transcripts (94.9% differential expression), and hnRNP UL1 ranked 4177 out of 47254 total transcripts (91.2% differential expression) (Table 3). Differential expression of hnRNP K, hnRNP R, hnRNP L, hnRNP M, and hnRNP UL1 in enterovirus and human rhinovirus co-infection was statistically significant (Table 3; $p=1.47\text{E-}07$ for hnRNP K, $p=1.46\text{E-}03$ for hnRNP R, $p=2.05\text{E-}03$ for hnRNP L, $p=4.41\text{E-}03$ for hnRNP M, and $p=1.75\text{E-}02$ for hnRNP UL1 respectively).

We obtained exact hnRNP K mRNA expression levels to directly compare hnRNP K expression in the blood in enterovirus infection to that of a patient with co-infection of enterovirus and human rhinovirus. hnRNP K was expressed at significantly higher levels in the blood of a patient with co-infection of enterovirus and human rhinovirus as compared to enterovirus infection only; this difference was statistically significant (Figure 3; $p<0.0001$). We calculated a mean fold change of 1.0814 ± 0.0153 in hnRNP K expression in enterovirus and human rhinovirus co-infected patient blood relative to enterovirus-only infected patient blood (Table 3).

Co-infection of influenza A and human rhinovirus is associated with differential expression of hnRNP A1, hnRNP D, hnRNP M, hnRNP AB, hnRNP H1, hnRNP A0, and hnRNP R.

To determine if hnRNPs were differentially expressed during influenza co-infection, we compared total gene expression in the blood of four patients with influenza A infection with that of four patients with co-infection of influenza A and human rhinovirus. We identified significant

differential expression of seven different hnRNPs in the blood of patients with influenza A and human rhinovirus co-infection (Table 4): this included hnRNP A1, hnRNP D, hnRNP M, hnRNP AB, hnRNP H1, hnRNP A0, and hnRNP R. When sorting all transcripts based on significance of difference in expression between the blood of patients with influenza A and human rhinovirus infection as compared to that of patients with influenza A infection only, hnRNP A1 ranked 404 out of 47254 total transcripts (99.1% differential expression), hnRNP D ranked 1159 out of 47254 total transcripts (97.5% differential expression), hnRNP M ranked 1248 out of 47254 total transcripts (97.4% differential expression), hnRNP AB ranked 1923 out of 47254 total transcripts (95.9% differential expression), hnRNP H1 ranked 1937 out of 47254 total transcripts (95.9% differential expression), hnRNP A0 ranked 2059 out of 47254 total transcripts (95.6% differential expression), and hnRNP R ranked 2569 out of 47254 total transcripts (94.6% differential expression). Differential expression of hnRNP A1, hnRNP D and hnRNP M, hnRNP AB, hnRNP H1, hnRNP A0, and hnRNP R in influenza A and human rhinovirus co-infection was statistically significant ($p=2.96E-07$ for hnRNP A1, $p=5.89E-05$ for hnRNP D, $p=8.42E-05$ for hnRNP M, $p=4.56E-04$ for hnRNP AB, $p=4.68E-04$ for hnRNP H1, $p=5.79E-04$ for hnRNP A0, and $p=1.26E-03$ for hnRNP R).

Co-infection of influenza B and human rhinovirus is associated with differential expression of hnRNP DL, hnRNP A0 and hnRNP K.

Finally, we also compared total gene expression in the blood of three patients with influenza B single infection with that of three patients with influenza B and human rhinovirus

co-infection, finding that hnRNP DL, hnRNP A0 and hnRNP K were each among the genes most differentially expressing during influenza B and human rhinovirus co-infection (Table 5). When sorting each transcript measured by microarray based on significance of change in expression between single infection and co-infection, hnRNP DL ranked 472 out of 47254 total transcripts (99.0% differential expression), hnRNP A0 ranked 1011 out of 47254 total transcripts (97.9% differential expression), and hnRNP K ranked 1723 out of 47254 total transcripts (96.4% differential expression). Differential expression of hnRNP DL, hnRNP A0 and hnRNP K in influenza B and human rhinovirus co-infection was statistically significant ($p=1.36E-05$ for hnRNP DL, $p=1.09E-04$ for hnRNP A0, and $p=4.45E-04$ for hnRNP K, respectively).

Infection with human rhinovirus infection only is associated with differential expression of hnRNP DL, hnRNP A0, hnRNP UL1, hnRNP M, hnRNP R and hnRNPA2B1 but not hnRNP K, and infection with influenza B only is associated with less significant differential expression of hnRNP K.

To determine whether differential expression of hnRNPs was specific to viral co-infection, we examined differential expression of hnRNPs in six patients with infection of human rhinovirus only. We observed significant differential expression of multiple hnRNPs, including hnRNP DL (Figure 4), as well as several other hnRNPs that were found to be differentially expressed in the context of viral co-infection, including hnRNP A0, hnRNP UL1, hnRNP M, hnRNP R, and hnRNP A2B1. However, hnRNP K, an hnRNP differentially expressed in the context of multiple viral co-infections involving human rhinovirus, was not differentially expressed in patients with infection of human rhinovirus only (Table 6). Moreover, while

hnRNP K differential expression could be observed in the blood of four patients over the course of influenza B infection only, it was both less significant (Table 7; $p=3.47\text{E-}02$) and less differential (Table 7; rank 6830 out of 47254 transcripts, or 85.5% differential expression) than in co-infection of influenza B and human rhinovirus (Table 5; rank 1723 out of 47254 transcripts, or 96.4% differential expression; $p=4.45\text{E-}04$). We conclude that differential expression of hnRNP K may be a specific feature of viral co-infections.

Discussion

We found significant differential expression of multiple heterogeneous nuclear ribonucleoproteins (hnRNPs) in human blood, in several viral co-infections including in a patient with viral co-infection of human rhinovirus and human coronavirus HKU1. Of all differentially expressed hnRNPs identified, differential expression of hnRNP K appeared to be most specific to viral co-infection as opposed to being a feature of viral infection in general. hnRNP K is phosphorylated by ERK on serine residues 284 and 353, leading to its localization in the cytoplasm, and mutation of these residues results in inability of hnRNP K to accumulate in the cytoplasm and function in translational regulation, inhibiting translation of messenger RNAs containing a 3' differentiation-control element (DICE)¹⁰. In the context of some viral infections, hnRNP K has been described as an interaction partner of viral proteins or important for the viral life cycle. hnRNP K can interact with the core protein of the dengue virus¹¹, as well as with the HIV-1 Nef protein¹². Interaction of hnRNP K with Nef is positively associated with transcription of HIV-1 viral genes through Tat¹².

1 Involvement of hnRNPs in the molecular biology of the coronavirus family has been described¹³;
2 this includes interaction between the SARS-CoV-1 nucleocapsid protein and hnRNP
3 A1¹⁴, as well as interaction of hnRNP Q with the 3' end of the transmissible gastroenteritis
4 coronavirus (TGEV) genome. Depletion of hnRNP Q resulted in decreased transcription of
5 TGEV viral RNAs¹⁵.
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8 By mining published microarray data⁶, we found specific differential expression of
9 hnRNP K in human blood in multiple viral co-infections including human coronavirus HKU1
10 and human rhinovirus co-infection, human rhinovirus and influenza B co-infection, as well as in
11 human rhinovirus and enterovirus co-infection. hnRNP K and other heterogenous
12 ribonucleoproteins may be relevant to fundamental transcriptional processes underlying infection
13 of a host or cell with more than one virus.
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Rank	ID	p-value	F	FC	Gene	Gene name
47	ILMN_1712357	0.0016619	12.17373	Day 0: 0.9920 ± 0.0063 Day 2: 0.9707 ± 0.0021 Day 4: 0.9763 ± 0.0054 Day 6: 0.9968 ± 0.0076 Day 21: 0.9875 ± 0.0019	HNRNPK	heterogeneous nuclear ribonucleoprotein K
201	ILMN_1753279	0.0066584	7.85157	Day 0: 0.9684 ± 0.0002 Day 2: 0.9785 ± 0.0063 Day 4: 0.9692 ± 0.0028 Day 6: 0.9786 ± 0.0030 Day 21: 0.9827 ± 0.0134	HNRNPA0	heterogeneous nuclear ribonucleoprotein A0
1321	ILMN_1761083	0.0424469	4.02436		HNRNPA3	heterogeneous nuclear ribonucleoprotein A3

Table 1: hnRNP K, hnRNP A0, and hnRNP A3 are differentially expressed in the blood during the course of co-infection of human coronavirus HKU1 and human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, F statistic, fold change of hnRNP gene expression when comparing HCoV HKU1 and human rhinovirus co-infected patient blood across infection time points as compared to baseline, gene and gene name are listed in this chart. GEO2R provides exact mRNA expression levels only for the 250 most differentially expressed genes.

Rank	ID	p-value	t	B	FC	Gene	Gene name
63	ILMN_2389582	6.52E-07	-8.62	6.41553	0.9398 ± 0.0149	HNRNPL	heterogeneous nuclear ribonucleoprotein L
4095	ILMN_3178792	1.98E-02	-2.64	-3.69833		HNRNPA2B1	heterogeneous nuclear ribonucleoprotein A2/B1

Table 2: hnRNP L and hnRNP A2B1 are differentially expressed in the blood during co-infection of respiratory syncytial virus A (RSVA) and human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, *t*, a moderated *t*-statistic, *B*, the log-odds of differential expression between the two groups compared, fold change of hnRNP gene expression when comparing RSVA and human rhinovirus co-infected patient blood to that of a patient with infection of RSVA only, gene and gene name are listed in this chart. GEO2R provides exact mRNA expression levels only for the 250 most differentially expressed genes.

Rank	ID	p-value	t	B	FC	Gene	Gene name
99	ILMN_3179371	1.47E-07	9.7220474	7.843739	1.0814 ± 0.0153	HNRNPK	heterogeneous nuclear ribonucleoprotein K
1661	ILMN_2175894	1.46E-03	3.9582065	-1.200071		HNRNPR	heterogeneous nuclear ribonucleoprotein R
1866	ILMN_2389582	2.05E-03	-3.7852547	-1.533925		HNRNPL	heterogeneous nuclear ribonucleoprotein L
2412	ILMN_1745385	4.41E-03	3.3968987	-2.285096		HNRNPM	heterogeneous nuclear ribonucleoprotein M
4177	ILMN_1690268	1.75E-02	2.6966665	-3.616366		HNRNPUL1	heterogeneous nuclear ribonucleoprotein U like 1

Table 3: hnRNP K, hnRNP R, hnRNP L, hnRNP M, and hnRNP UL1 are differentially expressed in the blood during co-infection of enterovirus and human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, *t*, a moderated *t*-statistic, *B*, the log-odds of differential expression between the two groups compared, fold change of hnRNP gene expression when comparing enterovirus and human rhinovirus co-infected patient blood to that of a patient with infection of enterovirus only, gene and gene name are listed in this chart. GEO2R provides exact mRNA expression levels only for the 250 most differentially expressed genes.

Rank	ID	p-value	F	Gene	Gene name
404	ILMN_1663447	2.96E-07	11.6192	HNRNPA1	heterogeneous nuclear ribonucleoprotein A1
1159	ILMN_2321451	5.89E-05	6.8933	HNRNPD	heterogeneous nuclear ribonucleoprotein D
1248	ILMN_1745385	8.42E-05	6.6178	HNRNPM	heterogeneous nuclear ribonucleoprotein M
1923	ILMN_1651262	4.56E-04	5.3783	HNRNPAB	heterogeneous nuclear ribonucleoprotein A/B
1937	ILMN_3246409	4.68E-04	5.3598	HNRNPH1	heterogeneous nuclear ribonucleoprotein H1 (H)
2059	ILMN_1753279	5.79E-04	5.2107	HNRNPA0	heterogeneous nuclear ribonucleoprotein A0
2569	ILMN_3177285	1.26E-03	4.6797	HNRNPR	heterogeneous nuclear ribonucleoprotein R

Table 4: hnRNP A1, hnRNP D, hnRNP M, hnRNP AB, hnRNP H1, hnRNP A0, and hnRNP R are differentially expressed in co-infection of influenza A and human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, *t*, a moderated *t*-statistic, *B*, the log-odds of differential expression between the two groups compared, gene and gene name are listed in this chart. GEO2R provides exact mRNA expression levels only for the 250 most differentially expressed genes.

Rank	ID	p-value	F	Gene	Gene name
472	ILMN_1653432	1.36E-05	10.48201	HNRNPDL	heterogeneous nuclear ribonucleoprotein D like
1011	ILMN_1753279	1.09E-04	7.94119	HNRNPA0	heterogeneous nuclear ribonucleoprotein A0
1723	ILMN_3260017	4.45E-04	6.46004	HNRNPK	heterogeneous nuclear ribonucleoprotein K

Table 5: hnRNP DL, hnRNP A0 and hnRNP K are differentially expressed in the blood during co-infection of influenza B and human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, F statistic, gene and gene name are listed in this chart.

Rank	ID	p-value	F	FC	Gene	Gene name
121	ILMN_1653432	7.6E-05	6.69436	Day 0: 0.9865 ± 0.161 Day 2: 0.9947 ± 0.0139 Day 4: 0.9940 ± 0.0132 Day 6: 1.0049 ± 0.0152 Day 21: 1.0258 ± 0.0138 Spring: 1.0258 ± 0.0209	HNRNPDL	heterogeneous nuclear ribonucleoprotein D like

Table 6: Differential expression of hnRNP DL in the blood of patients with human rhinovirus infection.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, F statistic, fold change in hnRNP DL gene expression at each timepoint over the course of Rhinovirus infection as compared to baseline, gene and gene name are listed in this chart.

Rank	ID	p-value	F	Gene	Gene name
481	ILMN_3177285	1.38E-03	4.6146	HNRNPR	heterogeneous nuclear ribonucleoprotein R
484	ILMN_1753279	1.39E-03	4.61024	HNRNPA0	heterogeneous nuclear ribonucleoprotein A0
565	ILMN_3180966	1.81E-03	4.43725	HNRNPUL1	heterogeneous nuclear ribonucleoprotein U like 1
1243	ILMN_2321451	6.81E-03	3.58028	HNRNPD	heterogeneous nuclear ribonucleoprotein D
1319	ILMN_1791575	7.56E-03	3.51471	HNRNPLL	heterogeneous nuclear ribonucleoprotein L like
1573	ILMN_2334587	1.03E-02	3.32327	HNRNPC	heterogeneous nuclear ribonucleoprotein C (C1/C2)
1775	ILMN_1745385	1.25E-02	3.20232	HNRNPM	heterogeneous nuclear ribonucleoprotein M
1936	ILMN_2175894	1.43E-02	3.11784	HNRNPR	heterogeneous nuclear ribonucleoprotein R
2074	ILMN_1751368	1.59E-02	3.05498	HNRNPD	heterogeneous nuclear ribonucleoprotein D
3061	ILMN_3273854	2.91E-02	2.68501	HNRNPA2B1	heterogeneous nuclear ribonucleoprotein A2/B1
3540	ILMN_1781764	3.54E-02	2.56698	HNRNPH2	heterogeneous nuclear ribonucleoprotein H2 (H')
3743	ILMN_3246409	3.8E-02	2.52445	HNRNPH1	heterogeneous nuclear ribonucleoprotein H1 (H)
3798	ILMN_3244579	3.89E-02	2.5101	HNRNPCL3	heterogeneous nuclear ribonucleoprotein C-like 3
10340	ILMN_3179371	1.51E-01	1.6914	HNRNPK	heterogeneous nuclear ribonucleoprotein K

Table 7: Differential expression of hnRNPs, including hnRNP A0 and hnRNP M, but not hnRNP K over the course of infection with human rhinovirus.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, F statistic, gene and gene name are listed in this chart.

Rank	ID	p-value	F	Gene	Gene name
6830	ILMN_3260017	3.47E-02	3.0738	HNRNPK	heterogeneous nuclear ribonucleoprotein K

Table 8: Differential expression of hnRNP K in patient blood over the course of influenza B infection.

The rank of differential expression, probe ID, *p*-value with respect to global differential expression, F statistic, gene and gene name are listed in this chart.

A

hnRNP K
HCoV HKU1 and Rhinovirus

B

hnRNP A0
HCoV HKU1 and Rhinovirus

Figure 1: hnRNP K and hnRNP A0 are differentially expressed in the blood during human coronavirus HKU1 and human rhinovirus co-infection, and their expression significantly decreases during over the course of viral co-infection.

hnRNP K (A) and hnRNP A0 (B) gene expression levels are graphically represented in the blood of two patients with co-infection of HCoV HKU1 and human rhinovirus, with mean mRNA expression levels of hnRNP K and hnRNP A0 marked at each time point, and the result of a statistical test evaluating significance of difference in hnRNP gene expression as compared to baseline for each statistically significant time point.

Figure 2: hnRNP L is differentially expressed in the blood during RSVA and human rhinovirus co-infection, at significantly lower levels as compared to RSVA infection only.

hnRNP L mRNA expression levels are graphically represented in the blood of a patient with RSVA infection only (left) and in the blood of a patient with co-infection of RSVA and rhinovirus (right), with mean mRNA expression level of hnRNP L marked, and the result of a statistical test evaluating significance of difference in hnRNP gene expression between co-infection and single infection listed above.

Figure 3: hnRNP K is differentially expressed in the blood during enterovirus and human rhinovirus co-infection, at significantly higher levels as compared to enterovirus infection only.

hnRNP K mRNA expression levels are graphically represented in the blood of a patient with enterovirus infection only (left) and in the blood of a patient with co-infection of enterovirus and rhinovirus (right), with mean mRNA expression level of hnRNP K marked, and the result of a statistical test evaluating significance of difference in hnRNP gene expression between co-infection and single infection listed above.

hnRNP DL Rhinovirus infection

Figure 4: hnRNP DL is among the genes most differentially expressed in patient blood over the course of rhinovirus infection.

hnRNP DL mRNA expression levels are graphically represented in $n=6$ patients with infection of rhinovirus only, with mean hnRNP DL mRNA levels marked and with statistically significant changes in hnRNP DL gene expression relative to baseline listed above each time point as an exact p -value.