

Table S1: Biological Processes enriched among high perturbed proteins. Biological process, overlap proteins/total proteins in process, pvalue of overlap.

	6 hrs	18 hrs	30 hrs	42 hrs
	<p>neutrophil degranulation 86/187, 2.888E-28</p> <p>mRNA axis splicing, via spliceosome 57/236, 4.1309E-26</p> <p>spliceosomal complex assembly 57/241, 1.3034E-25</p> <p>mRNA trans splicing, via spliceosome 56/233, 1.4758E-25</p> <p>spliceosomal conformational changes to generate catalytic conformation 56/234, 1.8929E-25</p>	<p>alternative mRNA splicing, via spliceosome 69/237, 2.93E-35</p> <p>spliceosomalRNP assembly 67/246, 4.03E-35</p> <p>spliceosomal complex assembly 57/241, 1.3034E-25</p> <p>mRNA trans splicing, via spliceosome 65/233, 8.67E-35</p> <p>spliceosomal conformational changes to generate catalytic conformation 65/234, 1.19E-34</p>	<p>alternative mRNA splicing, via spliceosome 54/237, 3.51E-29</p> <p>mRNA axis splicing, via spliceosome 53/236, 2.9E-28</p> <p>mRNA splicing, via spliceosome 54/252, 9.12E-28</p> <p>mRNA trans splicing, via spliceosome 52/233, 1.13E-27</p> <p>spliceosomal conformational changes to generate catalytic conformation 52/234, 1.41E-27</p>	<p>neutrophil degranulation 109/187, 3.11E-42</p> <p>alternative mRNA splicing, via spliceosome 70/237, 1.2E-40</p> <p>mRNA trans splicing, via spliceosome 69/233, 3.85E-40</p> <p>spliceosomal complex assembly 70/241, 4.28E-40</p> <p>spliceosomal conformational changes to generate catalytic conformation 69/234, 5.20E-40</p>
	<p>neutrophil degranulation 109/187, 1.67E-42</p> <p>tRNA aminoacylation for protein translation 55/179, 3.04E-29</p> <p>viral RNA editing 42/119, 2.0E-25</p> <p>viral transcription 42/119, 2.0E-25</p> <p>spliceosomal complex assembly 56/241, 4.71E-23</p>	<p>SRP-dependent cotranslational protein targeting to membrane, docking 68/88, 1.42E-48</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 69/92, 5.69E-48</p> <p>SRP-dependent cotranslational protein targeting to membrane 70/100, 2.19E-45</p> <p>viral transcription 71/119, 7.67E-59</p> <p>viral RNA editing 71/119, 7.67E-59</p>	<p>neutrophil degranulation 86/187, 2.888E-28</p> <p>alternative mRNA splicing, via spliceosome 76/237, 2.82E-41</p> <p>mRNA trans splicing, via spliceosome 75/233, 7.13E-41</p> <p>spliceosomal conformational changes to generate catalytic conformation 75/234, 1E-40</p> <p>spliceosomal complex disassembly 75/234, 1E-40</p>	<p>SRP-dependent cotranslational protein targeting to membrane, docking 68/88, 9.92E-74</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 69/92, 3.40E-73</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence recognition 69/102, 5.09E-68</p> <p>SRP-dependent cotranslational protein targeting to membrane 68/100, 2.70E-67</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence processing 68/108, 8.96E-61</p>
	<p>neutrophil degranulation 99/487, 6.97E-43</p> <p>alternative mRNA splicing, via spliceosome 9/237, 1.07E-24</p> <p>spliceosomalRNP assembly 60/246, 1.37E-24</p> <p>mRNA trans splicing, via spliceosome 58/233, 2.7E-24</p> <p>spliceosomal complex assembly 59/241, 2.75E-24</p>	<p>tRNA aminoacylation for protein translation 74/179, 1.02E-43</p> <p>neutrophil degranulation 121/187, 1.44E-43</p> <p>viral transcription 61/119, 4.11E-43</p> <p>viral RNA editing, 61/119 4.11E-43</p> <p>alternative mRNA splicing, via spliceosome 89/237, 1.8E-39</p>	<p>alternative mRNA splicing, via spliceosome 64/237, 8.06E-36</p> <p>spliceosomal complex assembly 64/241, 2.42E-35</p> <p>mRNA trans splicing, via spliceosome 63/233, 2.63E-35</p> <p>spliceosomal conformational changes to generate catalytic conformation 63/234, 3.45E-35</p> <p>spliceosomal complex disassembly 63/234, 3.45E-35</p>	<p>SRP-dependent cotranslational protein targeting to membrane, signal sequence recognition 70/102, 3.79E-71</p> <p>SRP-dependent cotranslational protein targeting to membrane, docking 69/88, 3.7891E-71</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 70/92, 1.68E-70</p> <p>SRP-dependent cotranslational protein targeting to membrane 70/100, 3.38E-66</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence processing 69/108, 5.9000E-61</p>
	<p>SRP-dependent cotranslational protein targeting to membrane, docking 64/88, 7.46E-59</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 64/92, 3.08E-57</p> <p>SRP-dependent cotranslational protein targeting to membrane 65/100, 1.05E-54</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence recognition 65/102, 7.28E-54</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence processing 65/108, 1.06E-51</p>	<p>SRP-dependent cotranslational protein targeting to membrane, docking 136/187, 1.29E-40</p> <p>alternative mRNA splicing, via spliceosome 99/237, 8.04E-39</p> <p>spliceosomalRNP assembly 91/236, 3.59E-38</p> <p>mRNA axis splicing, via spliceosome 89/236, 4.35E-38</p> <p>mRNA trans splicing, via spliceosome 88/233, 9.91E-38</p>	<p>SRP-dependent cotranslational protein targeting to membrane, docking 64/88, 8.76E-59</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 65/92, 2.47E-58</p> <p>nucleol-transcribed mRNA catabolic process, 5'-3' exomecyclic nonsense-mediated decay 70/111, 2.12E-57</p> <p>nucleol-transcribed mRNA catabolic process, nonsense-mediated decay 73/125, 2.43E-56</p> <p>tRNA aminoacylation for protein translation 81/179, 2.48E-54</p>	<p>SRP-dependent cotranslational protein targeting to membrane, signal sequence recognition 70/102, 3.79E-71</p> <p>SRP-dependent cotranslational protein targeting to membrane, docking 69/88, 3.7891E-71</p> <p>SRP-dependent cotranslational protein targeting to membrane, translocation 70/92, 1.68E-70</p> <p>SRP-dependent cotranslational protein targeting to membrane 70/100, 3.38E-66</p> <p>SRP-dependent cotranslational protein targeting to membrane, signal sequence processing 69/108, 5.9000E-61</p>
JAL				

Table S2: Metabolic pathways enriched among reactions present in GSMs. Biological process, overlap proteins/total proteins in process, pvalue of overlap.

	6 hrs	18 hrs	30 hrs	42 hrs
H37Ra	Fatty acid activation,24/37,1.34E-21 Keratan sulfate biosynthesis,20/59,3.10E-11 Citric Acid Cycle,9/17,1.05E-07 Oxidative Phosphorylation,5/6,3.72E-06 Keratan sulfate degradation,15/75,1.54E-05	Fatty acid oxidation,27/29,3.46E-32 Fatty acid activation,25/37,3.44E-23 Fatty acid oxidation, peroxisome,17/19,8.58E-20 Keratan sulfate degradation,25/75,1.27E-13 Transport, Extracellular,5/51,1.23E-09	Fatty acid oxidation,27/29,4.87E-34 Fatty acid activation,25/37,7.41E-25 Transport, Extracellular,5/51,1.15E-07 Keratan sulfate degradation,14/75,1.21E-05 Fatty acid elongation,7/25,0.000142	Nucleotides,51/167,2.33E-22 Fatty acid oxidation, peroxisome,18/19,6.47E-21 Carnitine shuttle,33/107,8.75E-15 Keratan sulfate biosynthesis,20/59,3.23E-10 Transport, Extracellular,17/51,0.000202
H37RV	Fatty acid oxidation, peroxisome,18/19,7.64E-22 Pyruvate Metabolism,12/31,6.69E-08 Nucleotides,26/167,2.45E-06 Keratan sulfate degradation,15/75,1.81E-05 Valine, Leucine, and Isoleucine Metabolism,9/30,3.24E-05	Pyrimidine Biosynthesis,2/8,0.00145 Limonene and pinene degradation,2/9,0.001851 beta-Alanine metabolism,2/11,0.002789 Tryptophan metabolism,3/44,0.003771 Triacylglycerol Synthesis,2/13,0.003901	Fatty acid oxidation,27/29,1.85E-35 Keratan sulfate degradation,31/75,2.10E-23 Chondroitin sulfate degradation,17/44,1.23E-12 Fatty acid elongation,7/25,7.07E-05 C5-Branched dibasic acid metabolism,4/8,0.00023	Carnitine shuttle,33/107,4.54E-33 Pyrimidine Biosynthesis,3/8,0.000393 Vitamin B6 Metabolism,3/9,0.000578 Nucleotides,8/167,0.011902 Limonene and pinene degradation,2/9,0.012432
BND	Fatty acid activation,24/37,1.34E-21 Citric Acid Cycle,9/17,1.05E-07 Transport, Extracellular,11/51,1.20E-05 Glycine, Serine, and Threonine Metabolism,9/30,2.91E-05 Valine, Leucine, and Isoleucine Metabolism,9/30,2.91E-05	Fatty acid oxidation,27/29,2.61E-35 Keratan sulfate degradation,31/75,3.07E-23 Chondroitin sulfate degradation,22/44,6.39E-19 Pyrimidine Biosynthesis,6/8,2.07E-07 Transport, Extracellular,6/51,1.493E-06	Fatty acid oxidation,28/29,7.50E-36 Keratan sulfate biosynthesis,20/59,4.72E-12 Transport, Extracellular,5/51,3.21E-08 Valine, Leucine, and Isoleucine Metabolism,8/30,9.92E-05 Citric Acid Cycle,6/17,0.000141	Fatty acid oxidation, peroxisome,18/19,3.35E-27 Carnitine shuttle,33/107,9.53E-26 Pyrimidine Biosynthesis,3/8,0.001395 Starch and Sucrose Metabolism,4/21,0.003129 Nucleotides,10/167,0.019321
JAL	Fatty acid activation,24/37,1.16E-27 Keratan sulfate biosynthesis,20/59,6.76E-16 Purine Catabolism,5/11,1.52E-05 Salvage Pathway,3/3,3.73E-05 Pyruvate Metabolism,7/31,5.02E-05	Nucleotides,78/167,1.08E-38 Fatty acid oxidation,27/29,2.37E-26 Fatty acid oxidation, peroxisome,18/19,3.66E-18 Vitamin B6 Metabolism,8/9,4.55E-08	Fatty acid oxidation,27/29,2.96E-37 Carnitine shuttle,33/107,3.14E-22 Nucleotides,23/167,5.11E-08 Pyruvate Metabolism,9/31,1.45E-06 Inositol Phosphate Metabolism,8/67,0.003092	Vitamin B6 Metabolism,3/9,0.003241481 Galactose metabolism,4/12,0.000637665 Fatty acid activation,8/373,66E-05 Carnitine shuttle,33/107,3.50E-23 Fatty acid oxidation, peroxisome,18/19,8.33E-26

Table S3: Metabolic pathways enriched among high flux carrying reactions. Biological process, overlap proteins/total proteins in process, pvalue of overlap.

	6 hrs	18 hrs	30 hrs	42 hrs
H37Ra	Transport, Extracellular,144/511,1.30E-49 Nucleotides,43/167,2.97E-12 Miscellaneous,6/13,0.000303 Transport, Endoplasmic Reticular,1/94,0.002202 Pyruvate Metabolism,8/31,0.002391	Transport, Extracellular,137/511,6.50E-41 Nucleotides,45/167,8.49E-13 Vitamin A Metabolism,13/35,2.95E-06 Transport, Mitochondrial,34/189,1.57E-05 Transport, Endoplasmic Reticular,1/94,0.001527	Transport, Extracellular,139/511,1.53E-47 Nucleotides,39/167,2.84E-10 Vitamin A Metabolism,12/35,8.03E-06 C5-Branched dibasic acid metabolism,4/8,0.002091 Transport, Mitochondrial,26/189,0.002212	Transport, Extracellular,136/511,4.39E-48 Nucleotides,38/167,2.67E-10 Vitamin A Metabolism,11/35,3.06E-05 Transport, Mitochondrial,25/189,0.00238 Transport, Endoplasmic Reticular,3/94,0.040606
H37RV	Transport, Extracellular,144/511,1.55E-43 Nucleotides,48/167,5.37E-14 Transport, Mitochondrial,33/189,8.88E-05 Vitamin A Metabolism,10/35,0.000639 Purine Catabolism,4/11,0.011665	Transport, Extracellular,149/511,1.58E-46 Nucleotides,44/167,2.83E-11 Vitamin A Metabolism,13/35,5.68E-06 Carnitine shuttle,1/107,0.00029 Transport, Mitochondrial,30/189,0.001036	Transport, Extracellular,139/511,4.28E-49 Nucleotides,33/167,2.75E-07 Vitamin A Metabolism,10/35,0.000201 Urea cycle/amino group metabolism,7/25,0.002002 Transport, Mitochondrial,24/189,0.005814	Transport, Extracellular,133/511,1.37E-42 Nucleotides,40/167,7.21E-11 Vitamin A Metabolism,13/35,1.21E-06 Transport, Peroxisomal,1/79,0.008553 Transport, Mitochondrial,21/189,0.030873
BND	Transport, Extracellular,136/511,5.75E-40 Nucleotides,50/167,4.19E-16 Transport, Mitochondrial,33/189,4.01E-05 Vitamin A Metabolism,10/35,0.000464 Carnitine shuttle,1/107,0.000499	Transport, Extracellular,142/511,7.31E-47 Nucleotides,43/167,5.14E-12 Vitamin A Metabolism,13/35,2.08E-06 Transport, Endoplasmic Reticular,1/94,0.00195 FC5-Branched dibasic acid metabolism,4/8,0.002497	Transport, Extracellular,155/511,5.98E-58 Nucleotides,32/167,4.25E-06 Vitamin A Metabolism,12/35,1.36E-05 Transport, Peroxisomal,1/79,0.006234 Transport, Mitochondrial,25/189,0.007262	Transport, Extracellular,147/511,3.86E-49 Nucleotides,41/167,2.06E-10 Vitamin A Metabolism,11/359,37E-05 Pyruvate Metabolism,10/31,0.000153 Transport, Mitochondrial,25/189,0.009348
JAL	Transport, Extracellular,147/511,3.86E-49 Nucleotides,41/167,2.06E-10 Vitamin A Metabolism,11/359,37E-05 Pyruvate Metabolism,10/31,0.000153 Transport, Mitochondrial,25/189,0.009348	Transport, Extracellular,145/511,6.27E-42 Nucleotides,51/167,2.49E-15 Vitamin A Metabolism,13/35,7.29E-06 Transport, Mitochondrial,32/189,0.000368 Citric Acid Cycle,6/17,0.002948	Transport, Extracellular,141/511,6.33E-50 Nucleotides,39/167,2.10E-10 Vitamin A Metabolism,14/35,1.41E-07 Transport, Mitochondrial,24/189,0.006689 Purine Catabolism,4/11,0.007423	Transport, Extracellular,145/511,1.99E-56 D-alanine metabolism,3/3,0.000447 Nucleotides,4/167,0.002103 Transport, Mitochondrial,25/189,0.002282 Vitamin A Metabolism,8/35,0.003137

Table S4: Metabolic pathways enriched among virulence specific reactions. Biological process, overlap proteins/total proteins in process, pvalue of overlap.

	6 hrs	18 hrs	30 hrs	42 hrs
H37RV	<p>Transport, Extracellular, 37/511, 9.59E-07</p> <p>Pyruvate Metabolism, 8/31, 4.43E-06</p> <p>Nucleotides, 18/167, 5.05E-06</p> <p>C5-Branched dibasic acid metabolism, 4/8, 7.07E-05</p> <p>Purine Catabolism, 3/11, 0.004506</p>	<p>Nucleotides, 19/167, 9.14E-09</p> <p>Transport, Mitochondrial, 17/189, 1.75E-06</p> <p>Miscellaneous, 4/13, 0.000198</p> <p>Transport, Nuclear, 6/62, 0.003102</p> <p>Vitamin A Metabolism, 4/35, 0.008545</p>	<p>Miscellaneous, 3/13, 0.001822</p> <p>Citric Acid Cycle, 3/17, 0.004006</p> <p>Transport, Mitochondrial, 9/189, 0.008319</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.009862</p> <p>Transport, Extracellular, 17/511, 0.011433</p>	<p>Vitamin A Metabolism, 5/35, 1.01E-05</p> <p>Transport, Nuclear, 4/62, 0.001775</p> <p>Miscellaneous, 2/13, 0.005368</p> <p>Nucleotides, 5/167, 0.011414</p> <p>Glycolysis/Gluconeogenesis, 2/31, 0.02753</p>
BND	<p>Purine Catabolism, 5/11, 4.20E-06</p> <p>Transport, Mitochondrial, 15/189, 6.06E-05</p> <p>Transport, Extracellular, 26/511, 0.000232</p> <p>Transport, Nuclear, 7/62, 0.000807</p> <p>Pyruvate Metabolism, 5/31, 0.000937</p>	<p>Nucleotides, 21/167, 1.26E-09</p> <p>Transport, Mitochondrial, 16/189, 2.58E-05</p> <p>Vitamin A Metabolism, 6/35, 0.000256</p> <p>Valine, Leucine, and Isoleucine Metabolism, 5/30, 0.000964</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.017196</p>	<p>Transport, Mitochondrial, 18/189, 2.15E-07</p> <p>Nucleotides, 12/167, 0.00037</p> <p>Transport, Nuclear, 6/62, 0.002648</p> <p>Transport, Extracellular, 20/511, 0.007615</p> <p>Pentose Phosphate Pathway, 2/18, 0.058693</p>	<p>Nucleotides, 14/167, 4.38E-08</p> <p>Vitamin A Metabolism, 6/35, 7.58E-06</p> <p>Vitamin B6 Metabolism, 3/9, 0.00022</p> <p>Citric Acid Cycle, 3/17, 0.001594</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.005263</p>
JAL	<p>Nucleotides, 20/167, 1.11E-08</p> <p>Transport, Mitochondrial, 20/189, 9.04E-08</p> <p>Purine Catabolism, 5/11, 5.65E-06</p> <p>Vitamin A Metabolism, 4/35, 0.012308</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.017829</p>	<p>Nucleotides, 27/167, 3.72E-14</p> <p>Transport, Mitochondrial, 22/189, 7.94E-09</p> <p>Transport, Nuclear, 6/62, 0.006497</p> <p>Arginine and Proline Metabolism, 4/33, 0.011825</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.019449</p>	<p>Nucleotides, 21/167, 3.83E-10</p> <p>Transport, Nuclear, 8/62, 0.00012</p> <p>Transport, Mitochondrial, 13/189, 0.00059</p> <p>Transport, Extracellular, 20/511, 0.013815</p> <p>C5-Branched dibasic acid metabolism, 2/8, 0.015355</p>	<p>Nucleotides, 32/167, 5.77E-27</p> <p>Vitamin A Metabolism, 6/35, 2.42E-05</p> <p>Galactose metabolism, 3/12, 0.00099</p> <p>Transport, Nuclear, 4/62, 0.018544</p> <p>NAD Metabolism, 2/23, 0.053907</p>

Table S5: Metabolic pathways enriched clinical strains (BND and JAL) in compare to reference strains (Ra and Rv). Common pathways are presented in this table.

	6 hrs	18 hrs	30 hrs	42 hrs
Common to bnd/ra and bnd/rv	Biotin Metabolism Sphingolipid Metabolism Transport, Extracellular Tyrosine metabolism	Bile Acid Biosynthesis Biotin Metabolism Glycolysis/Gluconeogenesis Nucleotides 'Transport, Extracellular' 'Transport, Golgi Apparatus' 'Transport, Lysosomal' 'Transport, Mitochondrial' 'Transport, Peroxisomal' 'Tryptophan metabolism' 'Tyrosine metabolism' Propanoate Metabolism	'Glycolysis/Gluconeogenesis' 'Transport, Extracellular' 'Transport, Mitochondrial' 'Tryptophan metabolism'	'Aminosugar Metabolism' 'Glycerophospholipid Metabolism' 'Keratan sulfate biosynthesis' 'Nucleotides' 'Pyruvate Metabolism' 'Taurine and hypotaurine metabolism' 'Transport, Endoplasmic Reticular'
Common to jal/rv and jal/ra	'Aminosugar Metabolism' 'R Group Synthesis' 'Transport, Extracellular' 'Transport, Mitochondrial' 'Tryptophan metabolism'	'Blood Group Biosynthesis' 'Fatty Acid Metabolism' 'Glycerophospholipid Metabolism' 'Glycolysis/Gluconeogenesis' 'R Group Synthesis' 'Transport, Endoplasmic Reticular' 'Transport, Extracellular' 'Transport, Mitochondrial' 'Tryptophan metabolism'	'Blood Group Biosynthesis' 'R Group Synthesis' 'Transport, Endoplasmic Reticular' 'Transport, Extracellular' 'Transport, Mitochondrial'	'Keratan sulfate biosynthesis' 'Nucleotides' 'Transport, Extracellular' 'Transport, Mitochondrial'
Common to bnd/ra, bnd/rv, jal/rv, jal/ra	'Transport, Extracellular'	'Glycolysis/Gluconeogenesis' 'Transport, Extracellular' 'Transport, Mitochondrial' 'Tryptophan metabolism'	'Transport, Extracellular' 'Transport, Mitochondrial'	'Bile Acid Biosynthesis' 'Keratan sulfate biosynthesis' 'Nucleotides' 'Transport, Extracellular' 'Transport, Mitochondrial'

Table S6: Metabolic pathways enriched among virulence specific modules. Biological process, overlap proteins/total proteins in process, p-value of overlap.

Module Number (Number of reactions)	Enriched Metabolic Pathways ,overlap reactions/totalreactions in pathway, p-value of overlap
M1 (24)	<ul style="list-style-type: none"> Purine Catabolism, 3/11, 3.66E-05 Pyrimidine Catabolism, 2/19, 0.006098 Nucleotides, 3/167, 0.068765
M2 (59)	<ul style="list-style-type: none"> Citric Acid Cycle, 4/17, 0.000109 Alanine and Aspartate Metabolism, 3/12, 0.000715 Glutamate metabolism, 1/12, 0.159288
M3 (78)	<ul style="list-style-type: none"> Nucleotides, 48/167, 1.45E-47 Transport, Mitochondrial, 27/189, 1.04E-16 Galactose metabolism, 1/12, 0.198922
M4 (9)	<ul style="list-style-type: none"> Glycerophospholipid Metabolism, 2/51, 0.005979 Miscellaneous , 1/13, 0.030473 Carnitine shuttle, 1/107, 0.204438
M5 (12)	<ul style="list-style-type: none"> Vitamin A Metabolism, 9/35, 3.87E-17 Arginine and Proline Metabolism, 1/33, 0.096271 Transport, Extracellular, 1/511, 0.326085
M6 (6)	<ul style="list-style-type: none"> Arginine and Proline Metabolism, 3/33, 1.22E-05 Transport, Mitochondrial, 1/189, 0.234145 Transport, Extracellular, 1/511, 0.393578
M7 (14)	<ul style="list-style-type: none"> Citric Acid Cycle, 4/17, 2.82E-07 Glutamate metabolism, 2/12, 0.000831 Folate Metabolism, 1/50, 0.157556