Genomic Signatures Predict Migration and Spawning Failure in Wild Canadian Salmon

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Long-term population viability of Fraser River sockeye salmon (*Oncorhynchus nerka*) is threatened by unusually high levels of mortality as they swim to their spawning areas before they spawn. Functional genomic studies on biopsied gill tissue from tagged wild adults that were tracked through ocean and river environments revealed physiological profiles predictive of successful migration and spawning. We identified a common genomic profile that was correlated with survival in each study. In ocean-tagged fish, a mortality-related genomic signature was associated with a 13.5-fold greater chance of dying en route. In river-tagged fish, the same genomic signature was associated with a 50% increase in mortality before reaching the spawning grounds in one of three stocks tested. At the spawning grounds, the same signature was associated with 3.7-fold greater odds of dying without spawning. Functional analysis raises the possibility that the mortality-related signature reflects a viral infection.

For 60 years preceding the early 1990s, approximately 8 million sockeye salmon (*Oncorhynchus nerka*) returned annually from the Pacific Ocean to Canada's Fraser River basin to spawn. However, since then, sockeye salmon productivity has declined precipitously to the point that returns in 2009 were less than the replacement rate. Consequently, the long-term viability of the wild salmon resource in British Columbia, worth over $1 billion dollars annually, is in doubt. Indeed, several of these Canadian stocks are at risk of extinction (*1*, *2*). In 2009, the prime minister of Canada announced a judicial inquiry into this salmon collapse, which has occurred despite substantial reductions in fisheries harvest. Contributing to the collapse have been massive (40 to 95%) mortalities of adult sockeye salmon before spawning, both in the Fraser River en route to spawning areas and on spawning grounds (*3*). The causal mechanisms of this premature mortality have eluded multidisciplinary research by scientists and fisheries managers (*4*). However, the three functional genomics studies presented here reveal a striking and consistent association between a powerful genomic signature and salmon mortality.

Seven of the last 10 summers have been the warmest on record for the Fraser River, and biotelemetry has revealed high losses of migrating sockeye in regions of elevated river temperature (*5*). Warmer water reduces the delivery of oxygen to the tissues (aerobic scope) of salmon (*6*) and allows more rapid development of infections (*7*). Our preliminary studies also suggest that some fish are stressed before they reach the river, further impairing their survival (*8*). The current study was undertaken to advance our mechanistic understanding of the role of salmon condition (before mortality events occur) on migration and spawning success in the river. We combined established methodologies of nonlethal biopsy of ocean- and river-caught salmon with watershed-scale biotelemetry to follow the fate of tagged fish migrating upstream (*9*, *10*). Functional genomics and tracking of individuals were used to correlate physiological profiles with failed migrations and reproduction. Gene expression was profiled in gill tissue, a respiratory and ionoregulatory organ that is highly responsive to stress, chemical exposure, and disease.

Returning adult salmon caught in the ocean and river were gastrically implanted with a radio transmitter—or a Peterson disc tag if caught at spawning areas—and biopsied for blood, gill, muscle, and fin tissues (*10*); fin tissue was used to genetically identify sockeye stocks (*11*). We tracked individual fish with radio-receivers deployed

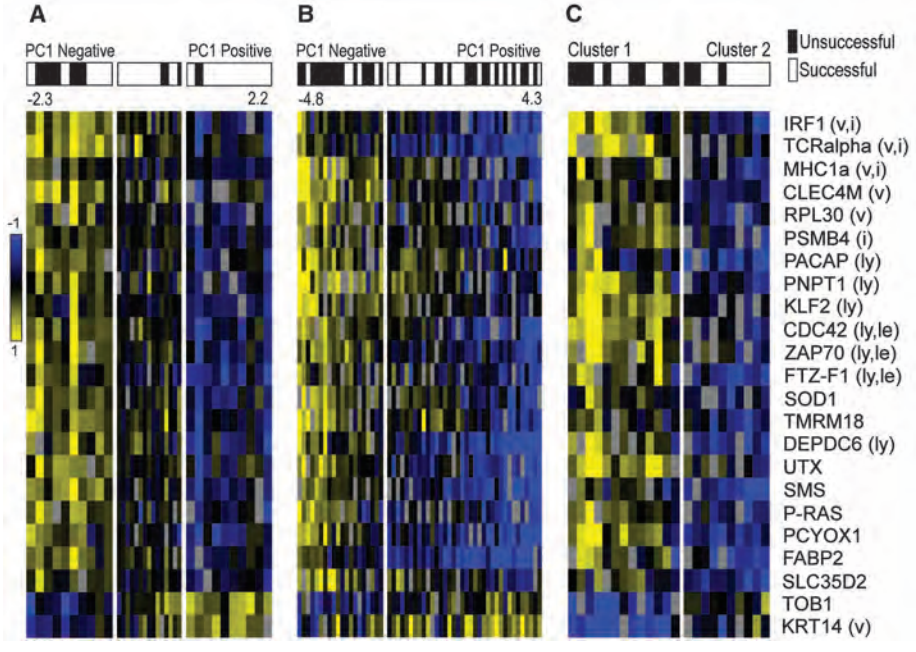

Fig. 1. Heatmaps of 23 annotated genes significantly associated with survivorship in all three studies. For (**A**) ocean-tagging and (**B**) freshwater-tagging studies, heatmaps reflect the ranking of individuals along the PC1 axis (rotational values shown above the heatmap), in which the associations with fate were strongest at the ends of the PC1 distribution, which are demarcated by white blocks. Migration success, depicted in the top bar, was reduced at the PC1-negative end of the axis for both studies. (**C**) For the spawning study, the heatmap reflects the relationships depicted by clustering significant genes from the freshwater PC1-based *t* test, with the white block differentiating the two emergent clusters and the black/white bar reflecting unsuccessful and successful spawners, respectively. (Right) Literature associations of genes with viruses (v), immune response (i), lymphocytes (ly), and leukemia (le) are depicted with letter codes in parentheses next to gene names. (Left) Expression levels are indicated by the color scale ranging from (up-regulated) yellow to (down-regulated) blue. Missing values are shown in light gray.

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throughout the Fraser watershed (fig. S1) to identify date of river entry (for ocean-tagged fish) and in-river fate (location the fish was last detected). Expression profiles were compared between fish that arrived at spawning areas (successful migrants) with those that perished en route. Previous biotelemetry data showed that large losses of sockeye in the upper river (above Hells Gate) (fig. S1) cannot be attributed to river fisheries, which are largely restricted to the lower river (*12*). Thus, to minimize interference from fisheries activities we contrasted expression profiles only for survivors and fish disappearing above Hells Gate in the ocean-tagging study (n = 35 salmon), comprising Late Shuswap Adams fish released 215 and 300 km from the river mouth, in Johnstone Strait and Juan de Fuca Strait, respectively (fig. S1 and table S1). The larger freshwater-tagging study (n = 104 salmon) occurred 69 km upstream of the river mouth on Late Shuswap (largely Adams), Chilko, and Scotch Creek stocks that perished throughout the Fraser River drainage but survived at least 2 days after tagging (to minimize tagging and handling effects). Because large numbers of fish [for example, >80% (*3*)] can die on the spawning areas before spawning, we tagged fish at the Weaver Creek spawning area (fig. S1) and compared the genomic signatures of 11 failed and 12 successful spawners. The ocean and freshwater studies used a salmonid 16K feature cDNA microarray (*13*, *14*), in which 11,535 of the 16,008 genes have gene annotations, whereas the spawning study used a salmonid 32K feature cDNA microarray (*15*), which contained an additional 16K genes, 7513 with gene annotations (*16*, *17*).

Supervised analyses of the ocean-tagging data (analysis of variance and computer algorithm) to detect genes differentially expressed between successful and unsuccessful migrants did not yield a significant result, suggesting that a single physiological mechanism was not likely to be responsible for all river mortality. Alternately, by taking an unsupervised principal component (PC) analysis approach we identified the underlying gene expression patterns in the data and assessed the top five PCs for associations with fate. Among the top five PCs, only PC1 (explaining 12% of the variance in the data) yielded a ranking of fish that showed a significant correlation with survival (Mann-Whitney U = 183, with P = 0.03). Further data inspection revealed a complex relationship between fate and PC1, with enrichment at the negative and positive ends of the PC1 distribution, encompassing approximately 60% of the fish in the study (Fig. 1A). Upper river mortalities were twice as common in the PC1 negative and three times less common in the PC1 positive ends, corresponding to an odds ratio (OR) of 13.5. Moreover, arrival at the receiver adjacent to Adams River spawning areas was on average 15 days faster for successful PC1-negative migrants than successful PC1-positive migrants, 10 days faster after river entry. In 2006, successful spawners also swam upstream slower than fish that failed [20.0 versus 15.5 km/day (*18*)]. Taken together, these results showed that up to 60% of fish contained a gene expression signature in seawater >200 km from the river that was predictive of in-river fate, which in 2006 represented over 2.4 million Late Shuswap fish.

We hypothesized that a similar pattern would exist in the freshwater-tagging study. Comparing only successful migrants and upper-river mortalities (n = 56 salmon), the first PC of the freshwater-tagging data was related to PC1 of the ocean-tagging data (see below). Again, an over-representation of unsuccessful migrants was apparent on the extreme PC1-negative end of the distribution, with the odds of successful migration five times lower in the first third of PC1-negative fish as compared with all remaining fish in the study (χ^2, $P < 0.05$) (Fig. 1B). PC2 to PC5 showed no correlation with survival, and supervised analyses did not yield a significant result (*17*).

The larger freshwater-tagging study included fish that went missing throughout the Fraser River and sufficient sample sizes from three salmon stocks so as to facilitate a more precise analytical

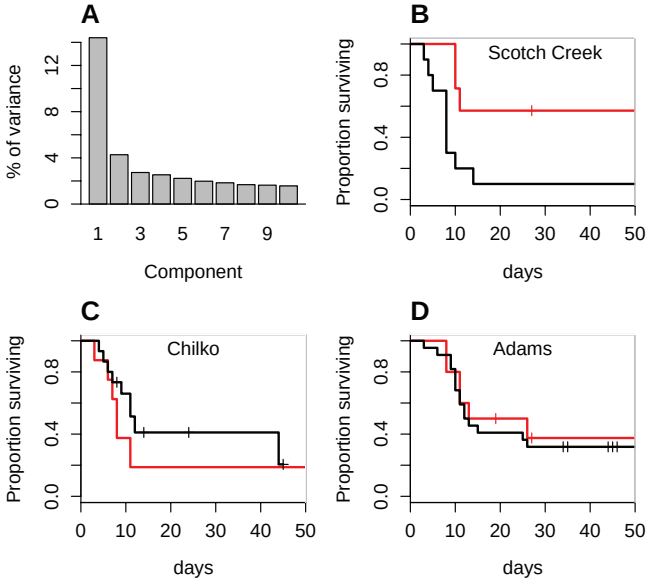

Fig. 2. Survivorship analysis revealed a significant interaction between stock and PC1 in fresh water. (**A**) Graphical representation of PC1 to PC10. (**B** to **D**) Survivorship curves for Scotch Creek, Chilko, and Late Shuswap Adams, respectively. Although in the analysis the value of PC1 was taken as a continuous variable, to graphically represent the correlation with survival the PC1 rotational values were divided into negative (<0, black line) and positive (>0, red line) categories.

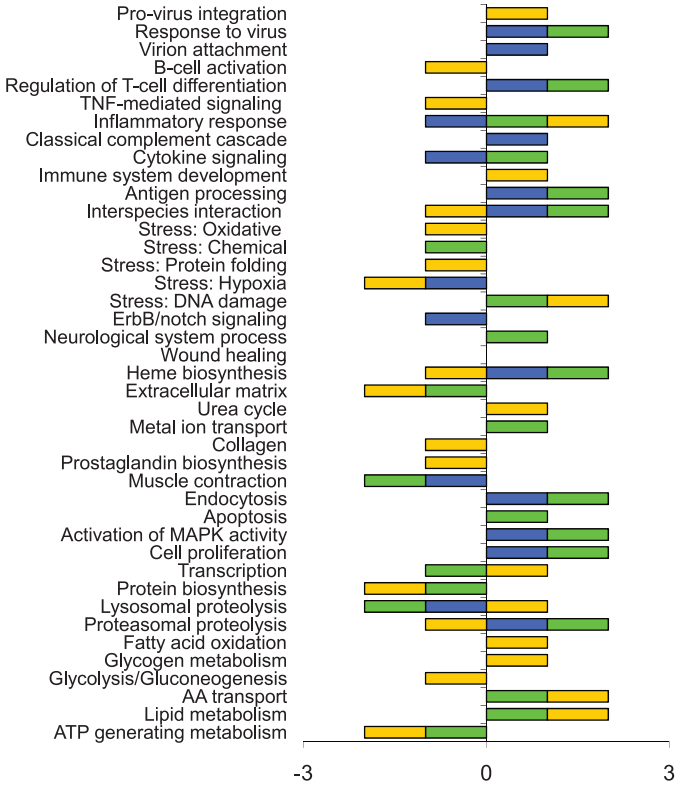

Fig. 3. Functional analysis of signatures associated with fate in (blue) saltwater, (green) freshwater, and (yellow) spawning studies. The axis indicates the number of studies in which a biological process (defined as a collection of molecular events with a defined beginning and end) was (positive) up- or (negative) down-regulated in the mortality- versus survivor-related PC1 signature. Biological processes differentially regulated with no clear indication of overall direction are not shown. A more detailed presentation is available in table S3.

approach. Using all but known fisheries losses for these stocks [n = 72 salmon; see (*17*) for fisheries analyses], the first four PCs along with stock and sex were included as explanatory variables in survivorship analysis (*17*). Parametric survival analysis revealed a significant stock *PC1 interaction [$F_{2,65}$ = 7.30, P = 0.026]. Further analysis revealed a significant relationship between PC1 and survival for Scotch Creek fish [$F_{1,14}$ = 4.97, P = 0.026] but not for Chilko or Late Shuswap salmon (P > 0.05) (Fig. 2). Although the stock *PC3 interaction [$F_{2,65}$ = 6.44, P = 0.040] was also significant, the relationship was not significant when individual stocks were considered (*17*). PC2, PC4, and sex were not explanatory. Differences observed among stocks suggest that some are more severely affected than others. However, other influences could include stock-specific differences in travel time to the receiver adjacent to spawning tributaries (averaging 12, 17, and 24 days, respectively, for Chilko, Scotch, and Late Shuswap), travel time from last receiver to spawning areas (7 days Chilko versus 1 day Scotch/Late Shuswap), and levels of subsequent mortality on spawning areas.

To obtain groups of significant genes for functional analysis, we used t tests to compare samples in the extreme PC1-positive and -negative quartiles for both studies. A reproducible pattern of gene expression correlated with fate emerged. 1603 genes were significant at P < 0.001 in saltwater, and 2762 genes were significant in fresh water. 498 genes were common to both independent data sets, of which 97% were directionally congruent and 90% were up-regulated in PC1-negative fish (fig. S2).

To test the hypothesis that the same genomic signature was also associated with premature mortality at the Weaver Creek spawning area, we used the significant genes from the freshwater t test to cluster successful and unsuccessful spawners. Two well-differentiated clusters emerged, with >70% of unsuccessful spawners in the cluster associated with the PC1-negative mortality-related signature. Salmon with this signature were 3.7 times less likely to spawn than those with a PC1-positive–related signature, despite reaching the spawning area. To assess changes in the signature that may occur closer to spawning, we conducted a t test between the two clusters; 2507 significant genes were resolved (P < 0.001), of which 1136 were on the 16K array, with 36% overlap for freshwater and/or saltwater t test gene lists, 98% of which were directionally congruent (Fig. 1C and fig. S2). The correlation between genomic signatures associated with poor survival throughout return migration was further supported by quantitative reverse transcription polymerase chain reaction validation of six genes (APR-3, ATP6V1C1, FKBP2, C4B, SCHC, and CYP46A1) that showed even more consistent up-regulation in the mortality-related signature fish in all three tagging studies than revealed on microarrays (table S2).

Physiological differentiation along the PC1 axis escalated appreciably during migration into the river and toward spawning areas, with 25 biological processes differentially affected in the ocean, 34 in fresh water, and 47 at spawning (Fig. 3 and table S3) (*17*). Furthermore, an intensification of complement-mediated inflammatory and perforin-mediated apoptotic processes occurred for fish containing the mortality-related signature. Immune stimulation of these same fish was indicated by T-cell activation/proliferation and induction of a Th1 cellular immune response through interferon activation of the virus-specific innate JAK/STAT pathway. Some of the most consistent and/or significantly up-regulated genes (such as Mx, STAT1, IRF1, PRF1, MHC1a, PCSK5, and TCRα) have known linkages with viral activity (Fig. 1C and table S4). Moreover, 65% of affected biological processes were consistent with responses to viral infections (table S3); within these processes, many key regulators co-opted by or activated in response to viruses were differentially expressed (*17*). These data indicate that fish containing the genomic signature correlated with elevated mortality may be responding to viral infection [details are in (*17*)]. Linkages also existed with genes associated with leukemia, most notably cell lymphoblastic leukemia-lymphoma (fig. S3 and tables S3 and S4).

This correlative data set cannot be used to assign cause to the association between a preexisting signature and subsequent mortality. However, we can eliminate the possibility that this signature simply relates to the inevitable senescence of salmon after spawning because the mortality-survival–associated PC1 signature showed relatively stronger differentiation on the spawning area, when salmon were within 1 to 3 weeks of death, than in the ocean, when salmon were 3 to 10 weeks from death. The relatively stronger association with survival in the ocean-tagging study also suggests tagging effects did not appreciably influence the genomic relationships of PC1 with mortality (*17*). Moreover, because the mortality-related signature preexisted before river entry, it cannot reflect a response to stress of moving from seawater to fresh water. In fact, few indications of a general stress response existed within the mortality-related signature; DNA damage was the only stress-specific biological process up-regulated, as indicated by elevated expression of more than 20 genes (such as KIN, RAD51, CRY5, and NSMCE2) (Fig. 3). However, these fish could have experienced salinity stress in seawater induced by a premature transcriptional shift in osmoregulatory genes [Na^+/K^+ adenosine triphosphatase (ATPase) isoforms 1a, 1b, and a3 (fig. S5) and PRL, SHOP21, CIRBP, CLIC5 SLC5A1, and FXYD3] better suited for fresh water (*17*). Indeed, elevated chloride and osmolarity were anti-correlated with PC1 of ocean-tagged fish (Spearman rank = –0.33 and –0.27, respectively), supporting a 2006 tagging study that associated plasma ionic imbalances with coastal mortality (*19*) and salinity challenge experiments that revealed higher mortality for sockeye held in saltwater as compared with isoosmotic or fresh water (*20*). As a result, we speculate that osmoregulatory dysfunction of salmon containing the mortality-related signature may have contributed to ocean mortality and possibly stimulated faster entry into fresh water.

This combination of watershed-scale biotelemetry and functional genomics of wild salmon in nature has yielded new insight into one potential physiological mechanism associated with survivorship during return migration. Migrating salmon are expected to markedly transform gene expression, given the required physiological demands associated with upstream swimming, environmental shifts, maturation, fuel depletion, and senescence. Our study revealed a mechanistic signature associated with premature mortality of salmon measurable >1 month to <1 week ahead of death and throughout the river. Our hypothesis is that the genomic signal associated with elevated mortality is in response to a virus infecting fish before river entry and that persists to the spawning areas.

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Supporting Online Material
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Materials and Methods
Supplemental Results
Figs. S1 to S5
Tables S1 to S4

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The Structure of Human 5-Lipoxygenase

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The synthesis of both proinflammatory leukotrienes and anti-inflammatory lipoxins requires the enzyme 5-lipoxygenase (5-LOX). 5-LOX activity is short-lived, apparently in part because of an intrinsic instability of the enzyme. We identified a 5-LOX–specific destabilizing sequence that is involved in orienting the carboxyl terminus, which binds the catalytic iron. Here, we report the crystal structure at 2.4 angstrom resolution of human 5-LOX stabilized by replacement of this sequence.

Leukotrienes and lipoxins are potent mediators of the inflammatory response derived from arachidonic acid (AA). When leukocytes are activated, AA is released from the nuclear membrane by the action of cytosolic phospholipase A_2 and binds 5-lipoxygenase–activating protein (FLAP). The increased Ca^{2+} concentration of the activated cells simultaneously promotes translocation of 5-LOX to the nuclear membrane, where it acquires its substrate from FLAP (*1*, *2*). AA is converted to leukotriene A_4 in a two-step reaction that produces the 5*S*- isomer of hydroperoxyeicosatetraenoic acid (5*S*-HPETE) as an intermediate (*3*, *4*).

Autoinactivation of 5-LOX activity has been described, and this loss of activity is perhaps important in limiting the synthesis of its pro- and anti-inflammatory products (*5*). Previous reports indicate that non–turnover-based inactivation is a consequence of an O_2 sensitivity linked to the oxidation state of the catalytic iron (*6*). However, not all LOXs display this hypersensitivity to O_2. For example, 8*R*-LOX activity is stable despite a solvent-exposed iron coordination sphere equivalent to that in 5-LOX (*7*). In similar conditions, 50% of 5-LOX activity is lost in 10 hours (*8*). We reasoned that 5-LOX–specific destabilizing features may confer susceptibility to non–turnover-based inactivation. Regulatory mechanisms that facilitate transient activation include targeted degradation, phosphorylation, and allosteric control of enzyme activities. Autoinactivation as a consequence of intrinsic protein instability may play a similar role. For example, the instability of the tumor suppressor protein p53, relative to its orthologs such as p73, has been proposed to have a functional role (*9*).

On the basis of the crystal structures of two AA-metabolizing lipoxygenases [an 8*R*-LOX from *Plexaura homomalla* (*7*, *10*) and a 15-LOX from rabbit reticulocyte (*11*, *12*)], each with ~40% sequence identity to 5-LOX, we identified a 5-LOX–specific lysine-rich region near the C terminus of the enzyme that might confer instability (*13*). In the 8*R*- and 15-LOX structures, a turn centered on amino acid 655 (5-LOX numbering) leads from the C-terminal helix to the C-terminal segment and allows the terminal carboxylate to penetrate the LOX body and bind the catalytic iron (Fig. 1, A and B). In most LOXs, amino acid 655 is a highly conserved Leu, with its side chain pointing toward an invariant Arg (Arg^{651}). A striking 5-LOX–specific feature is Lys in place of Leu at this position as part of a di- or tri-Lys peptide (fig. S1). Although numerous salt links anchor the C-terminal helix to the

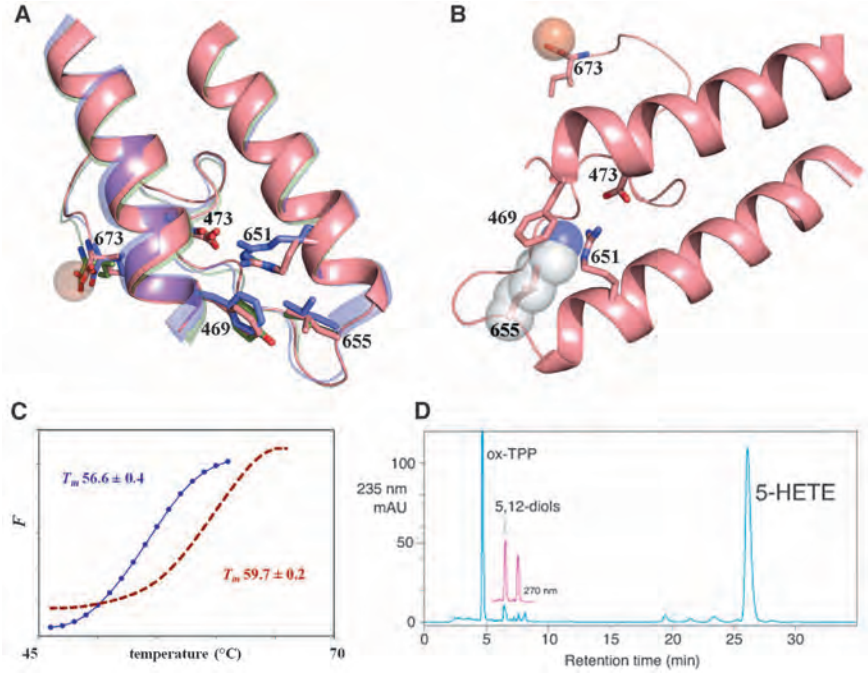

Fig. 1. Stabilization of human 5-LOX. (**A**) Superposition of the C-terminal regions of the structures of 15-, 8*R*-, and Stable-5-LOX. The C-terminal segment that leads to the catalytic Fe emanates from the helix that terminates at amino acid 655 (5-LOX numbering; Stable-5-LOX, pink; 8*R*-LOX green; 15-LOX, blue). Highly conserved amino acids (Leu and Phe/Tyr) and an invariant salt link (Asp-Arg) are depicted in stick rendering. (**B**) Detail of the turn at the end of the terminal helix. The 5-LOX–specific Lys (replaced in Stable-5-LOX with Leu) is modeled at position 655 as its most common rotamer (transparent sphere rendering). As positioned, it would interfere with the invariant salt-link and cation-π interactions. All figures were generated with Pymol (*31*). (**C**) Thermal denaturation of Stable-5-LOX (red) and the parent enzyme Sol-5-LOX (blue). Fluorescence (*F*) is monitored as a function of temperature. T_m (with SD) 56.6°C (±0.4°) and 59.7°C (±0.2°) for Sol-5-LOX and Stable-5-LOX, respectively. (**D**) High-performance liquid chromatography chromatogram. Product analysis of Stable-5-LOX reveals both 5-HETE (5-HPETE reduced by the addition of triphenylphosphine, TPP) and leukotriene A_4 hydrolysis products (5,12-diols).

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Supporting Online Material for

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This PDF file includes:

Supplemental Material

Supplemental Methods

Field sampling

(*S1*) provides an overview of our radio-tracking and biopsy program, with detailed information on 2006 biopsies provided in (*S2*). The biopsy approach has been previously validated for telemetered sockeye salmon and does not result in altered behaviour or survival relative to fish that are only telemetered (*S3*).

Returning sockeye salmon targeted for radio-tracking studies were captured by commercial purse seines in saltwater in the two marine approaches around Vancouver Island, Johnstone Strait at the northern end of Vancouver Island, 215 km from the mouth of the Fraser River, where fish were sampled Aug 11-12, 16-19, and 24-27, and Juan de Fuca Strait at the southern end of Vancouver Island, 300 km from the Fraser River, where fish were sampled Aug 4-10 (Fig. S1). A drifting tangle net was used to catch fish for freshwater tagging in the lower Fraser River at Glenlyon Provincial Park, 10 km south of Mission, where fish were sampled Aug 1-Sept 1.

Sockeye salmon collected at all three locations were dip netted from the nets and placed into a sampling trough with flowing seawater for sampling. The tips of 4-6 gill filaments (approximately 0.3 g) were cut and immediately frozen in a liquid nitrogen (LN_2) dry shipper or on dry ice. In Johnstone Strait, muscle biopsy samples were also taken with a 3 mm biopsy punch between the lateral line and the dorsal fin. Blood plasma samples were taken from all fish and frozen for analysis of hormone and ion levels (*S4*). An adipose fin clip was sampled from all fish and preserved in 95% ethanol for individual DNA stock identification. Physiological sampling and radio-tagging were performed within 3 minutes to minimize stress on the fish and fish were immediately returned to the ocean or river to continue migration. Migration progress and timing of individually tagged fish was

reconstructed from data downloaded from radio signal receivers deployed along the Fraser River to natal sub-watersheds by LGL Limited.

Weaver Creek sockeye salmon spawn in an artificial spawning channel which has a controlled entrance and no exit, situated 100 km from the ocean (Fig S1). Females were dip-netted out of the entrance of the spawning channel, physiologically sampled as above, tagged with Petersen discs on several dates (Oct. 5-6, Oct. 13, and Oct. 19) and immediately returned to the spawning channel. Moribund fish were recovered daily and their gonads examined to assess whether they had spawned or not.

Through our study design and analysis, we minimized the potential confounding effects of handling on our results. First, handling time by our experienced team was minimized such that fish were handled for no more than a few minutes following capture, and immediately returned to the ocean or river where they were caught. Tagging and handling effects have been estimated in previous studies to account for about 15% of mortality, and these effects are largely limited to the first 1-2 days after capture (*S1-3*). Tagging-related mortality may differentially affect fish that are already stressed, potentially inflating differences in performance between genomic signatures. We attempted to minimize the impact of tagging-related mortality in our studies by removing fish that died within 2 days of capture. Moreover, in the saltwater study the analysis was further limited to fish lost in the upper river (above Hells Gate) and survivors; hence, only fish that had survived at least 10 days were included. The saltwater study also minimized stress associated with capture and tagging of fish when they are concurrently being stressed by a recent shift in salinity/temperature environments.

Microarray Methods

Total RNA isolation

Field collected samples were initially stored in a charged liquid nitrogen cryo-shipper and transferred to -80 ^{o}C upon arrival to the lab. Total RNA was purified from individual fish gill

using Magmax™-96 for Microarrays Kits (Ambion Inc, Austin, TX, USA) with a Biomek FXP (Beckman-Coulter, Mississauga, ON, Canada) automated liquid-handling instrument. Two gill filaments per fish were homogenized with stainless steel beads in TRI-reagent (Ambion Inc, Austin, TX, USA) on a MM301 mixer mill (Retsch Inc., Newtown, PA, USA). 100 µl aliquots of homogenate were pipetted into 96 well plates and extractions were carried out according to the manufacturer's instructions using the "No-Spin Procedure" on the Biomek FXP. In the final step, RNA was eluted with RNAase-, DNAase-free water and RNA yield was determined by measuring the A_{260} of the eluate. Purity was assessed by measuring the A_{260}/A_{280} ratio of the eluate. Solutions of RNA were stored at −80 °C until use for cDNA synthesis or quantitative RT-PCR.

aRNA Labelling and Arrays

Because the tissue samples were small, we first amplified the total RNA to obtain sufficient RNA to run on a microarray slide. 500 ng to 5 µg of total RNA was amplified 1x using a MessageAmp™II-96 kit (Ambion, TX, USA), performed manually according to manufacturer's instructions. Five micrograms of aRNA were reverse transcribed into cDNA and labelled with Alexa dyes using the Invitrogen Indirect Labelling Kit, with modifications from the manufacturer's instructions. Briefly, the cDNA was purified using Zymo-25 Clean-Up columns (Zymo Research, Orange, CA) and eluted using the 2X coupling buffer, supplied by Invitrogen. During dye labelling, samples were processed individually by first adding DMSO, then cDNA to the Alexa dye tube and incubating for 1h at room temperature. All individual (experimental) samples were fluorescently tagged with Alexa 555 and references were labelled with Alexa 647. Samples and references were cleaned up by adding 50 µl of DNA binding buffer (Zymo) to each Alexa tube and then combining the sample and references for each slide into Zymo-25 Clean-Up columns. The unbound portion of the labelled cDNA was removed by centrifugation at 13,000 rpm/min. The labelled cDNA was washed three times with DNA wash buffer (Zymo) and eluted in 9 µl of 1X TE buffer. Two microlitres of poly dA were added to the targets, which were then denatured for 10 min at 80 °C, followed by the

addition of 125 µl of pre-warmed SlideHybe3 buffer (Ambion, TX, USA) before loading into the hybridization chamber in Tecan-HS4800 Pro Hybridization Station (Tecan Trading AG, Switzerland).

Salmon Arrays

Each fish examined in the array studies was run on a single slide against a reference control that was a pool of all of the fish used in the study. Microarray data were expressed in terms of normalized (background corrected) $\log_2$ ratios between each fish and the reference control.

All slides were processed on Tecan-HS4800 Pro Hybridization Station (Tecan Trading AG, Switzerland). All steps from washing, hybridization, denaturation, and slide drying were carried out automatically.

Fluorescent images were scanned using a Perkin Elmer ScanArray Express (Perkin Elmer, Boston, MA), adjusting the PMT gain for optimized visualization of each image. The images were quantified using Imagene (BioDiscovery, El Segundo, CA, www.biodiscovery.com).

Expression data were managed using a local installation of BASE [19822003]. BASE was customized slightly to support Imagene two-file formatting. Each slide was normalized in BASE using the print-tip LOESS method.

The number of missing values, mean signal-to-noise log-ratio and quality metrics from arrayQualityMetrics [19106121] and arrayQuality [19544454] in Bioconductor were used to assess slide quality. Slides were removed from further experimental analysis if two or more plots were flagged on the arrayQualityMetrics report after data normalization, if more than 50% missing spots were identified by the SNR and missing spots report, if there were more than 30% missing spots and an experimentally low SNR value as identified by the SNR and missing spots report, or if the slide had spatial problems as identified by the plots from the arrayQuality package and substantiated by the spatial plots score of the raw microarray data in the arrayQualityMetrics report. All slides in the saltwater and freshwater studies were

assessed using these metrics, and based on these criteria, 6% of slides were typically considered low quality and removed.

For saltwater and freshwater studies, the data for each retained slide was further processed to remove poor-quality spots. Flagged spots were treated as missing, as were spots with a SNR less than 2. In a set of slides considered a single data set, genes with more than 50% missing values were removed. For procedures such as PCA that require matrices without missing values, missing data were imputed using an average of the existing probe intensities.

For the spawning ground study, normalization was performed in GeneSight as outlined in (*S5*).

Statistical Analyses

We used both unsupervised and supervised approaches to evaluate potential associations of the gene expression data with migration and spawning success.

ANOVAs were performed comparing successful migrants with those that died en-route to spawning grounds to assess whether a single physiological signal was associated with most mortality occurring in the river.

Principal component analysis (PCA) was applied as an unsupervised method to reduce dimensionality and identify the main transcriptional trajectories in the array data. This approach, as detailed in (*S6*), orders both samples and genes according to their contribution to each eigenvector, which provides a global picture of the dynamics of gene expression describing the relationship between sample variability and changes in gene expression. Singular Value Decomposition (SVD) provides a representation maximising variance across samples and a ranking of genes characterising this variation. We used the ranking of individuals along each of the top five principal components to look for correlations with survival based on a Mann-Whitney U test and Yate's chi-square statistics. Spearman rank

correlations with blood plasma variables, including levels of chloride, glucose, lactate, and sodium, osmolarity, and Na^+/K^+ ATPase activity were also conducted.

Parametric survival analysis (an extension of generalised linear models) was used to look for differences between physiological classes of fish in survival to the spawning ground. This analytical method is advocated for time-dependent data (*S7*) as these data tend to violate the constant-variance assumption of other regression techniques. Censored residual diagnostic analyses showed a lognormal error structure to be the most appropriate (*S8*). PCA generated a value for each principal component for each individual fish, and this value was used as a linear explanatory variable within the analysis. In addition, stock and sex of the individual were included as categorical explanatory variables and all interactions were investigated. Non-significant terms were removed in a stepwise fashion. Although in the analysis the value of PC1 was taken as a continuous variable, to graphically represent its correlation with survival, it was grouped into rotational values >0 or <0.

Support vector machines (SVMs) (*S9*) are a set of related supervised learning methods used for classification and generalising a function from training data. The training data consists of pairs of input objects and desired outputs, and output of the function predicts a class label of the input object (classification). The task of the supervised learner is to predict the value of the function for any valid input object after having seen a number of training examples. To achieve this, the learner has to generalize from the presented data to unseen situations in a "reasonable" way. Viewing input data as two sets of vectors in an n-dimensional space, a SVM will construct a separating hyper plane in that space, which maximizes the margin between the two data sets. In this study we used Gist (*S10*) as an implementation of the SVM, with training data comprised of gene expression data and binary class labels of "Reached the spawning grounds = true or false". Learning quality was assessed by leave-one-out cross validation.

T-tests of expression data were performed in GeneSight (Biodiscovery, El Segundo, CA, www.biodiscovery.com). Heatmaps were constructed using matrix2png software (*S11*).

Functional Analysis

The salmonid 16K array contains about 6,500 unique salmon genes that are annotated (contain a gene ID and gene ontology) and cover a broad spectrum of biological processes and molecular functions. By statistically contrasting the function (gene ontologies) of the genes significantly associated with an expression signature with the representation of gene ontologies across all genes on the array, we can ascertain which gene ontologies (biological, molecular, cellular) are statistically over-represented in the signature. In this study, we used the gene lists from t-tests significant at $p<0.001$ for functional analysis in the publicly available program Database for Annotation, Visualization and Integrated Discovery (DAVID) (*S12*). An expanded Gene Set Enrichment Analysis (GSEA), which considers the ranking of all genes as opposed to simply those passing a specific p-value cut-off, was employed using Pathway Studio® (*S13*) and included gene ontologies and additional manually curated pathways from Ariadne. Taken together, these analyses defined the functional signature of the data. We then compared the functional signature(s) to published experimental microarray, proteomic and quantitative RT-PCR data to explore potential linkages (i.e. which biological processes were similarly affected in controlled experimental studies). We further explored the data using the literature mining program Information Hyperlinked Over Proteins (iHOP) (*S14*) to establish additional linkages of *specific genes* (i.e. those of high statistical relevance or consistency) with physiological and biological processes uncovered in other studies, and looked for common physiological associations among these genes. Given our iHOP results, we also searched the Ariadne ResNet® (*S13*) knowledge database for protein associations with the terms "vir" and "leukemia", and included these groups in GSEA. A relational network based on these terms was constructed in Pathway Studio®.

Quantitative Reverse-Transcriptase PCR (qRT-PCR)

QRT-PCR was performed to validate our microarray results for six significant genes and to assess transcription of Na^+ K^+-ATPase isoforms to further explore the relationship of our fate-related profile and osmoregulation. Total RNA was used to synthesize cDNA. Two-step reverse transcription-PCR was performed using SuperScript^{Tm} III First-Strand Synthesis SuperMix for qRT-PCR (Invitrogen, CA, USA), and Power SYBR Green PCR Master Mix (Applied Biosystems, CA, USA) according to guidelines from the manufacturer. Reverse transcription was performed on 1 µg total RNA template and a 1:5 dilution of the resulting cDNA was used as template in qRT-PCR.

The qRT-PCR assays were performed on an ABI 7900HT PCR system (Applied Biosystems, CA, USA) in 384-well plates using 20 µl reaction volumes containing 1X Power SYBR Green PCR master mix (Applied Biosystems, CA, USA) with 300 nM of forward and reverse primers and 2 µl of diluted cDNA. The standard cycling conditions were 95°C for 15 min followed by 40 cycles of 94°C for 15s and 60°C for 1 min. All samples were run in duplicate and non-template controls included.

The cycle threshold (Ct) value was determined by the ABI 7900HT Sequence Detection System (SDS) Relative Quantification ΔΔCt Study. Target gene expression (unknown sample) was normalised to a reference (endogenous control) gene (Acidic ribosomal phosphoprotein PO [ARP]) and adjusted for amplification efficiency (E) from each PCR kinetic curve (*S15*). For each target gene, average E of the PCR reactions was calculated from triplicates of the two samples. Efficiencies between 0.9 and 1.1 were accepted. Expression levels (RQ) relative to an average Ct value of five fish sampled in the lower river and containing the survivor-related signature were then calculated by the ΔΔCt method adjusted for E. T-tests of qRT-PCR data were performed in excel.

Supplemental Results

Potential for handling/tagging effects

While we made every effort to limit potential effects of tagging and handling on our data, we cannot completely discount the possibility that delayed mortality due to handling and tagging could have affected the strength of our genomic relationships with mortality. We argue, however, that these effects would be minimal in our ocean-tagging study, as only fish that successfully arrived to the river – at least 6 days following tagging – and reached Hells Gate – at least 4 more days travel time – were included in our analysis. During that time some mortality-related signature fish may have died due to effects unrelated to handling and tagging, which means that we may, in fact, be underestimating the effects of the PC1 mortality-related signature if it is also associated with marine mortality; this is a strong possibility given linkages of this signature with osmoregulatory stress in the ocean. In the freshwater study and spawning studies, we treated fish that fell back in the river or that were not observed past 2 days post-tagging as tagging-related mortalities, and did not include them in our analyses.

PC1 effects on fisheries captures

We minimized the effects that fisheries would have in the resolution of genomic signatures associated with natural mortality because we limited our ocean-tagging study to fish that had migrated past the point in the river where major fisheries occur. Hence, while fish tagged in the ocean were exposed to the same lower river fisheries as those tagged in the lower river, these fish were not included in the ocean study. For the freshwater dataset, we included fisheries-caught fish in our study, and expect that some additional lower river losses were from unreported fisheries. We examined whether or not eigenvectors 1-3 were correlated with the probability of being caught in a fishery by including mortalities attributed to fisheries in an additional PCA analysis of the freshwater microarray data (N=100). Logistic regression showed no relationship between capture probability and PC1 [$f(1,100) = 0.19$, $p = 0.84$), PC2

235 [f(1,100)=0.06, p=0.88], or PC3 [f(1,100)=0.87, p=0.24]. There were also no effects of
236 stock or sex, and no interactions (all p > 0.1). These findings were consistent with a study
237 that determined that physiological profiles from basic blood analyses (e.g., ions, metabolites,
238 hormones) were similar for Fraser River sockeye that were captured in fisheries and those
239 that survived to spawning grounds (*S16*).
240
241 *PC3 in the freshwater-tagging study*
242 Parametric survival analysis revealed significant stock*PC interactions for both PC1 and PC3,
243 but whereas analyses based on individual stocks were significant for PC1 (Scotch Creek only),
244 none were significant for PC3. There was no overlap in the 400 top-scoring genes for PC1 and
245 PC3, suggesting that these reflected distinct gene expression signatures. Biological processes
246 enriched among genes scoring high for PC3 include actin cytoskeleton, angiogenesis, and
247 regulation of lymphocyte differentiation (positively-correlated genes) and translation
248 (negatively correlated genes).
249
250 *Functional analysis of the signature associated with poor survival*
251 Sixty-five percent of the biological processes revealed in functional analysis of PC1-
252 associated genes in the ocean, freshwater, and at spawning were consistent with viral activity
253 in fish with the mortality-related signature. Moreover, many regulators co-opted by viruses
254 or differentially regulated in response to viral infections were differentially regulated within
255 these processes in mortality-related signature individuals. Below, we outline briefly some of
256 the key functional linkages with viral activity within the mortality-related signature.
257 Reductions in protein biosynthesis, as observed in freshwater and at spawning, are
258 consistent with a chronic response to stress, but are perhaps more consistent with
259 interference by a viral pathogen to minimize host antiviral response (reviewed by *S17-18*).
260 Of note are key regulators of the capped cellular mRNA translation system (E1F4G1, E1F4G2,
261 EIF4E, EIF2B3) and the 25-A Rnase L system (ABCE1, EEF1D) often targeted by viruses that

were differentially expressed in the mortality-related signature fish, with a signature that appears notably pro-viral (up-regulation viral translation (+) WARS, PABPC4, SARS1, IARS2, DARS). Proteasomal proteolysis, up-regulated in mortality-related signature fish in saltwater and freshwater and down-regulated at spawning, is critical for the maintenance of cell homeostasis. The proteasome is also important for antigen presentation and can facilitate entry and replication of some viruses (*S19*). Four gamma interferon-inducible proteasomal genes with roles in antigen presentation, PSMB4, 5, 8, and 9, were up-regulated in mortality-related signature fish, along with other elements of the Th1 antigen presentation machinery (MHC1, TCRα, TAP2, TAPBPL, ERP57). Apoptotic shifts were notable in all tagging locations, with the strongest up-regulation observed in freshwater. Twenty pro- and anti-apoptotic proteins known to interact with and/or respond to viruses were differentially regulated. Notably, PRF1, specifically involved in lysis of viral infected cells, was up-regulated in mortality-related signature fish in all tagging locations. Other up-regulated pro-apoptotic proteins involved in host-viral interactions include HTATIP2, PDCL3, BNIP1 and SCARB1. Transcription of viral-co-opted anti-apoptotic proteins F10 and RRAGA was up-regulated in the lower river, while the pro-apoptotic FADD protein was down-regulated. Viral-mediated pathogenesis can result from disturbance of intracellular signal cascades; viral activation of the MAPK/ERK signalling pathway, up at all three locations, is common (*S20*). Endocytosis serves as a route of entry for many viruses, and was also up-regulated in mortality-related signature fish at all tagging locations. Alternately, all three major constituents of the cytoskeleton were down-regulated in mortality-related signature fish, with diminished transcription of actin at all three locations, cytokeratin in freshwater and at spawning, and tubulin in the lower river only. Dysregulation of cytoskeletal function resulting in cell rounding is induced by most RNA viruses (*S17*).

Patterns associated with stress and immunity in mortality-related signature fish were also consistent with a response to viral infection. The transcriptional activity of genes involved in cellular immunity, defense, and viral response are outlined in Table S4, and we

briefly touch on key indicators of viral activity below. Although most stress responses were down-regulated in mortality-related signature fish, a powerful response to DNA damage was observed both in freshwater and at spawning. Viruses can enhance DNA damage responses and hijack these responses to facilitate their own replication (*S21*). DNA damage responses can also increase apoptosis and reduce tumorogenicity in oncogenic viruses (*S22*). Viruses induce Th1 cellular immune responses, largely through interferon activation of the virus-specific innate pathway JAK/STAT (*S23*). Thirteen interferon responsive genes were differentially regulated in mortality-related signature fish, with 10 up-regulated (STAT1, IRF1, MX, GIG1, IFI30, ABCE1, IFIT5, IFI6, CRFB6, and IFNGR1), and 4 down-regulated (IFTM3, IRF4, IIP2, and PRKRIR). Fourteen genes within the JAK/STAT pathway were also differentially regulated, with eight induced in mortality-related signature fish (STAT1, STAT3, IL13RA2, EPOR, SPRY2, CSF3R, BCL2L1, SOCS1) and six down-regulated (PIM1, PIK3CB, F2, SOS1), including two negative regulators (SOCS4, SOCS5) of the pathway. Intracellular immune responses stimulate apoptosis and/or inflammation through activation of the complement cascade; 29 genes involved in the complement system were differentially regulated, with C4B, C1QBP, C13ORF15, C5R1, CFD, ERCC2, F13B, PRF1, MBL1, and S100B consistently stimulated, and C1QG, CD18, SVEP1, PSP-A, LGALS2, CFB, and CD59 down-regulated in mortality-related signature fish. Acute inflammatory responses often follow cell lysis and release of infective particles in diseased tissues and signal the beginning of pathogenicity. In gill tissue, inflammatory responses can affect capacity for gas exchange and osmoregulation, leading to morbidity (*S24-25*). Acute inflammation was up-regulated in mortality-related signature fish in freshwater. EXOSC6, MGll, CSF1, ALOX5, C7, LTB4R, PARP4, IL13RA2, EPHX2, MMP25, IKBKAP, and PXN1 are pro-inflammatory proteins that were increasingly enhanced in the first 20^{th} percentile of PC1-negative fish in freshwater, i.e. in fish that carried the lowest probability of survival.

In addition to the above, genes involved in the induction of an anti-viral state (PCSK5, STAT1), viral defense response (BNIP3L, DDX58), viral inflammatory response (LTB4R), and

316 response to virus (15 genes) were further indications of an activated anti-viral immune
317 response in mortality-related signature fish. Also stimulated were genes indicative of pro-
318 viral activity, including those involved in viral recognition (LGALS9), reception (CXCR4B,
319 PVRL3, HYAL2), entry (SCARB1, MAPK3, CTSB, ICAM1), replication (RAD51, DNAJC3, HSPB1,
320 CSNK2A1, RPA1, MGLL, TOPOII, LGALS9, SOCS1, ILF3, CCL19, RHOA, HDAC1, EIF2S1),
321 integration (FLI1), transcription (ATF4), pre-mRNA splicing (SFPQ, LOC397773), transport
322 (RPL30, NCL, BAT1A, STAU1, DDX23, EIF5, CTK2-A, DOHH), encapsidation (EF-1AO), lytic
323 replication (UBQ1), release (SGTA), and viral induced stress (KIN). The strong differential
324 regulation of lymphocyte differentiation, proliferation and activation was also indicative of
325 pathogen and/or disease stimulation. Many of these genes are active in leukemia-related
326 diseases (Fig. S3, Table S4). In fact, an over-representation of genes involved in cell
327 lymphoblastic leukemia lymphoma was significant at spawning ($p<0.05$) and nearly
328 significant in the lower river ($p=0.056$) (Table S3). These data suggest that lymphocytes
329 may be a potential target for the purported viral infectivity.
330 Some elements of the functional signature may be due to mechanisms not directly
331 related to viral infections. Sockeye naturally cease feeding before river entry. Among the
332 shifting metabolic pathways within the mortality-related signature, some may indicate lower
333 energy reserves or alternatively higher energy demand. For example, the reduction in
334 oxidative metabolism is consistent with a stress-induced response, while up-regulation in
335 glycogen metabolism and fatty acid oxidation is often associated with food deprivation (*S26*).
336 While up-regulation of lipid metabolism in mortality-related signature fish may provide an
337 important source of energy for faster migration speeds (*S27*), it is also crucial for multiple
338 stages within the life-cycle of viruses, including viral entry, replication, maturation and
339 secretion (*S28*). There is some evidence that gill secondary lamellae, which are sites of gas
340 exchange, are also targeted within the mortality-related signature fish. Pillar cells maintain
341 structural integrity of secondary lamellae and contain collagen fibrils and actomyosin
342 contractile proteins (*S29*). These structural constituents were down-regulated in mortality-

related signature gills, as was haemoglobin to transport oxygen and prostaglandin biosynthesis (prostaglandins regulate contraction and relaxation of smooth muscle tissue). Alternately, heme biosynthesis and ADRB1, a potent controller of heart rate and blood pressure, were up-regulated in mortality-related signature gills in saltwater and freshwater. Notably, SP-A, a protein that is down-regulated in respiratory distress syndrome (*S30*), was severely down-regulated in mortality-related signature fish at spawning.

What motivates mortality-related signature fish to move more quickly into the river? (*S31*) speculated that the loss of hypo-osmoregulatory ability in saltwater motivates migrating salmon to enter freshwater. In saltwater, Na^+/K^+ ATPase is up-regulated to remove excess salt from the cells, a process that is largely driven by the alpha isoform. QRT-PCR assays revealed that transcriptional shifts associated with saltwater-freshwater transition of three of these receptors (isoform 1a—the freshwater form, and 1b—the saltwater form, and isoform a3) had already occurred for mortality-related signature fish in saltwater (Fig. S4). As well, prolactin, a key regulator of osmoregulation in freshwater (*S32*), Salmo salar hyperosmotic protein 21 (Shop21) and SLC5A1 were all up-regulated in mortality-related signature fish, most notably in freshwater. Genes generally down-regulated as fish moved from saltwater to freshwater environments, including FXYD3, a co-transporter of Na^+/K^+ ATPase, CLIC5, and CIRBP, were also transcribed at a lower level in mortality-related signature fish than fish containing a survivorship-related signature. In freshwater, we also found that gill Na^+/K^+ ATPase activity was lower in mortality-related signature fish ($p<0.05$), with the lowest activity in mortality-related signature fish that died ($p<0.001$).

Not all individuals containing mortality-related signature succumbed before spawning. To further elucidate biological processes most closely associated with (presumed) infection-related mortality (Table S3), we contrasted, within the mortality-related signature, survivors and fish that died in each study. Maladaptive processes exclusive to the mortality-related signature (i.e. not differentiated in PC1) included cell matrix adhesion, cofactor binding and cation-transporting ATPase activity. MSN, SUMO2, RHOA, IFIT5, TCTA, and CTK2-A, all genes

involved in viral responses or viral life cycle, were maladaptive when up-regulated in freshwater, while IQGAP1, HNRPA1, PBX2, JUNB, BANF1, HNRPA0, and GNB2I1 were maladaptive when down-regulated. Pathogenic virulence factors CDK7 and PPA1 were maladaptive when up-regulated in freshwater, while CD9, a viral virulence factor, was maladaptive when up-regulated in the ocean. These genes may provide powerful predictive biomarkers for mortality associated with the mortality-related signature in future.

Biological complexity in associations between physiology and survival

The mortality-related signature we identified does not account for all variance in survival observed in the river, but rather was most predictive in the most affected (extreme) fish. In the ocean, the highest odds ratios (OR 13.5-16) between successful and unsuccessful migrants were observed in the extreme 25-30% of samples on either end of PC1, accounting for up to 60% of the fish. There was little signal associated with survival in the intermediate fish. In freshwater, the odds ratio maximized (OR 10) at the extreme 20% of fish. Biologically, this is not too surprising. Whether fish are diseased or stressed, mortality is more likely to occur in individuals that are the most physiologically challenged. It is also unlikely that all mortality in the river is the result of a single mechanism. Our study highlights just one physiological signature resolved in gill tissue, although the PC3*stock association with survival may reflect a second potential mechanism (greater sample sizes will be required to fully assess the impact of this signature on survival). Additional physiological signatures may only exist in other tissues. Moreover, we expect that relationships between physiology and mortality to be strongly influenced by additional environmental stressors. Environmental conditions, like river temperature, vary over time, hence we expect the level of stress on the fish would also vary over time and in a stock-specific manner. We did not have the sample sizes to sufficiently address a temporal component in our data, but expect that this may be a factor that we can model in future.

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Table S1. Experimental designs for ocean-tagging (A) and freshwater-tagging (B) microarray studies. (A) The saltwater study contrasted fish from the Late Shuswap stock that arrived to the spawning grounds (successful migrants) with fish that went missing in the upper Fraser River (upper river mortalities) from Hell's Gate onward. This region of the river contains the highest water temperatures, lowest fisheries effects, and the greatest potential for physiologically-induced mortalities. (B) The freshwater study contained fish primarily from three stocks, Late Shuswap, Chilko, and Scotch Creek, and included fish that went missing throughout the Fraser River basin. Fishing losses were defined as fish reported as caught in in-river fisheries. Lower river mortalities were fish that went missing below Hells Gate. We expect that lower river losses could include both natural mortalities and unreported fisheries.

A

Fate	Johnstone Strait	Juan de Fuca Strait
Surviving migrants	18	7
Upper river mortalities	7	3
Total	25	10

B

Fate	Total Numbers		Late Shuswap		Chilko		Scotch Creek		Other	
	Males	Females	Males	Females	Males	Females	Males	Females	Males	Females
Surviving migrants	15	8	8	3	5	2	2	3	0	3
Fisheries losses	10	19	5	7	4	6	1	6	0	0
Lower river mortalities	5	11	4	2	1	5	0	4	0	0
Upper river mortalities	18	14	9	6	7	3	3	5	0	0
Total by sex	49	55	26	18	17	16	6	18	0	3
Total by stock			44		33		24		3	
Total slides	104									

Table S2. Quantitative RT-PCR validation of six genes significantly up-regulated in PC1 negative mortality-related signature (MRS) relative to PC1 positive survival-related signature (SRS) class fish. Significant p-values are bolded, with an asterisk (*) indicating differences that were not resolved (at $p<0.001$) on microarrays. Fold changes were calculated from fish used in t-tests. Sample locations are abbreviated as follows: Ocean-tagging (SW) sites include Juan de Fuca Strait (JDFS) and Johnstone Strait (JS), while freshwater-tagging (FW) was performed at Whonnock (W). For the qRT-PCR, the two ocean tagging sites are shown separately.

Gene Name	Gene Symbol	Accession Number(s)	Function	qRT-PCR: Significance between MRS and SRS classified individuals				Microarray: Significant fold changes between MRS/SRS classified individuals			Primers
				JDFS	JS	W	Spawn	SW	FW	Spawn	
Apoptosis-related protein 3	APR-3	CA055280	apoptosis	**0.028**	**0.000**	**0.002**	0.124	1.814	3.127		F-ACAGATGTCCGGTCTGGTTGC R-ACCTGTCCAGGAGGCAATGC
Vacuolar ATP synthase subunit C	ATP6V1C1	CB512532	proton transport, host-virus interaction	**0.044**	**0.001**	0.180	**0.007***	1.276	0.965		F-ACCACCCGCAACAACAACC R-GACACCTTCTTCACCACACCTT
Peptidyl-prolyl cis-trans isomerase C	FKBP2	CB516817, CK990954, CA064475, CA052011	protein folding	**0.035**	**0.000**	**0.002**	0.062	1.025	2.878		F-GAGTTTGACAGCAGCATTCCAAG R-AGTTTCCTCTTCTCTCCCTCACAC
Complement C4-1	C4B	CA060294, CB518123, DW539321	complement cascade, defense response, positive regulation of phagocytosis	0.057	**0.000**	**0.037**	**0.029**	1.887	2.958	1.968	F-TTGCGTTGGTTGGTTTCACTG R-AGACAGGATGACATAACAGTGGAG
Succinate dehydrogenase cytochrome b560 subunit	SCHC	CB504264	TCA, electron transport	**0.009**	**0.001**	**0.016***	**0.011***	0.706			F-AGCTAAGTTTGGCATTGCCTTCC R-CCCGAGCGATACACCTCAGG
Cytochrome p450 46A	CYP46A1	CA053404, CA769694	lipid metabolism, electron transport	**0.003***	0.194	0.068	0.145		1.775		F-TCTTCAACCTGTTTGGACAGAGG R-CAGGTACAGACTGCTGAAGGC
Acidic ribosomal phosphoprotein P0	ARP	CA045397	Housekeeping Gene								F-GAAGGCTGTGGTGCTCATGG R-TCCTCCTTGGTGAAGACAAAGC

Table S3. Functional analysis of the signatures associated with fate in ocean (SW), freshwater (FW), and spawning (SG) tagging studies. Analyses were performed in Database for Annotation, Visualization and Integrated Discovery (DAVID; *12*) and Pathway Studio® (*13*), based on SW, FW, and SG t-test gene lists. Up- and down-regulated genes ($p<0.001$) within each dataset were analysed separately within DAVID against the backdrop of the 16K (SW and FW) or 32K (spawning) feature microarrays, with annotations based on UniProt IDs. In Pathway Studio, analyses were performed using 1) the entire gene list with fold-change used to rank genes, 2) based on up- and down-regulated genes ($p<0.001$), and 3) based on enriched sub-networks (biological processes [pathways] significant only in this analysis are highlighted with an asterisk). Biological processes associated with poor survivorship within the PC1 mortality-related signature (MRS) were generated from DAVID analysis of t-tests between fish that survived to spawning areas (successful migrants) versus those that perished en-route (unsuccessful migrants) in SW and FW-tagging studies or successful versus unsuccessful spawners ($p<0.01$). Processes up-regulated in MRS fish or mortality within the MRS are highlighted in yellow, down-regulated in blue, and differentially regulated with no particular direction in grey.

MRS-SRS Significance						Poor Survival					
SW	FW	SG	Pathways	DAVID	Pathway Studio	SW	FW	SG	Stress	Viral Response	Other
			METABOLISM								
	<0.05	<0.05	Cellular metabolism/cellular protein metabolism	x		0.05	<0.05				metabolism down in senescence
	<0.001	<0.001	ATP generating metabolism/Oxidative phosphorylation	x	x	0.05	0.05		down-regulated under stress		down-regulated with senescence
	<0.01	<0.01	Lipid metabolism/biosynthesis--membrane lipid bilayers	x	x		<0.05			viral life-cycle	
	<0.05	<0.01	AA transport/metabolism	x	x						starvation
		<0.001	Insulin action		x						
		<0.01	Glycolysis		x				up-regulated under stress		
		<0.05	Gluconeogenesis		x					HIV impairs glucose metabolism	
		<0.05	Glycogen metabolism		x		<0.05				starvation
		<0.01	Fatty acid oxidation		x						starvation
		<0.05	Carbohydrate metabolism	x			<0.05				
			GENE EXPRESSION								
	<0.05	<0.05	Transcription	x	x						
	<0.001		Nucleotide and ribonucleotide biosynthesis								
			PROTEINS								
<0.05	<0.05	<0.001	Ubiquitin-dependent protein catabolic process	x	x				heat shock activates	role in antigen presentation, can be blocked by viruses	down-regulated with senescence
<0.05	<0.05	<0.05	Cysteine/serine-threonin proteinase/lysosome	x							
<0.001	<0.001	<0.001	Translation/protein biosynthesis	x	x	<0.01	<0.001		down-regulated under stress	viral mediated inhibition to enhance replication, evasion	down-regulated with senescence
	<0.01	<0.001	Translation elongation	x	x						
			CELLULAR PROCESSES								
<0.01	<0.001	<0.001	Cell proliferation		x	<0.05			heat stress activates (gill)	numerous avenues of control by viruses	leukemia/cancer
<0.001	<0.001	<0.001	Apoptosis/cytolysis	x	x				stress activation	limit viral replication, viral controlled release	leukemia/cancer
<0.001	<0.01	<0.05	Activation of MAPK activity		x					virus infection can induce and sustain activation of the ERK/MAPK pathway	
<0.01	<0.001	<0.01	Endocytosis		x					viral entry	
	<0.01	<0.05	Actin/cytoskeleton/extracellular matrix	x		<0.05	<0.05			viral-mediated disruption leads to cell rounding	actin down-regulated in gill with senescence
			BLOOD PROCESSES								
<0.001	<0.01	<0.05	Heme biosynthesis	x	x					correlated with viral production	
<0.05	<0.001	<0.05	Angiogenesis/wound healing	x	x						
<0.001		<0.05	Response to hypoxia	x	x						
			SIGNALING								
	<0.05		Neurological system process	x							
<0.01			ErbB/notch signaling and calmodulin binding	x	x				heat stress repressed (gill)	oncogenic viruses up-regulate	

			STRESS AND DISEASE								
<0.01		<0.01	Stress: Protein folding	x	x	<0.05		general, heat shock			
	<0.001	<0.001	Stress: DNA damage		x				can be hijacked to enhance viral replication (Herpes); activates an anti-cancer barrier in virus induced malignancies (KSHV)	cellular homeostasis under stress	
	<0.05		Stress: Chemical/hormone/temperature	x			<0.05	toxins, heat shock			
			Response to stimulus	x				<0.05			
		<0.001	Oxidative stress		x						
			Iron storage/ferritin	x		<0.01					
NA*	NA*	NA*	Antigen processing and presentation			<0.05	<0.05		pathogen activation	adaptive immunity down-regulated with senescence	
<0.001	<0.001	<0.05	Interspecies interaction between organisms		x						
		<0.05	Immune system development/regulation/process	x				stress activation	pathogen activation		
<0.001	0.063		Cytokine signaling		x			injury activation			
<0.01			Classical complement cascade	x	x			injury, stress activation	pathogen activation		
<0.01	<0.01	<0.05	Inflammatory response		x			injury, stress activation			
		<0.05	Tumor necrosis factor-mediated signaling pathway		x			general stress activation	anti-viral apoptosis		
<0.001*			Virion attachment, binding of host cell surface receptor						Viral entry		
<0.05*			Regulation of defense response to virus by virus		x				viral control of host immune response		
	<0.01*	<0.001*	Response to virus	x	x				host response to virus		
		<0.05	Pro-virus integration		x				retroviruses		
		<0.05	Viral life cycle		x				viral		
<0.01	<0.01	<0.05	Regulation of T-cell differentiation		x				pathogen activation	leukemia/cancer	
<0.001*		<0.05	T-cell proliferation		x				viral proteins can regulate	leukemia/cancer	
<0.001	<0.001	<0.001	B-cell activation		x				viral proteins can regulate	leukemia/cancer	
<0.001*		<0.05	B Lymphocyte proliferation		x				pathogen activation	leukemia/cancer	
	0.056	<0.05	Cell Lymphoblastic Leukemia-Lymphoma		x				Leukemia virus	leukemia/cancer	
			OTHER								
<0.05	0.054	<0.05	Muscle proteins/muscle contraction	x							
<0.05	<0.01	<0.05	Regulation of heart contraction/heart rate/vasodilation		x					down-regulation may signal dysfunctional gas exchange in gill	
		<0.01	Prostaglandin biosynthetic process								
		<0.05	Collagen								
	<0.05	<0.05	Transport/localization	x	x						
	<0.01		Metal ion transport	x							
		<0.05	Urea cycle	x			<0.05				
			Cofactor binding	x			<0.01				
			Cell matrix adhesion	x			<0.05				
			ATPase activity/hydrolase activity	x			<0.05				

485 Table S4. Genes significantly ($p<0.001$) differentiating the mortality-related signature
486 (MRS) from the survival-related signature (SRS) in PC1 of fish in the ocean (SW),
487 freshwater (FW) and spawning (SG) studies involved in anti- and pro-viral processes,
488 leukemia, inflammation and general immunity. Associations were determined through
489 gene ontologies and literature mining in iHOP (*14*) and ResNet/Pathway Studio® (*13*).
490 To reduce redundancy, genes annotating to multiple immune/inflammatory pathways
491 were shown only once. For example, many genes involved in the complement cascade
492 are also involved in innate and humoral immunity and inflammatory responses. Genes
493 without uniprot IDs were not included in DAVID functional analyses, and those without
494 gene symbols were not included in Pathway Studio® analyses. Full gene annotations
495 for the 16K GRASP and 32K cGRASP microarrays are provided at (*S33*). Fold change
496 values reflect MRS versus SRS class fish used in t-tests, with yellow indicating genes
497 up-regulated in MRS fish and blue down-regulated. Note that salmon are residual
498 tetraploid, hence most genes carry duplicated copies. All significant expressed
499 sequence tags (ESTs) are shown, some of which represent duplicated copies of the
500 same gene and others duplicated genes. There is no attempt to distinguish the two.
501 However, we expect that duplicated genes, especially those involved in immune
502 responses, can show divergent expression patterns consistent with new evolving
503 functional roles.
504

Accession (32K slide)	Not on 16K slide (x)	Uniprot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
												Viral Role
CA062981		Q92824	2.28	2.E-04	3.38	2.E-08			Up	PCSK5	Proprotein convertase PC5	Anti-viral state
CB517982		P42224			2.31	7.E-08			Up	STAT1	Signal transducer and activator of transcription 1, 91KDA	Anti-viral state, interferon induction; Jak-STAT; Leukemia
DW536206	x	P42224					2.59	1.E-03	Up	STAT1		Anti-viral state, interferon induction; Jak-STAT; Leukemia
CA050625					3.68	2.E-12			Up	GIG1	Interferon-inducible protein Gig1	Anti-viral response: Interferon
CA062399							1.76	9.E-05	Up		Interferon-gamma receptor alpha chain [Oncorhynchus mykiss]	Anti-viral response: Interferon
CA058205		P13284			1.50	2.E-05			Up	IFI30	Gamma-interferon-inducible protein IP-30	Anti-viral response: Interferon
CB514343		P13284			1.36	6.E-04			Up	IFI30		Anti-viral response: Interferon
EG876435	x	P13284					1.22	4.E-04	Up	IFI30		Anti-viral response: Interferon
CB511987		Q9NPA8	1.50	3.E-05	2.90	9.E-06			Up	IFI6	Interferon-induced protein 6-16 precursor	Anti-viral response: Interferon
CA054084		Q13325	1.32	6.E-04	2.53	2.E-05			Up	IFIT5	Interferon-induced protein with tetratricopeptide repeats 5	Anti-viral response: Interferon
EG920887	x	Q8JH68					3.44	2.E-05	Up	MXA	Interferon-inducible Mx protein	Anti-viral response: Interferon
CK990878			0.78	3.E-04	1.13	7.E-05			Up	CRFB6	Helical cytokine receptor CRFB6 [Tetraodon nigroviridis]	Anti-viral response: Interferon
CA058269		Q99062			2.09	5.E-07			Up	CSF3R	CD114 antigen	Anti-viral response: Interferon; Jak-STAT, Leukemia
CB511515			2.09	4.E-06	2.45	2.E-07	2.45	3.E-04	Up	IRF1		Anti-viral response: Interferon; Leukemia
CA058315		P10914			1.15	8.E-04			Up	IRF1	Interferon regulatory factor 1	Anti-viral response: Interferon
CB511472			1.26	5.E-04	1.54	8.E-04			Up	IRF1		Anti-viral response: Interferon
CA058829		Q13217			1.37	1.E-04			Up	DNAJC3	Interferon-induced, double-stranded RNA-activated pK inhibitor	Anti-viral response: Interferon; Viral replication
CB514703	x	Q13217	-1.26	3.E-04					Down	DNAJC3	Interferon-induced, double-stranded RNA-activated pK inhibitor	Anti-viral response: Interferon; Viral replication
CB500486		Q01628			-2.49	5.E-04	-3.34	4.E-04	Down	IFITM3	Interferon inducible protein 1	Anti-viral response: Interferon
CB492283		P26376			-2.29	5.E-04			Down	IFITM3		Anti-viral response: Interferon
CB509903					-1.34	7.E-04			Down	IIP2	Interferon inducible protein 2	Anti-viral response: Interferon
CB511902		Q15306	-1.11	7.E-04	-1.26	2.E-06			Down	IRF4	Interferon regulatory factor 4	Anti-viral response: Interferon, Leukemia
CA063144		O43422					-2.32	6.E-04	Down	PRKRIR	58 kDa interferon-induced protein kinase-interacting protein	Anti-viral response: Interferon
CB499141			-1.07	5.E-05					Down		Nuclear autoantigen GS2NA	Anti-viral defense
DY714826	x	Q6Q899					2.50	6.E-05	Up	DDX58	DEAD-box protein 58	Anti-viral defense
CA057909		Q58EQ7	1.32	1.E-05					Up	BNIP3L		Anti-viral defense
CA056426		Q3T013			1.31	2.E-04			Up	BNIP3L	BCL2/adenovirus E1B interacting protein 3-like	Anti-viral defense
DY701282	x	O60238					2.78	3.E-05	Up	BNIP3L		Anti-viral defense
CA059190		Q15722			2.48	4.E-05			Up	LTB4R	Leukotrien B4 receptor	Anti-viral inflammatory
CA058715		Q9BX59			1.53	2.E-04			Up	TAPBPL	Tapasin-related protein precursor	Anti-viral: cellular immunity
CB511230		Q49TU5	0.71	3.E-04					Up		TAP2	Anti-viral: cellular immunity
CB516976			1.81	9.E-05	2.06	9.E-07	2.65	1.E-05	Up		T cell receptor alpha chain	Anti-viral: cellular immunity
CA060068		Q8JG64	0.91	8.E-04					Up	ERP57	Glucose-regulated thiol oxidoreductase 58 kDa protein	Anti-viral: cellular immunity
CB516939			1.83	2.E-04	1.85	1.E-04			Up		Onmy-LDA gene for MHC class I antigen	Anti-viral: cellular immunity
CA053702					0.86	3.E-04			Up		Sasa-MRSA1 gene for MHC class I antigen	Anti-viral: cellular immunity
CA052285			1.14	1.E-04					Up		nonclassical MHC class I antigen (Onmy-LAA) gene	Anti-viral: cellular immunity
CA051947					2.08	2.E-04			Up		non-classical MHC class I antigen (Onmy-UAA) gene	Anti-viral: cellular immunity
CA043257		P15979			-1.15	3.E-04			Down	BF2		Anti-viral: cellular immunity
CA770758		P15979					-3.35	6.E-07	Down	BF2		Anti-viral: cellular immunity
CA041995		P15979					-2.86	5.E-04	Down	BF2	MHC B-F histocompatibility F10 antigen	Anti-viral: cellular immunity
CA044026		P15979					-2.73	4.E-04	Down	BF2		Anti-viral: cellular immunity
CA044472		P15979					-5.30	1.E-07	Down	BF2		Anti-viral: cellular immunity
CA050346					-1.00	2.E-05			Down	BF2		Anti-viral: cellular immunity
CA039982		Q95460			-1.23	4.E-05	-3.14	5.E-04	Down	MR1	MHC Class I histocompatibility antigen-like protein (isoform CRA_c)	Anti-viral: cellular immunity
CA050178		Q95460					-3.09	2.E-04	Down	MR1		Anti-viral: cellular immunity
CA041689							-3.35	3.E-05	Down		Mhc1ze protein [Danio rerio]	Anti-viral: cellular immunity
CA061919		O08573			2.11	9.E-10	1.93	3.E-04	Up	LGALS9	Galectin-9	Viral recognition, replication
CA063987		Q12891			2.45	3.E-08			Up	HYAL2	Hyaluronidase-2 precursor	Viral receptor; Host-virus interaction
CB512927		Q9JLB9			1.38	5.E-04			Up	PVRL3	Poliovirus receptor-related protein 3 precursor	Viral receptor
CA054133		Q7YS92	1.80	7.E-04	2.58	5.E-08			Up	CXCR4B	C-X-C chemokine receptor type 4	Viral receptor
CB514351		Q8WTV0			1.31	8.E-04			Up	SCARB1	Scavenger receptor class B member 1	Viral entry, apoptosis
CB517887		Q28806			3.48	4.E-07			Up	ICAM1	CD54 antigen	Viral entry; Leukemia; lymphocyte adhesion/transfection,
CA770032		P07688	1.12	5.E-05	1.65	2.E-04			Up	CTSB		Viral entry; Leukemia
CB496605		P07688			-1.59	4.E-04			Down	CTSB	Cathepsin B	Viral entry; Leukemia
CB493838		P43233					-2.43	8.E-04	Down	CTSB		Viral entry; Leukemia
CA058127		P02751			-1.78	3.E-05			Down	FN1	Fibronectin 1	Viral entry; Leukemia; Inflammatory
CA057332		Q63844			-0.81	4.E-04			Down	MAPK3	Mitogen-activated protein kinase 3	Viral entry, replication; Leukemia
CA055725		P62888	1.43	2.E-04	2.18	2.E-04	2.07	1.E-04	Up	RPL30	Cytoplasmic dynein light chain	Viral transport
CA062672		Q9Z1N5	1.08	3.E-04					Up	BAT1A	HLA-B-associated transcript 1	Viral transport
CA060166		Q7ZUX6			2.25	5.E-07			Up	DOHH	Deoxyhypusine monooxygenase	Viral transport
CA052976		P15771			2.48	2.E-06			Up	NCL		Viral transport; Leukemia
CA043214		P19338			-1.33	2.E-04			Down	NCL	Protein C23	Viral Transport; Leukemia
EG789958		P09405					-2.91	3.E-06	Down	NCL		Viral Transport, Leukemiia
CK991313		P10995			1.42	3.E-05			Up		Actin alpha 2	Viral transport, trafficking; retroviral replicatoin
CA050547		P55010			1.45	5.E-09			Up	EIF5	Eukaryotic translation initiation factor 5	Viral transport, trafficking; retroviral replicatoin
CA057833		P17844			-1.18	1.E-03			Down	DDX5	RNA helicase p68	Viral transport, trafficking; retroviral replicatoin
CA057667		P79955			2.43	1.E-07			Up	CTK2-A	Carboxy-terminal kinesin 2	Viral transport; Viral interaciton (gag-pol)
CA053679		P17507			1.82	7.E-06			Up	EF-1AO	Elongation factor 1 alpha 0	Viral encapsidation
CB497678		Q92005			-1.45	1.E-04	-3.03	1.E-04	Down	EF1A	Elongation factor 1 alpha	Viral encapsidation
CA051187		P11226	1.28	6.E-04	1.85	9.E-07			Up	MBL2	Mannose-binding lectin	Viral life-cycle; Complement Cascade
CA048093		P26041	1.07	4.E-04					Up	MSN	Membrane-organizing extension spike protein	Viral life-cycle
CA060578		P26038			1.76	1.E-07			Up	MSN		Viral life-cycle
CA057910		Q9NZQ7			2.08	8.E-08			Up	CD274	Programmed death ligand 1	Viral life-cycle; Leukemia
CA054167		P61626			1.00	4.E-04			Up	LYZ	Lysozyme C II precursor	Viral life-cycle; Inflammatory
CA062728		P28799					1.29	5.E-04	Up	GRN		Viral life-cycle
CA039831		P28799	-0.96	1.E-05					Down	GRN	Proepithelin	Viral life-cycle
CA057574		P28799			-1.17	8.E-04			Down	GRN		Viral life-cycle
CA063170		P30932			-1.05	4.E-05			Down	CD9	CD9 antigen	Viral life-cycle
CB497163		O42248			-1.30	2.E-04	-2.40	2.E-04	Down	GNB2L1		Viral life-cycle
CB498500		O42248			-1.04	6.E-04	-2.87	2.E-05	Down	GNB2L1	Receptor of activated protein kinase C	Viral life-cycle
CA055402		O42248			-1.71	2.E-06			Down	GNB2L1		Viral life-cycle
CB493280		O42248					-2.99	4.E-06	Down	GNB2L1		Viral life-cycle
CA057932		P46940			-1.38	1.E-04			Down	IQGAP1	IQ motif containing GTPase activating protein 1	Viral life-cycle
DW561965		P46940					-1.60	4.E-04	Down	IQGAP1		Viral life-cycle
CB497380		Q9Y6X1			-1.14	6.E-04	-3.42	8.E-06	Down	SERP1		Viral life-cycle
CA042976		Q9Y6X1					-2.66	5.E-05	Down	SERP1	Ribosome-attached membrane protein 4	Viral life-cycle
EG915888		Q9Y6X1					-2.90	6.E-05	Down	SERP1		Viral life-cycle
CB502780		Q9Y6X1					-2.92	6.E-05	Down	SERP1		Viral life-cycle

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Accession (32K slide)	Not on 16K slide (x)	Unigrot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
CA059405		Q95RC0	1.32	1.E-04					Up	CG11412	N-acetyltransferase 12	Viral reproduction (+)
CA057947		Q8R431	1.24	6.E-04	1.34	6.E-04			Up	MGLL	Monoglyceride lipase	Viral replication
CA051449		P21868	1.06	3.E-06	2.18	1.E-10			Up	CSNK2A1	Casein kinase II subunit alpha	Viral replication (+); Leukemia
CK991184		P21868			1.31	1.E-04			Up	CSNK2A1		Viral replication (+); Leukemia
CA058211		O46374			1.15	2.E-05			Up	TOPOII	DNA topoisomerase 2-alpha	Viral replication
CA050897		P68101			2.01	2.E-04			Up	EIF2S1	Eukaryotic translation initiation factor 2 subunit alpha	Viral replication
CA058568		Q6NY74			2.19	3.E-06			Up	RPA1	Replication factor-A protein 1	Viral replication
CA050822		P04792			2.73	5.E-08			Up	HSPB1	heat shock protein HspB1	Viral replication; Leukemia
CA058647		O42227			1.93	1.E-04			Up	HDAC1	Probable histone deacetylase 1-B	Viral replication; Leukemia
CA056452		Q6NXA4			2.13	3.E-06			Up	ILF3	Interleukin enhancer-binding factor 3 homolog	Viral replication, life-cycle
CA063753		O70460			2.09	3.E-04			Up	CCL19	Chemokine CC-like protein [Pseudosciaena crocea]	Viral replication; Inflammatory
CB516783		Q9QUI0			1.12	4.E-05			Up	RHOA	Transforming protein RhoA	Viral replication; Leukemia NF kappa B
CA058431		O35716			1.13	3.E-04			Up	SOCS1	STAT-induced STAT inhibitor 1	Viral replication; Jak-STAT; Leukemia
CB517429		Q8VDW0			2.02	4.E-04			Up	DDX39	DEAD box protein 39	Retroviral replication
CA051391					1.42	3.E-04			Up		U88	Viral genome replication
CA054457		Q9QUI0	1.21	3.E-05	1.28	5.E-04			Up	RHOA		Viral replication
CA057217		Q9QUI0			0.99	3.E-04			Up	RHOA		Viral replication
CA041832		Q9QUI0					-2.61	5.E-05	Down	RHOA	Transforming protein RhoA precursor.	Viral replication
EG874260		Q9QUI0					-3.05	2.E-04	Down	RHOA		Viral replication
CB498910		Q9QUI0					-3.86	1.E-04	Down	RHOA		Viral replication
CA057305		P09651	-0.79	6.E-04	-1.02	1.E-05			Down	HNRNPA1	Heterogeneous nuclear ribonucleoprotein A1	Viral replication (+)
CB492364		P49312			-1.88	2.E-05			Down	HNRNPA1		Viral replication (+)
CB499829		P17742			-1.36	2.E-05	-1.92	4.E-04	Down	PPIA	Peptidyl-prolyl cis-trans isomerase A	Viral genome replication
CB511232		P17742			-1.68	6.E-06			Down	PPIA		Viral genome replication
CA770356		Q6NWF6	-0.57	2.E-04			-2.49	9.E-06	Down	KRT8		Viral replication
CB492778		Q6NWF6			-1.04	7.E-04			Down	KRT8		Viral replication
CB494172		Q6NWF6			-1.24	8.E-05			Down	KRT8	Cytokeratin-8	Viral replication
CK990533		Q6NWF6					-1.32	8.E-04	Down	KRT8		Viral replication
CB509919		Q6NWF6					-2.22	5.E-06	Down	KRT8		Viral replication
CB492983		P17742			-1.45	4.E-05			Down	PPIA	Peptidyl-prolyl cis-trans isomerase A	Viral reproduction
CB503106		Q06066			-1.31	2.E-04			Down	YBX1	Y-box-binding protein 1	Viral replication
CB497928		Q06066			-1.33	4.E-05			Down	YBX1		Viral replication
CA059006		O95793	-0.75	7.E-04					Down	STAU1	Double stranded RNA binding protein	Virus assemblies
CA058238		O95793			1.63	3.E-04			Up	STAU1		Virus assemblies
CA055146		P50552			-1.14	4.E-06			Down	VASP	Vasodilator-stimulated phosphoprotein	Viral particle maturation
CB493123		Q06507			-1.43	1.E-04			Down	ATF4	Activating transcription factor 4	Viral transcription; Leukemia NF kappa B
CA054017		Q6NW59					1.71	8.E-04	Up	ATF4	Activating transcription factor 4	Viral transcription; Leukemia NF kappa B
CA056351		Q6NZT5			2.39	1.E-09			Up	JUN	Proto-oncogene c-jun	Viral transcription; lytic cycle; oncogene; Leukemia
CB514911		Q14562			1.53	7.E-04			Up	DHX8	DEAH box protein 8	Viral export
CB496654		Q6P026					-2.51	7.E-05	Down	ZGC:77767	Barrier-to-autointegration factor	Provirus integration
CB491851		Q6P026					-4.13	5.E-04	Down	ZGC:77767		Provirus integration
DW536407	x	P41157					-2.07	8.E-05	Down	XLFLI	Retroviral integration site protein Fli-1 homolog	Provirus integration
CA057273		Q01543	1.61	7.E-06	1.67	3.E-07			Up	FLI1	Friend Leukemia virus integration 1	Provirus integration
CA054486		P62916			2.31	9.E-05			Up	GTF2B	Transcription initiation factor IIB	Transcription (host +)
CA057644		Q9NS37			2.28	6.E-06	1.43	7.E-04	Up	CREBZF	CREB/ATF bZIP transcription factor	Transcription (viral -)
CA050467		Q91ZR3	1.75	4.E-05	2.57	2.E-07			Up	CREBZF		Transcription (viral -)
CB512785		Q04637	1.61	3.E-04	2.38	5.E-08			Up	EIF4G1	Eukaryotic translation initiation factor 4 gamma 1	Translation (host -)
CA051191		P48597			2.10	3.E-06			Up	EIF4E	Eukaryotic translation initiation factor 4E	Translation (host -); Leukemia
CB512340		Q96I38			1.69	7.E-05			Up	EEF1D	Eukaryotic translation elongation factor 1 delta	Translation (host -)
CA052650		P61221			2.70	5.E-08			Up	ABCE1	RNase L inhibitor	Translation (host -), interferon inducible
CA051580		Q15543	0.99	3.E-04	2.24	4.E-08			Up	TAF13	Transcription initiation factor TFIID subunit 13	Translation (host -)
CA053785		Q6PIH5			1.55	1.E-04			Up	Polr2e	DNA-directed RNA polymerases I, II, and III subunit RPABC1	Translation (host -)
CA051681		Q15545			1.61	2.E-05			Up	TAF7	Transcription initiation factor TFIID subunit 7	Translation (host -)
CA051151		Q99JX1	1.46	5.E-04	3.06	6.E-10			Up	TAF11	Transcription initiation factor TFIID subunit 11	Translation (host -)
CA057322		Q16514					-2.39	2.E-04	Down	TAF12	Transcription initiation factor TFIID subunit 12	Translation (host -)
CA052257		Q95L46			-2.27	2.E-07			Down	EIF4G2	Eukaryotic translation initiation factor 4 gamma 2	Translation (host -)
CA053441		P70541			-1.75	4.E-05			Down	EIF2B3	Translation initiation factor eIF-2B subunit gamma	Translation (viral -)
CA063353		Q5R9I5			1.14	3.E-04			Up	Dars	Aspartate--tRNA ligase	Translation (viral +)
CA051935		Q5ZKA2			2.50	4.E-08			Up	IARS2	Isoleucine--tRNA ligase	Translation (viral +)
CA059238		Q13310			2.12	1.E-07			Up	PABPC4	Poly(A)-binding protein 4	Translation (viral +)
CB515851		Q6P799			1.49	1.E-07			Up	SARS1	Seryl-tRNA(Ser/Sec) synthetase	Translation (viral +)
CB512171		P17248			2.91	5.E-08			Up	WARS	Tryptophan--tRNA ligase	Translation (viral +)
CB517721		Q93034			3.49	1.E-09			Up	CUL5	Cullin-5	Translation (viral -)
CA050095		O75534	-1.57	1.E-05					Down	CSDE1		Translation: IRES-containing RNAs
CA060542		O75534			-1.42	6.E-05			Down	CSDE1	N-ras upstream gene protein	Translation: IRES-containing RNAs
CK991116		O75534			-0.90	4.E-04			Down	CSDE1		Translation: IRES-containing RNAs
CK990411					1.19	5.E-04			Up		gag-pol polyprotein	Viral gag-pol
CB517722		Q05682	0.98	4.E-04	1.85	2.E-08			Up	CALD1	Caldesmon 1	Viral interaction (gag-pol)
CN442533		P79955			1.39	1.E-03			Up	CTK2-A	Carboxy-terminal kinesin 2	Viral interaction (gag-pol)
CK990445		Q05086			1.77	5.E-04			Up	UBE3A	E6AP ubiquitin-protein ligase	Viral interaction
CA050513		Q8K339			1.11	4.E-04			Up	KIN	Antigenic determinant of REC-A protein	Viral induced stress
CB517223		Q6AYE3			2.17	6.E-05			Up	TADA2L	ADA2-like protein	Viral interaction
CA056108		Q8HYC0	1.48	4.E-04	2.27	9.E-06	1.52	4.E-05	Up		C-type lectin domain family 4 member M	Viral interaction (host -)
CA063395		Q9PTP1			1.21	2.E-05			Up	PCNA		Viral interaction
CN442487		Q9PTP1	1.80	2.E-05	1.91	1.E-06			Up	PCNA	Proliferating cell nuclear antigen	Viral interaction
CA055611		Q9PTP1			-1.82	4.E-05			Down	PCNA		Viral interaction
CB490001		Q15004					-2.67	3.E-04	Down	KIAA0101	PCNA-associated factor	Viral interaction
DY716967	x	Q6QD59					3.07	6.E-06	Up	BNIP1	Vesicle transport protein SEC20	Viral Interaction, apoptosis
CB510372		Q8N0X7	-1.26	2.E-04					Down	SPG20	Trans-activated by hepatitis C virus core protein 1	Viral interaction
CA043952							-3.45	5.E-06	Down		VHSV-induced protein	Viral responsive protein
CB514983		Q3TQ03			2.24	6.E-06			Up	GM129	VHSV-induced protein-6	Viral responsive protein
CA051335		Q5RG82	0.80	7.E-04					Up	IVNS1ABPA	NS1-binding protein homolog A	Viral responsive protein
CB510048		P03934			-1.98	1.E-05			Down		IHNV related protein	Viral responsive protein
CB510834		Q6INU7	-1.20	6.E-04					Down	MGC80281	immune-related Hdd11	Viral responsive protein
CA064176		Q8MYQ4	1.23	1.E-04	1.30	4.E-05			Up	ubq-1	Ubiquitin 1	Viral lytic replication
CA057387		Q3SX43	1.14	7.E-04	1.75	1.E-06			Up	RRAGA	Ras-related GTP-binding protein A	Viral mediated anti-apoptosis
CB517023		Q43765	1.04	1.E-04	1.75	4.E-04			Up	SGTA		Virion release
CA053137		Q43765			1.52	6.E-06			Up	SGTA	Small glutamine-rich tetratricopeptide repeat-containing protein A	Virion release
CB514120		Q43765	-0.48	4.E-04					Down	SGTA		Virion release
CB517251		P35763	1.16	4.E-04	1.07	5.E-04			Up	PRF1		Virus-infected cell apoptosis; Complement; Leukemia
CB515603		P10820			1.33	2.E-05			Up	PRF1	Perforin 1	Virus-infected cell apoptosis; Complement; Leukemia
DY711337	x	P35763					3.02	6.E-04	Up	PRF1		Virus-infected cell apoptosis; Complement; Leukemia
CA052297		P25155			1.67	2.E-04			Up	F10	Virus-activating protease	Viral mediated coagulation, anti-apoptosis
CB514417		Q8BVF2			2.23	1.E-06			Up	PDCL3	Phosducin-like protein 3	Viral responsive; apoptosis
CA043836		Q8BVF2					-2.05	4.E-04	Down	PDCL3		Viral responsive; apoptosis
CA061236		Q61160			-1.19	2.E-04			Down	FADD	FAS-associated death domain protein	Viral responsive; apoptosis; Leukemia
CA059329		P08110			-1.34	1.E-05			Down	HSP90B1	Heat shock protein 90 kDa beta member 1	Virion binding, anti-apoptosis
CA055831		Q07021			1.76	5.E-05			Up	C1QBP	Complement C1Q subcomponent-binding protein, mitochondrial	Viral inhibition of lymphocyte proliferation
CA044550					-1.50	4.E-05			Down		BNIPXL-alpha	Viral interaction, apoptosis

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Accession (32K slide)	Not on 16K slide (x)	Uniprot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
CB515013		Q9BUP3			2.06	4.E-04			Up	HTATIP2	HIV-1 TAT-interactive protein 2	Host-virus interaction, apoptosis
CB493926		P05783			-1.05	2.E-04	-4.02	1.E-05	Down	KRT18	Keratin, type I cytoskeletal 18	Host-virus interaction, anti-apoptosis
CB494328		P05783					-2.03	7.E-06	Down	KRT18		Host-virus interaction, anti-apoptosis
CA058182		P41220	0.98	8.E-04	1.61	1.E-06			Up	RGS2	Regulator of G-protein signaling 2	Host-virus interaction
CA063869		Q05086			2.25	2.E-05			Up	UBE3A	E6AP ubiquitin-protein ligase	Host-virus interaction
CA062716		O60506			0.98	5.E-04			Up	SYNCRIP	Synaptotagmin-binding, cytoplasmic RNA-interacting protein	Host-virus interaction
CA051664		P15145			2.39	1.E-06			Up	ANPEP	Aminopeptidase N	Host-virus interaction; Leukemia
CA063426		O95197			1.41	2.E-04			Up	RTN3	Reticulon-3 (Neuroendocrine-specific protein-like 2)	Host-virus interaction
CA057058		Q86X55			1.90	3.E-07			Up	CARM1	Histone-arginine methyltransferase CARM1	Host-virus interaction
CB511531		O95197			2.66	2.E-07			Up	RTN3	Reticulon protein 3	Host-virus interaction
CA064425		O95197					2.03	2.E-04	Up	RTN3		Host-virus interaction
DY714878	x	Q9NWZ5					2.04	7.E-04	Up	UCKL1	Uridine/cytidine kinase-like 1	Host-virus interaction
DW548569	x	P80746					2.37	2.E-05	Up	ITGAV	Vitronectin receptor subunit alpha; CD51 antigen	Host-virus interaction
CB508776		Q9NWC2	1.52	5.E-05					Up	ATF7IP	MBD1-containing chromatin-associated factor 1	host-virus interactoin
CB512532		Q7T385	1.26	4.E-05	0.96	4.E-05			Up	ATP6V1C1	Vacuolar ATPase subunit C 1-A	Host-virus interaction
CA059245		P27449			2.05	4.E-06			Up	ATP6V0C		Host-virus interaction
CA058809		P27449			-1.28	2.E-05			Down	ATP6V0C	Vacuolar ATP synthase 16 kDa proteolipid subunit	Host-virus interaction
CB497797		P27449			-1.72	3.E-04			Down	ATP6V0C		Host-virus interaction
CA060885		P27449					-2.61	7.E-05	Down	ATP6V0C		Host-virus interaction
CA058544		Q9UI12			-1.18	1.E-04			Down	ATP6V1H	V-ATPase subunit H	Host-virus interaction
CA063314		Q15056	-0.87	6.E-05	-1.38	3.E-04			Down	EIF4H	Eukaryotic translation initiation factor 4H	Host-virus interaction
CB497757		P54725	-0.94	7.E-05	-0.74	1.E-03			Down	RAD23A	UV excision repair protein RAD23 homolog A	Host-virus interaction
CB493262		P62258	-1.28	7.E-05					Down	YWHAE	14-3-3 protein epsilon	Host-virus interaction
CK990577		P05141			-1.68	8.E-05			Down	SLC25A5	Solute carrier family 25 member 5	Host-virus interaction
CB499677		Q9NPY3			-1.46	9.E-04			Down	CD93	Complement component C1q receptor precursor	Host-virus interaction
CX251432	x	O00571					-2.62	2.E-04	Down	DDX3X	ATP-dependent RNA helicase DDX3X	Host-virus interaction
CA060424		P05388					-2.10	6.E-04	Down	RPLP0	60S acidic ribosomal protein P0	Host-virus interaction
DW577077	x	P23249					-1.68	3.E-04	Down	MOV10	Moloney leukemia virus 10 protein	Host-virus interaction
EG926400	x	P43405					-1.88	1.E-04	Down	SYK	Spleen tyrosine kinase	Host-virus interaction
CB514625		P42685	1.76	8.E-05	2.20	3.E-08			Up	FRK	Tyrosine-protein kinase Src42A	Signaling; similarity to retroviral proteins
CX148554	x	Q62245					-2.18	8.E-05	Down	SOS1	Son of sevenless homolog 1	Signaling by HBx of Hepatitis B virus; Jak-STAT
CA051774		Q01085			2.02	4.E-06			Up	TIAL1	TIA-1-related protein	West nile virus QNV pathway
CA058655		Q8N5M4			1.86	2.E-05			Up	TTC9C	TPR repeat protein 9C	Latency of epstien Barr virus
CB501187		Q5YF10			-1.42	4.E-04			Down		ORF077R [Rock bream iridovirus]	Viral protein sequence
CA054596		Q640B3	1.64	3.E-05	2.01	1.E-05			Up	PLD3	Phospholipase D3	Viral protein; Phospholipase D/Viral envelope
CA050290		Q2VF30	1.22	5.E-04	1.40	5.E-04			Up	ASSBSV_GP2	polyprotein [Atlantic salmon swim bladder sarcoma virus]	Endogenous Retrovirus
CB496828		Q304Z2			-0.91	2.E-05			Down		envelope protein [Atlantic salmon swim bladder sarcoma virus]	Endogenous Retrovirus
CA046853		P26369					-2.45	1.E-03	Down	U2AF2	Splicing factor U2AF 65 kDa subunit	Retroviral RNA premRNA splicing
CA059780		P51992			1.23	3.E-04			Up	LOC397773	Heterogeneous nuclear ribonucleoprotein A3 homolog 2	Retroviral RNA premRNA splicing
CA057291		Q8VIJ6			1.12	2.E-04			Up	SFPQ	Splicing factor, proline- and glutamine-rich	Retroviral RNA premRNA splicing
CA059122		P46777			1.73	9.E-08			Up	RPL5	60S ribosomal protein L5	Retroviral induced tumours
CA062248		Q92993	1.40	9.E-05	2.06	9.E-07			Up	HTATIP	HIV-1 Tat interactive protein	Retroviral induced tumours
EG784658	x	Q03172					-1.31	4.E-05	Down	HIVEP1	Zinc finger protein 40	Retroviral enhancer protein (HIV)
CA059303		Q9BUQ8			2.16	1.E-06			Up	DDX23	Probable ATP-dependent RNA helicase DDX23	Retroviral replication, transport
CB499003			1.83	3.E-05					Up	ERG	v-ets erythroblastosis virus E26 oncogene like, transcript variant 2	oncogene
CA054290		Q9JIW9			2.40	9.E-06	2.23	1.E-04	Up	RALB	Ras-related protein Ral-B	oncogene
CA050384		Q5ZMJ9			1.72	4.E-05			Up	CJMB04_1M2	Serine/arginine repetitive matrix protein 1	oncogene
CA056515		P54842			2.07	8.E-04			Up	MAFB	Transcription factor MafB	oncogene
DY704137	x	Q4JIM5					-2.21	4.E-06	Down	ABL2	Abelson murine leukemia viral oncogene homolog 2	oncogene
CA052165		P46109	-1.13	3.E-04					Down	CRKL	Crk-like protein	oncogene
CA060859		Q01543	-1.04	4.E-04					Down	FLI1	Fli-1 proto-oncogene; ERGB transcription factor	oncogene
CA061373		Q5C1C7			-1.05	5.E-04			Down		SJCHGC07628 protein [Schistosoma japonicum]	oncogene
CX353026	x	O43166					-3.31	1.E-06	Down		High-risk human papilloma viruses E6 oncoproteins targeted protein	oncogene
CA056522		Q6NZT5	-1.61	6.E-07					Down	JUNB	Transcription factor jun-B	oncogene; Leukemia
CA054491		P17275	-1.23	6.E-06					Down	JUNB		oncogene; Leukemia
												Immune-Related Genes
CA057650		P00746	1.43	7.E-04					Up	CFD	Complement factor D (Adipsin)	Complement Cascade
CA060294		P0C0L4	1.89	6.E-05	2.96	7.E-05			Up	C4B		Complement Cascade
CB518123		P0C0L4	1.39	5.E-08	2.11	5.E-08			Up	C4B	Complement component 4A (Rodgers blood group)	Complement Cascade
DW539321		P0C0L4					1.97	3.E-04	Up	C4B		Complement Cascade
CA064377		P0C0L4					-2.24	2.E-05	Down	C4B		Complement Cascade
CB517251		P35763	1.16	4.E-04	1.07	5.E-04			Up	PRF1		Complement Cascade
CB515603		P10820			1.33	2.E-05			Up	PRF1	Perforin 1	Complement Cascade
DY711337		P35763					3.02	6.E-04	Up	PRF1		Complement Cascade
CA056142			1.38	1.E-04	1.63	2.E-04			Up		Complement receptor C1qR-like protein [Danio rerio]	Complement Cascade
CA064118					1.71	5.E-05			Up			Complement Cascade
CB514393		P97520			2.07	4.E-06			Up	C5R1	Complement component 5, receptor 1	Complement Cascade
CA052926		O14525			2.51	8.E-06			Up	ASTN1	Astrotactin 1	Complement Cascade
EG906932		Q9H4X1					1.97	1.E-04	Up	C13ORF15	Response gene to complement 32	Complement Cascade
CA055831		Q07021			1.76	5.E-05			Up	C1QBP	Complement C1q subcomponent binding protein	Complement Cascade
CB493785		P05160					1.29	3.E-04	Up	F13B	Protein-glutamine gamma-glutamyltransferase B chain	Complement Cascade
CA064204		P04271			1.75	8.E-04			Up	S100B	Protein S100-B	Complement Cascade
CB493785		P05160					1.29	3.E-04	Up	F13B	Protein-glutamine gamma-glutamyltransferase B chain	Complement Cascade
DY707553		O09047					1.57	3.E-04	Up	C3AR1	Complement component 3A receptor 1	Complement Cascade
CA052045		P10643			2.65	4.E-11			Up	C7	Complement protein component C7-1	Complement Cascade
CB511778		P10643					2.72	7.E-04	Up	C7	Complement component C7 precursor	Complement Cascade
CA049855		P10643	-1.43	3.E-06					Down	C7		Complement Cascade
CA049855		P10643	-1.10	7.E-04					Down	C7	Complement component 7-2	Complement Cascade
CA049855		P10643	-1.43	3.E-06					Down	C7		Complement Cascade
CB510662		P07360	-0.62	5.E-04					Down	C8G	Complement component C8 gamma chain	Complement Cascade
CA049564		Q7Z5W1	-0.91	1.E-05					Down		Ig gamma-2B chain C region	Complement Cascade
CA049564		Q7Z5W1	-0.91	1.E-05					Down		Ig gamma-2B chain C region	Complement Cascade
CB511059		Q9I926	-1.41	4.E-05					Down		Fucolectin-6 precursor.	Complement Cascade
CB492756		P05162	-1.52	5.E-04					Down	LGALS2	Beta-galactoside-binding lectin L-14-II	Complement Cascade
CA059458		Q9ES30	-0.75	9.E-04					Down	C1QTNF3	C1Q and Tumor necrosis factor related protein 3	Complement Cascade
CA063956		P31722	-0.88	8.E-04					Down	C1QG	Complement C1q subcomponent subunit C precursor	Complement Cascade
CB501016		P31722					-2.43	6.E-04	Down	C1QG		Complement Cascade
CB499677		Q9NPY3			-1.46	9.E-04			Down	CD93	Complement C1q subcomponent receptor 1CDw93	Complement Cascade
CA053079		P53714			-1.42	7.E-04			Down	CD18	Complement receptor C3 subunit beta	Complement Cascade
CA039055		Q90422			-0.89	1.E-04	-3.23	2.E-05	Down	CFB	Complement factor B	Complement Cascade
CB494645		O62680					-3.11	2.E-04	Down	CD59	Membrane attack complex inhibition factor	Complement Cascade
CA044810		P49874					-2.66	8.E-05	Down	PSP-A	Pulmonary surfactant-associated protein A	Complement Cascade
CA058662		Q4LDE5					-2.05	4.E-04	Down	SVEP1	Selectin-like osteoblast-derived protein	Complement Cascade
CB491356		Q02988					-2.84	2.E-04	Down		Mannose binding lectin	Complement Cascade

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Accession (32K slide)	Not on 16K slide (x)	Uniprot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
CA055298		P28070	1.00	7.E-05	2.02	5.E-07	1.71	6.E-05		PSMB4	Proteasome subunit beta type-4 precursor	Antigen presentation
CA049968		P28064	0.92	8.E-04					Up	PSMB8	Proteasome subunit beta type-8 precursor	Antigen presentation
CA053051		P97372			2.06	7.E-09			Up	PSME2	Proteasome activator complex subunit 2	Antigen presentation
CA051193		P28065			0.92	7.E-05			Up	PSMB9	Proteasome subunit beta type-9 precursor	Antigen presentation
CA064302		P28065			1.55	1.E-07			Up	PSMB9		Antigen presentation
CA064302		P28075	-1.03	7.E-04					Down	PSMB5	Proteasome subunit beta type-5 precursor	Antigen presentation
CA064302		P28074			2.03	4.E-08			Up	PSMB5	Proteasome subunit beta type-5 precursor	Antigen presentation
CA060476		P20036			1.69	9.E-06			Up	HLA-DPA1	HLA class II histocompatibility antigen, DP alpha chain precursor	Humoral Immunity
CA060063		P70195			1.99	2.E-05			Up	PSMB7	Proteasome subunit Z	Humoral Immunity
DY726774		Q8WV28					1.84	6.E-04	Up	BLNK	B-cell adapter containing a SH2 domain protein	Humoral Immunity
CA061789		P18469					1.57	2.E-04	Up	H2-EB1	MHC class II beta chain	Humoral Immunity
CA040008		P02787	-1.22	8.E-04					Down	TF	Serotransferrin I	Humoral Immunity
CA056544		P02787	-1.17	4.E-04					Down	TF		Humoral Immunity
CA042638		P15814	-0.71	3.E-06					Down	IGLL1	Immunoglobulin-related protein 14.1	Humoral Immunity
CB515138		P01854	-1.35	3.E-04					Down	IGHE	Immunoglobulin heavy chain	Humoral Immunity
CA060235		P06744			-1.23	4.E-04			Down	GPI	Phosphohexose isomerase	Humoral Immunity; Leukemia
CB503772		P04233					-3.48	6.E-04	Down	CD74	HLA class II histocompatibility antigen gamma chain	Humoral Immunity
CK990275		P04233					-2.10	9.E-04	Down	CD74		Humoral Immunity
CB512110		Q7Z3Y4					-2.00	2.E-05	Down		Immunoglobulin light chain	Humoral Immunity
CN442518		P20036					-2.94	3.E-04	Down	HLA-DPA1	HLA-SB alpha chain	Humoral Immunity
CB514060		P18469			-1.26	7.E-04			Down	H2-EB1	MHC class II beta chain	Humoral Immunity
CB509927		P05727	1.01	5.E-04					Up	APOA4	Apolipoprotein AIV	Innate Immunity
CA059493		Q8VCS0			1.60	3.E-06			Up	PGLYRP2	Peptidoglycan recognition protein long	Innate Immunity
CA051915					1.86	2.E-06			Up	CD80	CD80-like protein	Innate Immunity
CB517593		Q43597			2.32	6.E-09			Up	SPRY2	Sprouty homolog 2	Innate Immunity; Jak-STAT
CA054290		Q9JIW9			2.40	9.E-06	2.23	1.E-04	Up	RALB	Ras-related protein Ral-B	Innate Immunity; Inflammatory
CA051070		O77737					1.24	7.E-04	Up	BCL2L1	Bcl-2-like 1 protein	Innate Immunity; Jak-STAT
DY714826		Q6Q899					2.50	6.E-05	Up	DDX58	DEAD-box protein 58	Innate Immunity
CA063322		Q8WXH6	-1.05	9.E-04					Down	SOCS4	Suppressor of cytokine signaling 4	Innate Immunity; Jak-STAT (-)
CB514268		O54928	-1.48	2.E-07					Down	SOCS5	Cytokine-inducible SH2-containing protein 5	Innate Immunity; Jak-STAT (-)
CA048944		Q8BTI9			-1.22	3.E-04			Down	PIK3CB	PI3-kinase p110 subunit beta	Innate Immunity; Jak-STAT
CA056349		P68371	-0.76	2.E-04	-1.16	6.E-06			Down	TUBB2C	Beta-1-tubulin	Innate Immunity
CA055057		P68371					-2.06	6.E-04	Down	TUBB2C	Beta-tubulin	Innate Immunity
CA064086		P78417	1.63	4.E-08	1.33	6.E-06			Up	GSTO1	Glutathione transferase omega-1	Inflammatory
CA052962		P49263	0.80	2.E-04	1.65	1.E-07			Up	LOC398040	Pentraxin fusion protein precursor	Inflammatory
CA051187		P11226	1.28	6.E-04	1.85	9.E-07			Up	MBL2	Mannan-binding protein	Inflammatory
CA057947		Q8R431	1.24	8.E-04	1.34	6.E-04			Up	MGLL	Monoglyceride lipase	Inflammatory
CA054819		Q90678	1.27	3.E-05	2.15	1.E-10			Up	PLA2G7	Phospholipase A2 group VII	Inflammatory
CA057485		Q7YR37	0.77	1.E-03					Up	ABCF1	ATP-binding cassette 50	Inflammatory
CB499394		P07996	1.01	8.E-04					Up	THBS1	Thrombospondin-1	Inflammatory
CA062672		Q9Z1N5	1.08	3.E-04					Up	BAT1A	HLA-B-associated transcript 1	Inflammatory
CA044503		O95715	1.20	8.E-04					Up	CXCL14	Small-inducible cytokine B14	Inflammatory
CB500559			1.10	5.E-04					Up		Leukotriene B4 receptor 1	Inflammatory
CA059190		Q15722			2.48	4.E-05			Up	LTB4R	Leukotriene B4 receptor	Inflammatory
CA062973		Q4QQM1			2.06	4.E-06	1.18	2.E-04	Up	PLA2G4B	Phospholipase A2 group IVB (cytosolic)	Inflammatory
CA060154		P16109			1.81	4.E-05			Up	SELP	Granule membrane protein 140	Inflammatory
CA040983		Q9Y263			2.05	3.E-05			Up	PLAA	Phospholipase A-2-activating protein	Inflammatory
CA055654		P09917			1.33	5.E-04			Up	ALOX5	5-lipoxygenase	Inflammatory
CB512482		P32248	-1.24	8.E-05	1.28	4.E-04				CCR7	C-C chemokine receptor type 7 precursor	Inflammatory
CA062126		P80299			2.08	4.E-06			Up	EPHX2	Soluble epoxide hydrolase	Inflammatory
CB517585		Q6P0I8			2.19	1.E-06			Up	EXOSC6	Exosome component 6	Inflammatory
CB517194		O95163			1.46	1.E-05			Up	RP11-3J11.4	IkappaB kinase complex-associated protein	Inflammatory
CA064204		P04271			1.75	8.E-04			Up	S100B	S100 calcium-binding protein B	Inflammatory
CB517767		P21462			1.60	6.E-07			Up	FPR1	N-formylpeptide chemoattractant receptor	Inflammatory
CA051861		P83038			1.72	2.E-04			Up	HDAC4	Histone deacetylase 4	Inflammatory
CB517506		Q95LF0			2.49	2.E-05			Up	IL13RA2	Interleukin-13 receptor alpha-2 chain precursor	Inflammatory; Jak-STAT
CB516773		Q9NPA2			2.28	6.E-04			Up	MMP25	Membrane-type matrix metalloproteinase 6	Inflammatory
CB517816		Q9UKK3			2.20	5.E-05			Up	PARP4	Vault poly(ADP-ribose) polymerase	Inflammatory
CA052297		P25155			1.67	2.E-04			Up	F10	Virus-activating protease	Inflammatory
CB517887		Q28806			3.48	4.E-07			Up	ICAM1	Intercellular adhesion molecule 1	Inflammatory
CA041321		Q8NFU3					2.06	4.E-04	Up	F11R	Putative thiosulfate sulfurtransferase KAT	Inflammatory
CA055450		P30273					1.23	8.E-04	Up	FCER1G	IgE Fc receptor subunit gamma	Inflammatory
DW572589		Q15722					2.85	2.E-06	Up	LTB4R	Chemoattractant receptor-like 1	Inflammatory
DY704013		Q12986					1.95	5.E-04	Up	NFX1	Nuclear transcription factor, X box-binding, 1	Inflammatory
DY726774		Q8WV28					1.84	6.E-04	Up	BLNK	B-cell adapter containing a SH2 domain protein	Inflammatory
DW553572		Q8R2H1					3.10	1.E-04	Up	NFKBIL1	Inhibitor of kappa B-like	Inflammatory
CA062883		P25942					1.70	7.E-04	Up	CD40	Tumor necrosis factor receptor superfamily member 5	Inflammatory
CA061672		Q5ZL72					3.18	3.E-05	Up	HSP60	Heat shock protein 60	Inflammatory
CB515892		Q5ZL72	-1.34	1.E-05					Down	HSP60		Inflammatory
CA043151		P01044	-1.06	8.E-04			-2.11	1.E-03	Down	KNG		Inflammatory
CA044205		P01044	-1.22	9.E-04					Down	KNG	Kininogen I; Thiol proteinase inhibitor	Inflammatory
CA043177		P01044	-1.36	4.E-04					Down	KNG		Inflammatory
CB497601		P01048	-0.81	2.E-06					Down		Major acute phase protein	Inflammatory
CA063454		O75882	-1.37	5.E-05			-1.40	3.E-04	Down	ATRN	Mahogany homolog; DPPT-L	Inflammatory
CA055648		P15291	-1.50	2.E-04			-2.19	6.E-04	Down	B4GALT1	UDP-Gal:beta-GlcNAc beta-1,4-galactosyltransferase 1	Inflammatory
CA770237		Q2VLH6	-1.18	4.E-04					Down	CD163	CD163 antigen	Inflammatory
CA051685		O15553	-0.82	5.E-04					Down	MEFV	Marenostrin	Inflammatory
CB514497		P31230	-0.94	5.E-05					Down	SCYE1	Multisynthetase complex auxiliary component p43	Inflammatory
CB512344		P31230	-1.02	2.E-05					Down	SCYE1		Inflammatory
CB509791		P01009	-1.23	7.E-06					Down	SERPINA1	Hibernator-specific blood complex, 55 kDa subunit	Inflammatory
CA051328		Q61548	-1.29	3.E-04					Down	SNAP91	Clathrin coat-associated protein AP180	Inflammatory
CA040008		P02787	-1.22	8.E-04					Down	TF	Serotransferrin I	Inflammatory
CA056544		P02787	-1.17	4.E-04					Down	TF		Inflammatory
CA044603		Q9Y5S9			-1.66	2.E-05			Down	RBM8A	RNA-binding motif protein 8A	Inflammatory
CA038065		Q2VLG6			-1.79	6.E-05			Down	CD163	CD163 antigen	Inflammatory
CB488504		Q02734			-1.46	5.E-05			Down	ST3GAL3	N-acetyllactosaminide alpha-2,3-sialyltransferase	Inflammatory
CA041989					-1.27	5.E-07			Down			Inflammatory
CA769782					-1.51	2.E-06			Down		Carbonyl reductase	Inflammatory
CA038296					-1.46	1.E-06	-2.72	8.E-04	Down			Inflammatory
CB493123		Q06507			-1.43	1.E-04			Down	ATF4	Cyclic AMP-dependent transcription factor ATF-4	Inflammatory
CB495313		P21533			-1.51	4.E-05	-2.40	7.E-05	Down	RPL6	Neoplasm-related protein C140	Inflammatory
CA060895		Q02878			-0.78	3.E-04			Down	RPL6	TAX-responsive enhancer element-binding protein 107	Inflammatory
CK990925		Q02878					-1.76	3.E-04	Down	RPL6		Inflammatory
CA061344		Q60449			-1.19	1.E-04			Down	LY75	Lymphocyte antigen 75	Inflammatory
CB493194		P30044			-1.52	2.E-06			Down	PRDX5		Inflammatory
CB496561		P30044			-1.71	4.E-06			Down	PRDX5		Inflammatory
CA047665		P30044			-1.65	9.E-07	-2.96	4.E-06	Down	PRDX5	Peroxiredoxin 5	Inflammatory
CB496449		P30044					-3.01	2.E-04	Down	PRDX5		Inflammatory
CA055510		P30044					-3.36	1.E-05	Down	PRDX5		Inflammatory
CB492576		P09034			-0.94	8.E-04			Down	ASS	Citrulline--aspartate ligase	Inflammatory
CB492799		P09034					-2.41	9.E-05	Down	ASS		Inflammatory
CB507311		P26351					-2.62	6.E-04	Down		Beta thymosin	Inflammatory
CB496527							-3.44	5.E-05	Down			Inflammatory
CB491356		Q02988					-2.84	2.E-04	Down		Mannose binding lectin	Inflammatory
CB492684		P04083					-2.63	8.E-04	Down	ANXA1	Annexin-1	Inflammatory
CA043347		P53348					-2.70	1.E-04	Down	BTG1	B-cell translocation gene 1 protein	Inflammatory
EG821224		Q68Y88					-3.22	3.E-05	Down	CCL13	Small-inducible cytokine A13	Inflammatory
CA037585		P00734					-2.23	7.E-04	Down	F2	Coagulation factor II	Inflammatory; Jak-STAT
CB514528		P24801					-4.76	3.E-08	Down	LOC397735	Annexin-2-B	Inflammatory
CK991112		P24801					-2.13	2.E-04	Down	LOC397735		Inflammatory

Accession (32K slide)	Not on 16K slide (x)	Uniprot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
CA058052		Q24K30	2.05	9.E-06					Up		immune-related, lectin-like receptor 4	Immunity
CB515931		P15814	0.84	1.E-04					Up	IGLL1	Immunoglobulin-related protein 14.1	Immunity
CA055190		Q5DSV6	0.88	1.E-03	2.06	7.E-08			Up	BTY	Bloodthirsty	Immunity
CA053392		O15117	1.31	2.E-06	2.47	2.E-09			Up	FYB	FYN-T-binding protein	Immunity
CA050621		P14317	-1.01	2.E-04	1.59	3.E-06	1.14	1.E-03		HCLS1	Hematopoietic cell-specific LYN substrate 1	Immunity
CB515466		Q9P0V9	1.59	2.E-04	1.31	6.E-05			Up	SEPT10	Septin 10	Immunity
CA061415			1.92	3.E-04	3.00	1.E-09			Up	CSF1	macrophage colony-stimulating factor	Immunity
CA063730		Q62418	1.17	3.E-05	1.07	1.E-04			Up	DBNL	SH3 domain-containing protein 7	Immunity
CK990636		P54841	1.90	8.E-06					Up	MAFB	Transcription factor MafB	Immunity
CA051431		P02686	1.28	6.E-04	2.36	3.E-08			Up	MBP	Myelin basic protein	Immunity
CK990806		P61769			1.84	6.E-06			Up	B2M	Beta-2-microglobulin precursor	Immunity
CA058185		P17213			1.82	6.E-04			Up	BPI	Bactericidal permeability-increasing protein precursor	Immunity
CA052213		Q6TLE6			2.13	1.E-04			Up	ZGC:109721	Calcium release-activated calcium channel protein 1	Immunity
CB517208		Q91ZN1			1.30	2.E-06			Up	CORO1A	Coronin-like protein A	Immunity
CB512479		Q8GQP0			1.94	3.E-07			Up	CYP3A65	Cytochrome P450 3A27	Immunity
CA058817		P36201			3.48	5.E-05			Up	CRIP2	Cysteine-rich protein 2	Immunity
CA058622					2.31	2.E-05			Up		Cytochrome c oxidase subunit 1	Immunity
CA052539		P08267			0.93	9.E-04			Up	FTH1	Ferritin M	Immunity
CB513818					2.09	4.E-06			Up		Immune receptor intron	Immunity
CA053532		Q6PC62			2.03	3.E-10			Up	SPG21	Maspardin	Immunity
CA084302	x	P54132					2.91	3.E-05	Up	BLM	RecQ protein-like 3; DNA helicase, RecQ-like type 2	Immunity
CK991203		Q9Y6U3			1.86	1.E-06			Up	SCIN	Scinderin	Immunity
CA059823		Q8K1S5			1.49	3.E-04			Up	KLF11	TGFB-inducible early growth response protein 3	Immunity
CB516580		Q8WZ60			1.15	3.E-04			Up	KLHL6	Kallikrein-like gene	Immunity
CA054045		Q99JW2			2.26	5.E-07			Up	ACY1	N-acyl-L-amino-acid amidohydrolase; ACY-1	Immunity
CA062970		P00790			2.71	1.E-11	2.61	9.E-04	Up	PGA5	Pepsin A-4 precursor	Immunity
CB511649		Q5SNN7			2.03	3.E-08			Up	NITR9	Novel immune-type receptor 4	Immunity
DY740476	x	Q5SNN7					1.77	2.E-04	Up	NITR9	Novel immune-type receptor 9	Immunity
CB517440		P35579			-1.45	3.E-06	3.12	3.E-04		MYH9	Myosin heavy chain 9	Immunity
CA062239		P39019			2.31	2.E-07	2.22	2.E-04	Up	RPS19	40S ribosomal protein S19	Immunity
DY701766	x	Q9UKV3					2.23	4.E-05	Up	ACIN1	Acinus	Immunity
CA063255		Q9H7Z6					2.20	2.E-04	Up	MYST1	Probable histone acetyltransferase MYST1	Immunity
DY733752	x	Q92608					1.92	9.E-04	Up	DOCK2	Dedicator of cytokinesis protein 2	Immunity
CX356913	x	Q8BTF7					2.71	9.E-05	Up	LIG4	DNA ligase IV	Immunity
CA055774		P54279					2.17	3.E-04	Up	PMS2	DNA mismatch repair protein PMS2	Immunity
CB496527		P35579	-1.24	9.E-04					Down	MYH9	Myosin-9	Immunity
CA055793		Q9H3F6	-1.31	6.E-06					Down	KCTD10		Immunity
CB503917		Q9H3F6	-0.96	2.E-04					Down	KCTD10	Potassium channel tetramerisation domain containing protein 13	Immunity
CA048443		Q9H3F6	-0.95	9.E-07					Down	KCTD10		Immunity
CB511726		P49703	-1.27	1.E-05					Down	ARL4D	ADP-ribosylation factor-like protein 4L	Immunity
CB515069	x	Q6PA06					-1.91	9.E-04	Down	ARL6IP2	ADP-ribosylation factor-like protein 6-interacting protein 2	Immunity
CA057516		Q08477	-1.61	2.E-07					Down	CYP4F3	Leukotriene-B(4) omega-hydroxylase	Immunity
CA050155		Q91ZN1	-1.55	1.E-05					Down	CORO1A	Coronin-1A	Immunity
CA770681		P53634	-1.21	2.E-08					Down	CTSC	Dipeptidyl-peptidase I	Immunity
CB494269		Q6RY07	-1.02	5.E-05					Down	CHIA		Immunity
CB502129		Q6RY07	-1.68	5.E-05					Down	CHIA		Immunity
CB502688		Q6RY07	-1.31	3.E-04					Down	CHIA	AMCase	Immunity
CB493525		Q9BZP6					-3.09	1.E-05	Down	CHIA		Immunity
CB493930		Q9BZP6					-1.83	2.E-04	Down	CHIA		Immunity
CB498290		Q9BZP6	-1.40	8.E-05					Down	CHIA		Immunity
CB516206		Q9YGC1	-1.25	3.E-06					Down	BLNK	B-cell linker protein	Immunity
CA044199		Q05655	-0.75	2.E-04					Down	PRKCD	Protein kinase C, delta	Immunity
CB493455		Q804S5	-1.18	2.E-05					Down	MIB	Protein mind bomb	Immunity
CA060862		Q92835	-0.76	7.E-04					Down	INPP5D	SH2 domain-containing inositol-5-phosphatase 1	Immunity
CB514268		O54928	-1.48	2.E-07					Down	SOCS5	Suppressor of cytokine signaling 5	Immunity
CB516834		Q9BX59	-1.08	4.E-06					Down	TAPBPL	Tapasin-related protein precursor	Immunity
CB489043		O42197					-3.19	1.E-04	Down	B2M		Immunity
CB489190		O42197			-1.24	7.E-04	-3.71	5.E-04	Down	B2M		Immunity
CB496576		O42197			-2.11	1.E-04			Down	B2M		Immunity
CB498391		O42197			-2.19	5.E-04			Down	B2M	Beta 2 microglobulin	Immunity
CB505897		P61769					-3.55	3.E-04	Down	B2M		Immunity
CA042157		P61769					-3.25	1.E-04	Down	B2M		Immunity
CA061048		P61769					-3.42	1.E-04	Down	B2M		Immunity
CB496363		P17790			-1.50	5.E-06			Down		Blood-brain barrier HT7 antigen	Immunity
CA040209		Q5DSV6	-0.89	3.E-04					Down	BTY	Bloodthirsty	Immunity
CA052393	x	Q5DSV6					-2.20	5.E-05	Down	BTY		Immunity
CB514208		Q8HY81					-2.62	2.E-04	Down	CTSS	Cathepsin S	Immunity
CN442514		Q9ZZM6			-1.87	4.E-05			Down	COX1	Cytochrome c oxidase polypeptide I	Immunity
CN442537		Q9ZZM6			-2.18	4.E-04	-1.82	5.E-04	Down	COX1		Immunity
CA049433		Q920K4			-1.49	1.E-04	-1.65	7.E-04	Down	FTH1		Immunity
CB509708		P08267			-1.61	4.E-06	-3.36	2.E-05	Down	FTH1	Ferritin H	Immunity
CK990586		P08267					-2.34	3.E-05	Down	FTH1		Immunity
CK990703		P08267					-2.09	2.E-04	Down	FTH1		Immunity
CA056744		P08267					-3.05	4.E-04	Down	FTH1		Immunity
CB487639		P49947					-2.65	2.E-04	Down	FTH1		Immunity
CB497884		P49947					-3.41	6.E-06	Down	FTH1		Immunity
CB505282		P08267					-3.75	2.E-06	Down	FTH1		Immunity
CB507396		P08267			-1.15	5.E-06			Down	FTH1	Ferritin M	Immunity
CB508292		P08267					-3.08	2.E-04	Down	FTH1		Immunity
CB510731		P08267			-1.01	2.E-04	-2.60	9.E-04	Down	FTH1		Immunity
CK990310		P49947					-2.56	2.E-04	Down	FTH1		Immunity
CK990827		P02794					-2.24	4.E-05	Down	FTH1		Immunity
CA049966		O35601					-1.82	4.E-04	Down	FYB	FYN-binding protein	Immunity
CA058998		O35601	-0.95	1.E-05					Down	FYB	FYN-T-binding protein	Immunity
EG901382	x	Q12983					-1.92	5.E-04	Down	BNIP3	BCL2/adenovirus E1B 19 kDa protein-interacting protein 3	Immunity
CB502357		P51572					-2.71	4.E-04	Down	BCAP31	BCR-associated protein Bap31	Immunity
CB496437							-1.69	6.E-04	Down		Growth Hormone type 1	Immunity
CX041687	x	Q8BH66					-1.95	8.E-04	Down	SPG3A	GTP-binding protein 3	Immunity
CA058223		Q96PP9	-0.65	3.E-04					Down	GBP4	GTP-binding protein 4	Immunity
CA049299		Q90486			-1.67	2.E-04			Down	ZGC:92880	Hemoglobin subunit beta-1	Immunity
CA036745		Q90487					-2.30	2.E-05	Down	HBAA1	Hemoglobin alpha chain	Immunity
CA049294		Q90487					-3.07	2.E-04	Down	HBAA1		Immunity
CB515375		Q90487					-2.82	6.E-05	Down	HBAA1	Hemoglobin alpha-4 chain	Immunity
CB492780		Q3ZC46			-1.24	3.E-04			Down	ID2	Inhibitor of DNA binding 2	Immunity
CX036533	x	Q8NZ06					-1.21	2.E-04	Down	ILF2	Interleukin enhancer-binding factor 2 homolog	Immunity
CB496558		Q9Y244					-1.48	7.E-04	Down	POMP	Proteasome maturation protein	Immunity
CA061622		P28064					-2.76	1.E-05	Down	PSMB8		Immunity
CA052737		P28064					-2.98	3.E-04	Down	PSMB8	Proteasome subunit beta type-8 precursor	Immunity
CB496486		P28064					-2.28	3.E-04	Down	PSMB8		Immunity
CB498733		O95977			-1.83	1.E-06			Down	EDG6	Sphingosine 1-phosphate receptor Edg-6	Immunity
CB494461							-2.82	1.E-04	Down		Thymosin beta	Immunity
CB496624		Q9I955					-2.08	6.E-04	Down		Thymosin beta a	Immunity
CA050896		P26352			-0.97	3.E-05			Down		Thymosin beta-12	Immunity
CB502459		P54842			-1.03	3.E-04	-3.54	1.E-05	Down	MAFB	Transcription factor MafB	Immunity
CB492912		Q8K1S5	-1.35	1.E-04					Down	KLF11	Transforming growth factor-beta-inducible early growth response protein 3	Immunity
DW540506	x	Q8K1S5					-2.72	3.E-04	Down	KLF11		Immunity
DY696622	x	Q8K1S5					-1.59	2.E-04	Down	KLF11		Immunity

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Accession (32K slide)	Not on 16K slide (x)	Uniprot ID (DAVID input)	SW Fold-Change	SW p-value	FW Fold Change	FW p-value	Spawn Fold Change	Spawn p-value	MRS	Gene Symbol	Gene Name	Functional Link
												Role in Leukemia
CA062065		Q922M3			1.98	4.E-04	1.34	7.E-04	Up	KCTD10	BTB/POZ domain-containing protein TNFAIP1	T-cell leukemia virus; viral transfer
CA053490		Q7T2H3			1.89	2.E-05			Up		Tumour necrosis factor receptor	T-cell leukemia virus; viral transfer
CA062883		P25942					1.70	7.E-04	Up	CD40	Tumor necrosis factor receptor superfamily member 5	T-cell leukemia virus; viral transfer
CA052493		Q7T364					1.69	9.E-05	Up	TNFAIP8L	Tumor necrosis factor, alpha-induced protein 8	T-cell leukemia virus; viral transfer
CA050459		Q91917	0.99	1.E-04	2.04	6.E-06			Up	RAD51	xRAD51.2	Leukemia
CA058100		P31395	0.94	7.E-04	1.22	5.E-05			Up	STMN1	Stathmin	Leukemia
CA058281		P22897	1.05	8.E-05	1.56	1.E-04			Up	MRC1	CD206 antigen	Leukemia; Immunity
CA060333		P00493	2.38	5.E-04	3.36	5.E-04			Up	HPRT1	Hypoxanthine guanine phosphoribosyl transferase 1	Leukemia; Immunity
CB517850		Q9W719			1.96	8.E-07			Up	HPRT1		Leukemia; Immunity
CA052716		P43403	1.71	1.E-04	2.33	2.E-06	2.63	2.E-04	Up	ZAP70	Tyrosine-protein kinase ZAP-70	Leukemia; Immunity
CB514495		Q9PTJ3			1.73	1.E-04			Up	LMO2	LIM domain only protein 2	Leukemia; Immunity
CB517827		Q9Y275			1.47	3.E-06			Up	TNFSF13B	Tumor necrosis factor ligand superfamily member 13B	Leukemia; Immunity
DY736745	X	O75888					2.05	6.E-04	Up	TNFSF13	Tumor necrosis factor ligand superfamily member 13	Leukemia; Immunity
CB514943		Q52NJ4			2.81	9.E-09			Up	LOC595114	ADP-ribosylation factor-like protein 3.	Leukemia
CA060154		P16109			1.81	4.E-05			Up	SELP	P-selectin precursor	Leukemia
CA062952		Q5ZM60			1.60	7.E-04	1.58	3.E-04	Up	RCJMB04_3A	Hematopoietic PBX-interacting protein.	Leukemia
CA053550		Q6DGY3			2.75	1.E-10			Up	ZGC:92721	T-cell leukemia translocation-associated gene protein	Leukemia
CB511635		Q9NSI8			2.21	1.E-06			Up	SAMSN1	SAM domain-containing protein SAMSN-1	Leukemia progression
CA052902		P97814			3.47	6.E-09			Up	PSTPIP1	PEST phosphatase-interacting protein 1	Leukemia
CA050861		Q05397			1.25	3.E-04			Up	PTK2	Protein-tyrosine kinase 2	Leukemia
CA063576		P15927			2.36	3.E-08			Up	RPA2	Replication factor-A protein 2	Leukemia
CB511864		Q15546			1.48	1.E-05			Up	MMD	Progestin and adipoQ receptor family member XI	Leukemia; Differentiates myeloid/lymphoid
CA063629		P19235			1.48	4.E-04			Up	EPOR	Erythropoietin receptor precursor	Leukemia; Jak-STAT
CA058269		Q99062			2.09	5.E-07			Up	CSF3R	CD114 antigen	Leukemia; Jak-STAT
CA062955		Q16678			1.38	6.E-07			Up	CYP1B1	CYPIB1	Leukemia
CA054940		P09211			1.37	2.E-08			Up	GSTP1	Glutathione S-transferase PI	Leukemia
CA062753		O88890			1.61	2.E-06			Up	SH2D1A	T-cell signal transduction molecule SAP	Leukemia; Humoral Immunity
CA056997		P21980			2.63	1.E-04			Up	TGM2	Transglutaminase-2	Leukemia; Inflammatory
CA050446		P21980			1.39	1.E-05			Up	TGM2		Leukemia; Inflammatory
CA058102		P56261			1.72	8.E-04			Up	CEBPE	CCAAT/enhancer-binding protein epsilon	Leukemia; Immunity
CA057676		O42354			1.62	3.E-05			Up	MDM2	p53-binding protein Mdm2	Leukemia
CA054654		Q9CR16			2.62	9.E-08			Up	PPID		Leukemia
CA061270		Q9CR16			1.99	2.E-04			Up	PPID	40 kDa peptidyl-prolyl cis-trans isomerase	Leukemia
CB489000		Q9CR16					-2.70	1.E-04	Down	PPID		Leukemia
CA051023		Q08413			2.48	6.E-05	1.74	1.E-03	Up	MEF2C	Myocyte-specific enhancer factor 2C	Leukemia
CB515645		P41134			1.91	5.E-08			Up	ID1		Leukemia
CA052765		P41134			1.37	3.E-08			Up	ID1	Inhibitor of DNA binding 1	Leukemia
CB509856		P41134			-1.46	9.E-04			Down	ID1		Leukemia
CB492655		P41134			-1.55	4.E-05			Down	ID1		Leukemia
CA059961		Q9XSC9			1.57	1.E-04			Up	TCN2	Transcobalamin II	Leukemia
CB497346		Q9XSC9	-1.04	1.E-05					Down	TCN2		Leukemia
CB511881		O00300	-1.31	7.E-06					Down	TNFRSF11B		T-cell leukemia virus; viral transfer
CA051040		O00300			2.28	1.E-11			Up	TNFRSF11B	Osteoclastogenesis inhibitory factor	T-cell leukemia virus; viral transfer
EG815686		O08712					3.19	5.E-05	Up	TNFRSF11B		T-cell leukemia virus; viral transfer
CA055183		Q02880			1.21	6.E-04	1.68	5.E-05	Up	TOP2B	Novel protein similar to vertebrate topoisomerase (DNA) II beta 180	Leukemia
CA051008		P51686			2.50	4.E-09			Up	CCR9	C-C chemokine receptor type 9	Leukemia; Immunity
CA048961		P51686	-0.94	5.E-05					Down	CCR9		Leukemia; Immunity
CA059679		O18733			1.65	3.E-07			Up	MMP9		Leukemia; Immunity
CB499697		O18733	-1.08	1.E-04					Down	MMP9	Matrix metalloproteinase-9 precursor	Leukemia; Immunity
CB499697		O18733	-0.97	3.E-04					Down	MMP9		Leukemia; Immunity
CB499597		Q96FS4	-1.32	2.E-05	-1.40	8.E-04			Down	SIPA1	GTPase-activating protein Spa-1	Leukemia
CA062659		P21868	-0.89	8.E-04					Down	CSNK2A1	Casein kinase II subunit alpha	Leukemia
CB499801		P40424	-0.89	8.E-04					Down	PBX1	Homeobox protein PBX1; Homeobox protein PRL	Leukemia
CA058560		P09936	-0.97	1.E-04					Down	UCHL1	Ubiquitin thioesterase L1	Leukemia
CA053740		P09936			-1.43	4.E-04			Down	UCHL1		Leukemia
CA044861		Q62227	-1.45	7.E-04					Down	NR0B2		Leukemia
CA043660		Q62227			-1.49	3.E-05			Down	NR0B2	Orphan nuclear receptor SHP	Leukemia
CA037720		Q15466			-1.63	4.E-04			Down	NR0B2		Leukemia
CB492902		Q09327			-1.60	3.E-04	-2.66	6.E-04	Down	MGAT3	N-acetylglucosaminyltransferase III	Leukemia
CA061284		P31939			-1.44	5.E-04			Down	ATIC	Bifunctional purine biosynthesis protein PURH	Leukemia
CB503691		O08638			-1.40	8.E-05			Down	MYH11	Myosin heavy chain 11	Leukemia
CB497378		Q05982			-1.08	2.E-04	-2.28	4.E-04	Down	NME1	Tumor metastatic process-associated protein	Leukemia
CB511030		Q05982					-2.52	7.E-04	Down	NME1		Leukemia
CA060699		Q05982					-2.59	8.E-05	Down	NME1	Tumor metastatic process-associated protein	Leukemia
CB492030		Q05982					-2.81	3.E-04	Down	NME1		Leukemia
CA042095		Q05982					-3.11	3.E-05	Down	NME1		Leukemia
CA053607		Q800E4			-0.83	3.E-04			Down	NOTCH3	Notch 3	Leukemia
CB494190		Q9YI98			-1.38	1.E-04	-2.46	2.E-04	Down	OAZ1		Leukemia
CK990329		P54368			-1.12	2.E-04			Down	OAZ1	Ornithine decarboxylase antizyme	Leukemia
CA052405		Q9YI98					-2.12	6.E-04	Down	OAZ1		Leukemia
CB502959		Q01105			-1.11	3.E-05			Down	SET		Leukemia
CA041701		Q01105					-1.97	1.E-03	Down	SET	Phosphatase 2A inhibitor I2PP2A	Leukemia
CB497971		Q9EQU5					-2.23	3.E-04	Down	SET		Leukemia
CB493442		P30626			-1.25	1.E-04	-2.91	9.E-05	Down	SRI	22 kDa protein; CP-22; V19	Leukemia
CA061258		P27641			-1.71	3.E-04			Down	XRCC5	ATP-dependent DNA helicase II 80 kDa subunit	Leukemia
CB490715		O93257			-1.27	9.E-05			Down	XRCC6		Leukemia
CA062451		Q02248			-1.26	1.E-05			Down	CTNNB1	Beta-catenin	Leukemia; Immunity
CK990843		P11309			-0.89	8.E-04			Down	PIM1	Pim-1 oncogene	Leukemia; Innate Immunity; Jak-STAT
CA056678		Q2T9X3			-1.26	9.E-05			Down		CLL deletion region gene 6 protein homolog	Leukemia
CB502621		P42685					-2.60	2.E-04	Down	FRK	FYN-related kinase	Leukemia
CA769301		P10922					-1.91	4.E-05	Down	H1F0	Histone H1(0)-2	Leukemia
CB501872		O14907					-2.21	4.E-04	Down	TAX1BP3	Tax1-binding protein 3	Leukemia
CB496358		Q3ZC46			-1.39	1.E-04			Down	ID2	Inhibitor of DNA binding 2	Leukemia: Down-reg in Leukemia
CA038875		Q07820					-2.90	1.E-05	Down	MCL1	Bcl-2-related protein EAT/mcl1	Leukemia; anti-apoptosis
CB512191		Q9DGK4			-1.21	9.E-05	-2.12	3.E-04	Down	TCTP	Translationally-controlled tumor protein	Leukemia; anti-apoptosis
DW578992	X						1.79	2.E-04	Up		nuclear NF-kappaB activating protein [Siniperca chuatsi]	Leukemia NF kappa B
CB512167		Q3MHX1	1.46	6.E-05	2.73	2.E-09			Up	COMMD7	COMM domain containing protein 7.	Leukemia NF kappa B
CA054648		Q9UNN5	0.87	1.E-04	1.91	5.E-09			Up	FAF1	FAS-associated factor 1	Leukemia NF kappa B
CK990397		Q9NV92	0.90	2.E-04					Up	NDFIP2	NEDD4 family-interacting protein 2	Leukemia NF kappa B
CB514233		Q3SZ52	0.93	1.E-04	0.97	4.E-05			Up	UBE2V1	Ubiquitin-conjugating enzyme E2 variant 1	Leukemia NF kappa B
CA061983		O95163			1.72	5.E-04			Up	RP11-3J11.4	Elongator complex protein 1	Leukemia NF kappa B
CA052080		Q6DGL2			2.33	6.E-09	1.96	9.E-04	Up	ZGC:92870	NF-kappa-B inhibitor-interacting Ras-like protein 2	Leukemia NF kappa B
CK990547		Q14790			1.42	8.E-07			Up	CASP8	Caspase-8 precursor	Leukemia NF kappa B
CB514106		Q9P0L0			1.58	1.E-05			Up	VAPA	Vesicle-associated membrane protein-associated protein A	Leukemia NF kappa B
CA050798		Q9UDY8			1.77	9.E-06			Up	MALT1	Mucosa-associated lymphoid tissue lymphoma translocation protein 1	Leukemia NF kappa B
CA057016		Q8BY02			1.74	4.E-06	-2.41	1.E-04		NKRF	NF-kappa-B-repressing factor	Leukemia NF kappa B
DW553572	X	Q8R2H1					3.10	1.E-04	Up	NFKBIL1	NF-kappa-B inhibitor-like protein 1	Leukemia NF kappa B
CB495313		P21533			-1.51	4.E-05	-2.40	7.E-05	Down	RPL6	Neoplasm-related protein C140	Leukemia NF kappa B
CB509582		Q6DGP4			-1.48	7.E-05			Down	ZGC:92833	NEDD4 family-interacting protein 1	Leukemia NF kappa B
CB501033		Q6DGP4			-0.99	1.E-04			Down	ZGC:92833		Leukemia NF kappa B
CB509540		Q9NV92			-1.92	2.E-04			Down	NDFIP2	NEDD4 family-interacting protein 2	Leukemia NF kappa B
CA060895		Q02878			-0.78	3.E-04			Down	RPL6	TAX-responsive enhancer element-binding protein 107	Leukemia NF kappa B
CK990925		Q02878					-1.76	3.E-04	Down	RPL6		Leukemia NF kappa B
CA039839		Q9WUU8	-1.33	2.E-05					Down	TNIP1	Virion-associated nuclear shuttling protein	Leukemia NF kappa B (negative regulator)
DW577527	X	Q9WUU8					-1.49	3.E-04	Down	TNIP1		Leukemia NF kappa B (negative regulator)

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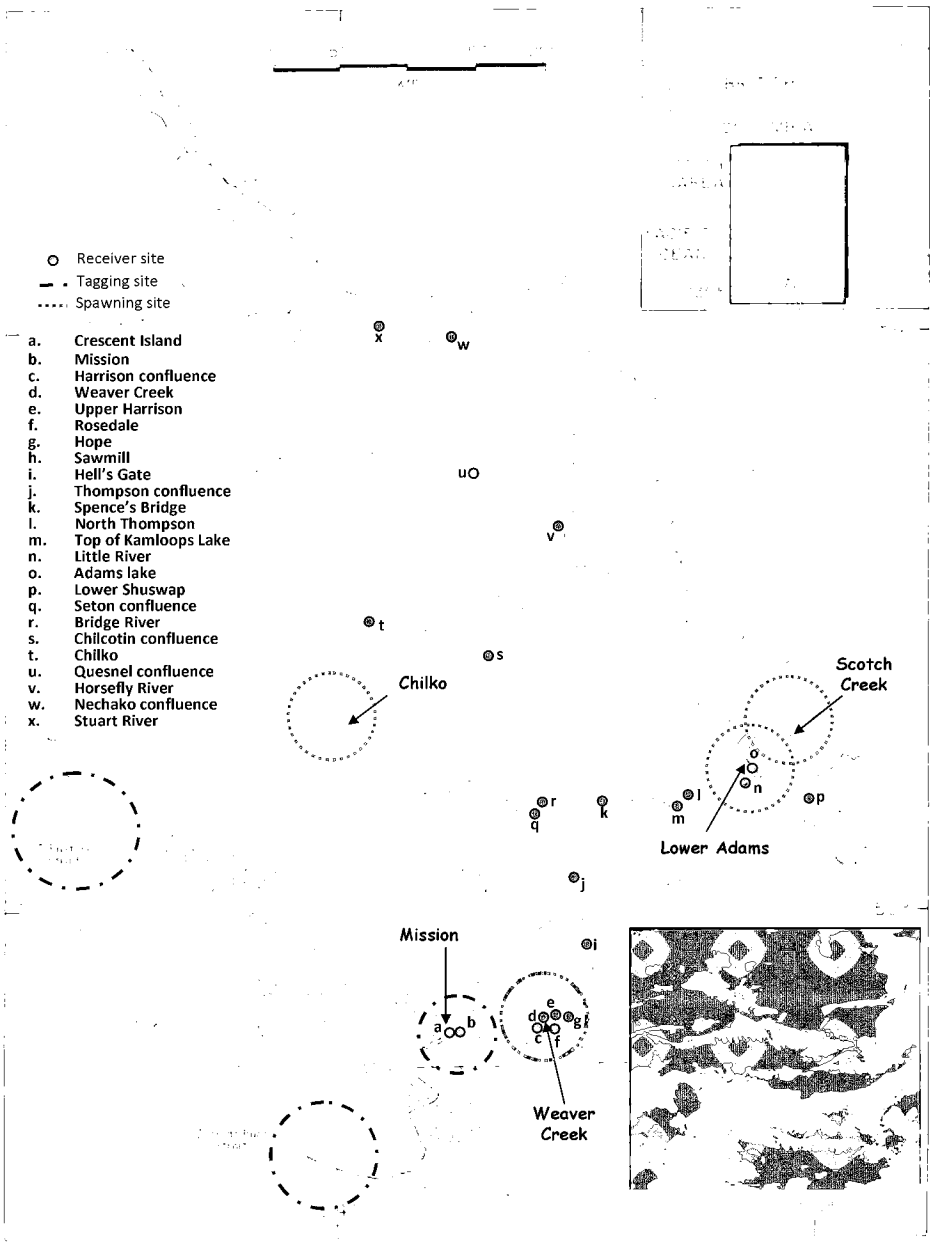

Figure S1. Map shows tagging locations (blue circles), receiver locations (red dots) and spawning sites (green circles) of Fraser River stocks used in genomic studies. Hells Gate (i), a challenging river passage through a narrow canyon of intense water flow, demarcates the upper and lower Fraser River basin. Because most major fisheries occur in the lower river and the highest river temperatures occur in the upper river, physiologically-based mortality may have a more profound effect in the upper river. Note that the last receiver to track Chilko stock fish (t) was 7-13 days travel time to the spawning area whereas the last receivers for Scotch and Late Shuswap stocks (n and o) were less than 1 day travel time to spawning areas.

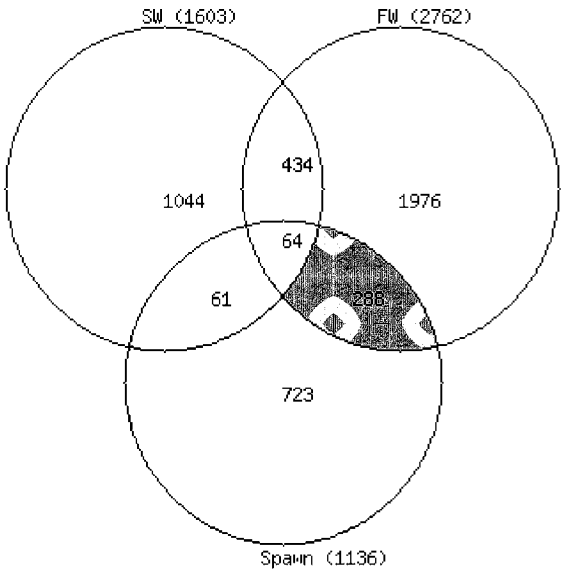

Figure S2. Venn diagram showing the overlap between genes significant ($p<0.001$) in PC1-based t-tests in saltwater (SW), freshwater (FW) and the Weaver Creek spawning area. Overlapping genes were >97% directionally congruent.

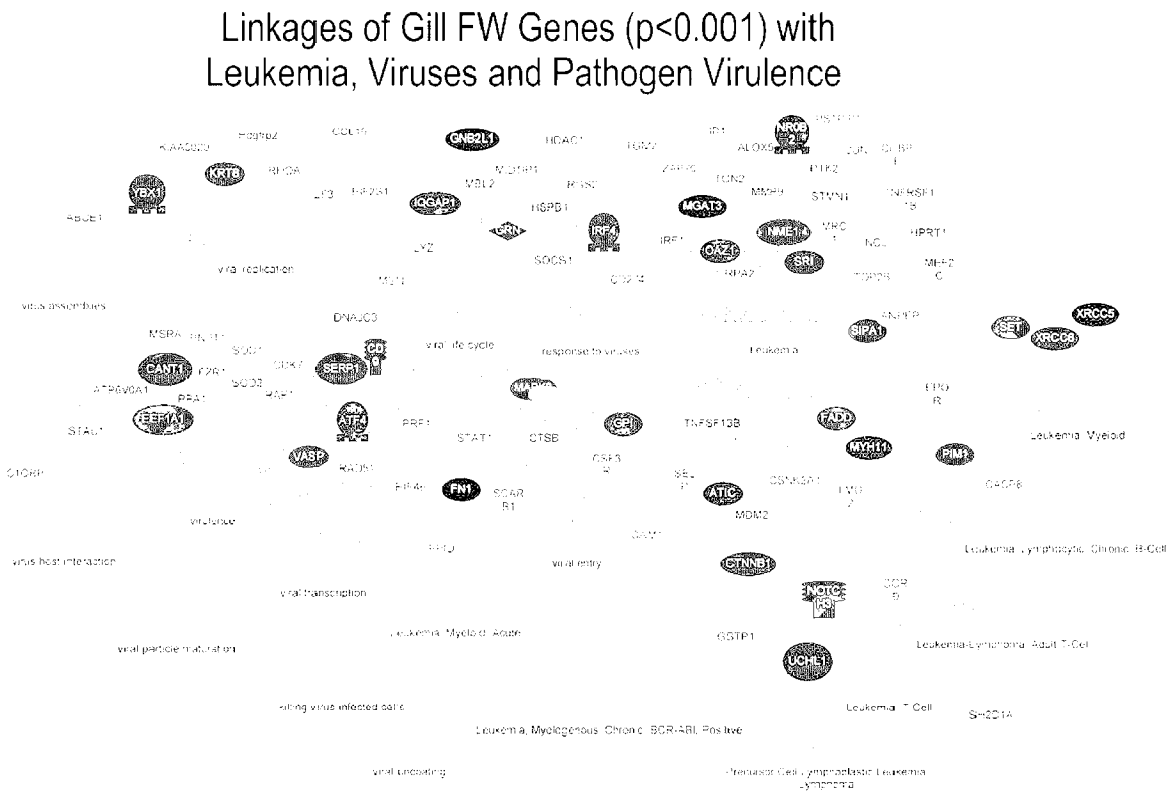

Figure S3. Pathway Studio network representation of linkages between genes significantly ($p<0.001$) differentiating PC1 negative mortality-related signature and PC1 positive survival-related signature classes of fish in the lower Fraser River with viral-related processes, leukemia, and pathogen virulence. Some additional relationships depicted in Table S3 were identified through iHOP and are not shown. Genes coloured yellow were up-regulated in mortality-related signature fish, those in blue down-regulated.

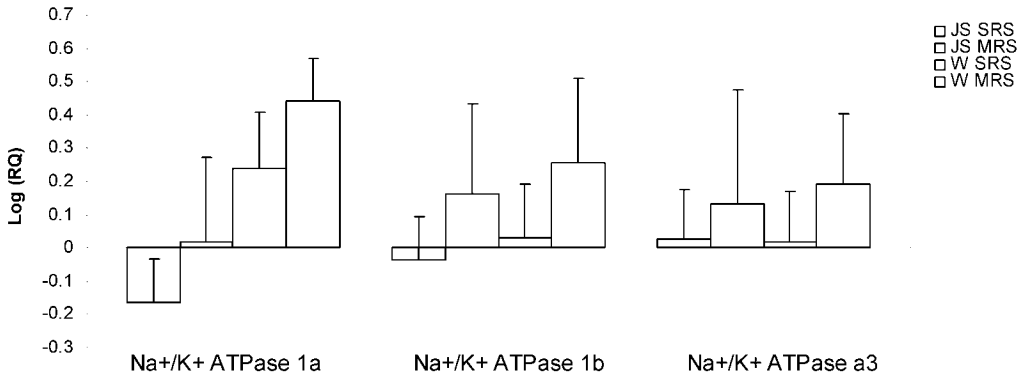

Figure S4. QRT-PCR of three isoforms of Na^+/K^+ ATPase in gill tissue of PC1 positive survival-related signature (SRS) and PC1 negative mortality-related signature (MRS) classified fish sampled in the marine environment in Johnstone Strait (JS) and in the Fraser River at Whonnock (W). Values shown are Log (RQ) plus one SD. Primers for isoform 1a (forward CCAGGATCACTCAATGTCACTCT, reverse GCTATCAAAGGCAAATGAGTTTAATATCATTGTAAAA) are outlined in (*S34*), for isoform 1b (forward CTGCTACATCTCAACCAACAACATT, reverse CACCATCACAGTGTTCATTGGAT) in (*S35*), and for isoform a3 (forward CCAGGTATTGAGTTCCGTGTG, reverse CAGCCTGAAATGGGTGTTCCT) in (*S36*). ARP housekeeping gene primers are shown in Table S2. Significant differences ($p<0.05$) in transcription of isoform 1a were observed between saltwater and freshwater and JS SRS fish versus all other samples, of isoform 1b between SRS and MRS fish in freshwater (almost significant in saltwater [$p=0.06$]) and between JS SRS versus all others, and of isoform a3 between SRS and MRS fish in freshwater.

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Supporting Online Material for

Genomic Signatures Predict Migration and Spawning Failure in Wild Canadian Salmon

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