

Supplementary table S1: Most enriched GO terms of biological processes among up-regulated genes with lake-specific differential expression between control and singly exposed sticklebacks

| GO.ID | Term | Overall | Up-regulated | Expected | classicFisher | FDR |
|------------|--|---------|--------------|----------|---------------|----------|
| GO:0006508 | proteolysis | 731 | 22 | 4.51 | 2.00E-10 | 8.02E-07 |
| GO:0006956 | complement activation | 7 | 4 | 0.04 | 4.60E-08 | 6.15E-05 |
| GO:0072376 | protein activation cascade | 7 | 4 | 0.04 | 4.60E-08 | 6.15E-05 |
| GO:0009308 | amine metabolic process | 327 | 12 | 2.02 | 6.30E-07 | 0.0006 |
| GO:0009063 | cellular amino acid catabolic process | 34 | 5 | 0.21 | 1.90E-06 | 0.0015 |
| GO:0009072 | aromatic amino acid family metabolic pro... | 16 | 4 | 0.1 | 2.30E-06 | 0.0015 |
| GO:0006959 | humoral immune response | 18 | 4 | 0.11 | 3.80E-06 | 0.0021 |
| GO:0006955 | immune response | 262 | 10 | 1.62 | 4.20E-06 | 0.0021 |
| GO:0009310 | amine catabolic process | 42 | 5 | 0.26 | 5.50E-06 | 0.0024 |
| GO:0016054 | organic acid catabolic process | 58 | 5 | 0.36 | 2.70E-05 | 0.0098 |
| GO:0046395 | carboxylic acid catabolic process | 58 | 5 | 0.36 | 2.70E-05 | 0.0098 |
| GO:0044106 | cellular amine metabolic process | 269 | 9 | 1.66 | 3.80E-05 | 0.0127 |
| GO:0002252 | immune effector process | 110 | 6 | 0.68 | 5.70E-05 | 0.0172 |
| GO:0002253 | activation of immune response | 68 | 5 | 0.42 | 6.00E-05 | 0.0172 |
| GO:0006520 | cellular amino acid metabolic process | 229 | 8 | 1.41 | 7.80E-05 | 0.0208 |
| GO:0050776 | regulation of immune response | 119 | 6 | 0.73 | 8.90E-05 | 0.0223 |
| GO:0050778 | positive regulation of immune response | 81 | 5 | 0.5 | 0.0001 | 0.0330 |
| GO:0006547 | histidine metabolic process | 5 | 2 | 0.03 | 0.0004 | 0.0706 |
| GO:0006548 | histidine catabolic process | 5 | 2 | 0.03 | 0.0004 | 0.0706 |
| GO:0009075 | histidine family amino acid metabolic pro... | 5 | 2 | 0.03 | 0.0004 | 0.0706 |
| GO:0009077 | histidine family amino acid catabolic pro... | 5 | 2 | 0.03 | 0.0004 | 0.0706 |
| GO:0006725 | cellular aromatic compound metabolic pro... | 105 | 5 | 0.65 | 0.0005 | 0.0838 |
| GO:0019439 | aromatic compound catabolic process | 7 | 2 | 0.04 | 0.0008 | 0.1342 |
| GO:0008152 | metabolic process | 7070 | 56 | 43.62 | 0.0010 | 0.1587 |
| GO:0019538 | protein metabolic process | 2794 | 29 | 17.24 | 0.0014 | 0.2213 |
| GO:0019752 | carboxylic acid metabolic process | 359 | 8 | 2.21 | 0.0016 | 0.2346 |
| GO:0043436 | oxoacid metabolic process | 359 | 8 | 2.21 | 0.0016 | 0.2346 |
| GO:0006082 | organic acid metabolic process | 363 | 8 | 2.24 | 0.0017 | 0.2420 |
| GO:0002684 | positive regulation of immune system pro... | 142 | 5 | 0.88 | 0.0018 | 0.2488 |
| GO:0042180 | cellular ketone metabolic process | 370 | 8 | 2.28 | 0.0019 | 0.2552 |

Supplementary table S2: Most enriched GO terms of biological processes among up-regulated genes with river-specific differential expression between control and singly exposed sticklebacks

| GO.ID | Term | Overall | Up-regulated | Expected | classicFisher | FDR |
|------------|---|---------|--------------|----------|---------------|--------|
| GO:0044275 | cellular carbohydrate catabolic process | 70 | 7 | 0.48 | 4.70E-07 | 0.0013 |
| GO:0046164 | alcohol catabolic process | 73 | 7 | 0.5 | 6.30E-07 | 0.0013 |
| GO:0016052 | carbohydrate catabolic process | 90 | 7 | 0.62 | 2.60E-06 | 0.0035 |
| GO:0006006 | glucose metabolic process | 94 | 7 | 0.65 | 3.50E-06 | 0.0035 |
| GO:0006096 | glycolysis | 44 | 5 | 0.3 | 1.20E-05 | 0.0096 |
| GO:0019318 | hexose metabolic process | 118 | 7 | 0.81 | 1.60E-05 | 0.0107 |
| GO:0005996 | monosaccharide metabolic process | 131 | 7 | 0.9 | 3.10E-05 | 0.0144 |
| GO:0044262 | cellular carbohydrate metabolic process | 296 | 10 | 2.04 | 3.30E-05 | 0.0144 |
| GO:0006066 | alcohol metabolic process | 240 | 9 | 1.65 | 3.80E-05 | 0.0144 |
| GO:0006007 | glucose catabolic process | 56 | 5 | 0.39 | 3.90E-05 | 0.0144 |
| GO:0006091 | generation of precursor metabolites and ... | 137 | 7 | 0.94 | 4.20E-05 | 0.0144 |
| GO:0019320 | hexose catabolic process | 57 | 5 | 0.39 | 4.30E-05 | 0.0144 |
| GO:0046365 | monosaccharide catabolic process | 58 | 5 | 0.4 | 4.70E-05 | 0.0145 |
| GO:0044282 | small molecule catabolic process | 533 | 13 | 3.67 | 6.30E-05 | 0.0180 |
| GO:0046034 | ATP metabolic process | 98 | 5 | 0.67 | 0.0006 | 0.1478 |
| GO:0006457 | protein folding | 99 | 5 | 0.68 | 0.0006 | 0.1478 |
| GO:0043968 | histone H2A acetylation | 6 | 2 | 0.04 | 0.0007 | 0.1627 |
| GO:0006936 | muscle contraction | 62 | 4 | 0.43 | 0.0009 | 0.1915 |
| GO:0003012 | muscle system process | 66 | 4 | 0.45 | 0.0011 | 0.2279 |
| GO:0051443 | positive regulation of ubiquitin-protein... | 8 | 2 | 0.06 | 0.0013 | 0.2566 |
| GO:0005975 | carbohydrate metabolic process | 471 | 10 | 3.24 | 0.0014 | 0.2606 |
| GO:0044281 | small molecule metabolic process | 3624 | 38 | 24.95 | 0.0014 | 0.2606 |
| GO:0046174 | polyol catabolic process | 9 | 2 | 0.06 | 0.0016 | 0.2841 |
| GO:0051351 | positive regulation of ligase activity | 10 | 2 | 0.07 | 0.0020 | 0.3391 |
| GO:0046483 | heterocycle metabolic process | 689 | 12 | 4.74 | 0.0025 | 0.3977 |
| GO:0009152 | purine ribonucleotide biosynthetic proce... | 87 | 4 | 0.6 | 0.0030 | 0.4626 |
| GO:0009260 | ribonucleotide biosynthetic process | 91 | 4 | 0.63 | 0.0035 | 0.5241 |
| GO:0009056 | catabolic process | 1026 | 15 | 7.06 | 0.0039 | 0.5512 |
| GO:0043967 | histone H4 acetylation | 14 | 2 | 0.1 | 0.0040 | 0.5585 |
| GO:0051438 | regulation of ubiquitin-protein ligase a... | 17 | 2 | 0.12 | 0.0060 | 0.7951 |

Supplementary table S3: Most enriched GO terms of biological processes among up-regulated genes with common differential expression between control and singly exposed sticklebacks

| GO.ID | Term | Overall | Up-regulated | Expected | classicFisher | FDR |
|------------|---|---------|--------------|----------|---------------|----------|
| GO:0006508 | proteolysis | 731 | 13 | 1.63 | 8.90E-10 | 3.57E-06 |
| GO:0006547 | histidine metabolic process | 5 | 2 | 0.01 | 4.80E-05 | 0.0385 |
| GO:0006548 | histidine catabolic process | 5 | 2 | 0.01 | 4.80E-05 | 0.0385 |
| GO:0009075 | histidine family amino acid metabolic pr... | 5 | 2 | 0.01 | 4.80E-05 | 0.0385 |
| GO:0009077 | histidine family amino acid catabolic pr... | 5 | 2 | 0.01 | 4.80E-05 | 0.0385 |
| GO:0006026 | aminoglycan catabolic process | 14 | 2 | 0.03 | 0.0004 | 0.2749 |
| GO:0005975 | carbohydrate metabolic process | 471 | 6 | 1.05 | 0.0005 | 0.2749 |
| GO:0000272 | polysaccharide catabolic process | 19 | 2 | 0.04 | 0.0008 | 0.4009 |
| GO:0016052 | carbohydrate catabolic process | 90 | 3 | 0.2 | 0.0010 | 0.4544 |
| GO:0008152 | metabolic process | 7070 | 23 | 15.8 | 0.0012 | 0.4891 |
| GO:0044238 | primary metabolic process | 6068 | 21 | 13.56 | 0.0018 | 0.6633 |
| GO:0009063 | cellular amino acid catabolic process | 34 | 2 | 0.08 | 0.0026 | 0.8619 |
| GO:0019538 | protein metabolic process | 2794 | 13 | 6.25 | 0.0033 | 1.0000 |
| GO:0009310 | amine catabolic process | 42 | 2 | 0.09 | 0.0039 | 1.0000 |
| GO:0006022 | aminoglycan metabolic process | 48 | 2 | 0.11 | 0.0051 | 1.0000 |
| GO:0009308 | amine metabolic process | 327 | 4 | 0.73 | 0.0056 | 1.0000 |
| GO:0016054 | organic acid catabolic process | 58 | 2 | 0.13 | 0.0074 | 1.0000 |
| GO:0046395 | carboxylic acid catabolic process | 58 | 2 | 0.13 | 0.0074 | 1.0000 |
| GO:0006027 | glycosaminoglycan catabolic process | 5 | 1 | 0.01 | 0.0111 | 1.0000 |
| GO:0043462 | regulation of ATPase activity | 5 | 1 | 0.01 | 0.0111 | 1.0000 |
| GO:0005976 | polysaccharide metabolic process | 79 | 2 | 0.18 | 0.0133 | 1.0000 |
| GO:0010043 | response to zinc ion | 6 | 1 | 0.01 | 0.0133 | 1.0000 |
| GO:0015695 | organic cation transport | 7 | 1 | 0.02 | 0.0156 | 1.0000 |
| GO:0006000 | fructose metabolic process | 9 | 1 | 0.02 | 0.0200 | 1.0000 |
| GO:0006032 | chitin catabolic process | 9 | 1 | 0.02 | 0.0200 | 1.0000 |
| GO:0046686 | response to cadmium ion | 10 | 1 | 0.02 | 0.0221 | 1.0000 |
| GO:0019674 | NAD metabolic process | 11 | 1 | 0.02 | 0.0243 | 1.0000 |
| GO:0006030 | chitin metabolic process | 12 | 1 | 0.03 | 0.0265 | 1.0000 |
| GO:0043270 | positive regulation of ion transport | 18 | 1 | 0.04 | 0.0395 | 1.0000 |
| GO:0042742 | defense response to bacterium | 23 | 1 | 0.05 | 0.0502 | 1.0000 |