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Full-length Article

# Minority stress and leukocyte gene expression in sexual minority men living with treated HIV infection

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ABSTRACT

Sexual minority (i.e., non-heterosexual) individuals experience poorer mental and physical health, accounted for in part by the additional burden of sexual minority stress occurring from being situated in a culture favoring heteronormativity. Informed by previous research, the purpose of this study was to identify the relationship between sexual minority stress and leukocyte gene expression related to inflammation, cancer, immune function, and cardiovascular function. Sexual minority men living with HIV who were on anti-retroviral medication, had viral load < 200 copies/mL, and had biologically confirmed, recent methamphetamine use completed minority stress measures and submitted blood samples for RNA sequencing on leukocytes. Differential gene expression and pathway analyses were conducted comparing those with clinically elevated minority stress ($n = 18$) and those who did not meet the clinical cutoff ($n = 20$), covarying reactive urine toxicology results for very recent stimulant use. In total, 90 differentially expressed genes and 138 gene set pathways evidencing 2-directional perturbation were observed at false discovery rate (FDR) < 0.10. Of these, 41 of the differentially expressed genes and 35 of the 2-directionally perturbed pathways were identified as functionally related to hypothesized mechanisms of inflammation, cancer, immune function, and cardiovascular function. The neuroactive-ligand receptor pathway (implicated in cancer development) was identified using signaling pathway impact analysis. Our results suggest several potential biological pathways for future work investigating the relationship between sexual minority stress and health.



## 1. Introduction

Sexual minority (non-heterosexual) individuals experience higher rates of both mental (Cochran et al., 2004; Cochran et al., 2000; Cochran et al., 2003; Hughes and Eliason, 2002; King et al., 2008; McCabe et al., 2003; Stall et al., 2001) and physical health problems (Cochran and Mays, 2007; Conron et al., 2010). Meyer's model of minority stress related to sexual minority status (hereafter termed "sexual minority stress"), which includes experiences and expectations of discrimination, internalization of societal stigma, and concealment of sexual orientation, has garnered significant empirical support in explaining the the health disparities that are observed among sexual minority individuals (Institute of Medicine, 2011; McCabe et al., 2010; Meyer, 2003). Studies also document relationships between sexual minority status and incidence of negative health outcomes such as cardiovascular disease (Conron et al., 2010; Fredriksen-Goldsen et al., 2013), obesity (Conron et al., 2010; Fredriksen-Goldsen et al., 2013), and diabetes (Fredriksen-Goldsen et al., 2013), though studies are generally limited due to delays in the inclusion of sexual orientation in many large-scale health data collection efforts (Sell and Holliday, 2014), and findings often differ between sexual minority subgroups. Compared to heterosexual men, sexual minority men evi-

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dence pre-clinical indicators of risk for negative health outcomes such as high levels of C-reactive protein, diastolic blood pressure, faster heart rate (Hatzenbuehler et al., 2013), and hypertension (Everett and Mollborn, 2013). Research is needed to begin to investigate the mechanisms that underly these health disparities among sexual minority people.

Studies are beginning to document associations between sexual minority stress processes and biological and physiological outcomes. For example, Frost et al. (2015) found that the experience of a prejudice event related to sexual minority status predicts subsequent report of a physical health problem, including problems such as hypertension, illness, or cancer. Other studies have examined cortisol responsiveness within the context of sexual minority stress. For example, lesbian, gay, and bisexual people raised in environments where minority sexual orientations are more highly stigmatized show blunted cortisol responses to social stress (Hatzenbuehler and McLaughlin, 2014). In addition, openness about one's sexual orientation in the workplace is related to higher overall cortisol levels on workdays among sexual minority men (Huebner and Davis, 2005). Further, the glucocorticoid resistance that can occur in response to chronic stress is related to both a failure to downregulate inflammation and a less effective immune response to a viral challenge (Cohen et al., 2012). Inflammation, in turn is an important predictor of other health conditions (e.g., high blood pressure; Chae et al., 2001) as well as greater risk for mortality for HIV-positive individuals (Tien et al., 2010) and among the general population (Kabagambe et al., 2011), while impaired immunity can increase vulnerability to disease. Sexual minority stress may also impact physiology through behavioral pathways, for example sexual minority stress is related to substance use (Hatzenbuehler et al., 2008; McCabe et al., 2010), which also impacts immune and inflammatory response (Cabral, 2006; Carrico et al., 2008; Cole et al., 1998; Pandrea et al., 2010; Sacerdote et al., 2012) and cardiovascular function (Darke et al., 2008; Lange and Hillis, 2001). In sum, while the exact mechanisms need further exploration, existing research on minority stress and chronic stress suggests that minority stress may be related to inflammation, as well as immune and cardiovascular function, which in turn may be related to poorer health outcomes observed among sexual minority people.

Most of the existing research demonstrating associations between sexual minority stress and biological outcomes has been conducted with HIV-positive populations. In the era prior to highly active anti-retroviral therapy, HIV-positive men who concealed their sexual minority status experienced accelerated progression of HIV, including faster progression to AIDS, AIDS mortality, and lower CD4+ T-cell counts (Cole et al., 1996b). Concealment of sexual minority status was also linked to greater likelihood of subsequent cancer or infection (Cole et al., 1996a). Similarly, discomfort with situations in which one's minority sexual orientation could be evident was associated with faster progression to AIDS, AIDS mortality, and lower CD4+ T-cell counts for sexual minority men living with HIV, though less so if one concealed their sexual orientation (Cole et al., 1997). Even after the widespread use of highly active antiretroviral therapy, the experience of victimization due to sexual orientation was shown to be related to greater HIV viral load, and internalized stigma was related to lower CD4+ T-cell counts (Norcini Pala et al., 2015). In the modern era of HIV treatment, studies with those who are receiving effective HIV treatment have the potential to elucidate the biological pathways whereby stress may contribute to inflammation and residual immune dysregulation (Lederman et al., 2013). In sum, the existing research among HIV positive persons supports the hypothesis that minority stress may be related to immune function, while also suggesting that cancer development may be related to minority stress. Inflammation, immune function, cancer, and cardiovascular function are all areas that may be considered in relationship to minority stress, based on previous work on minority stress and the health implications of chronic stress.

Emerging research indicates that our social surroundings, the stressors associated with those environments, and our perceptions of those stressors can change the expression of our genes (Slavich and Cole, 2013), thereby altering complex biological processes. For instance, we know that early adverse childhood experiences can influence subsequent inflammation (Miller and Cole, 2012) and that interpersonal stress (Miller et al., 2009) and social isolation (Cole et al., 2007) are related to expression of genes that drive inflammatory processes. Stress exposure is related to increased expression of pro-inflammatory genes and reduced expression of interferon response genes that are important for coordinating the immune response to novel pathogens (Cole et al., 2011; Slavich and Cole, 2013; i.e., genes that regulate against viral infections). Gene expression may have superior sensitivity in measuring biological stress responses over serum markers, as evidenced by sensitivity to stressors or interventions for stress management when no significant effects were detected in plasma inflammatory markers such as interleukin 6 (IL-6) and C-reactive protein (Creswell et al., 2012; Miller et al., 2009; Murphy et al., 2012). Gene expression may allow us to index responses to stress with greater precision because of the upstream role it plays within the cascade of biological events within the organism. Assessment of gene expression is a promising approach for tracking the impact of psychological stress on health as it is capable of measuring both biological responses to adversity (Slavich and Cole, 2013), and the reversal of those responses through interventions (Antoni et al., 2012; Black et al., 2013; Creswell et al., 2012).

The purpose of this exploratory study is to identify if sexual minority stress is related to differential expression of genes. Consistent with previous research and the minority stress model, genes implicated in inflammatory processes, immune function, cancer, and cardiovascular risk were examined. This model was tested within sexual minority men living with HIV who were receiving effective treatment for HIV, as the potentially deleterious effects of minority stress may be most evident in this population. We hypothesized that the association of minority stress with leukocyte gene expression would be independent of recent stimulant use.

## 2. Methods

Sexual minority men living with HIV with recent biologically verified methamphetamine use (verified through urine or hair toxicology testing) were recruited from substance abuse treatment programs, HIV medical clinics, AIDS service organizations, the community, and referrals from other participants. Data collected for this study were collected at the baseline visit of a randomized controlled trial and were collected prior to randomization. Participants met with study staff to provide informed consent, which included specific consent for blood specimen banking and analysis of gene expression. Inclusion criteria were: 1) 18 years of age or older; 2) identify as gay or bisexual or are sexually active with men (i.e., sexual minority); 3) provide documentation of HIV-positive serostatus; and 4) provide a urine or hair (only collected for those whose urine toxicology was negative) sample that is reactive for methamphetamine at the screening visit, which occurred prior to the baseline visit described here. Participants were selected for this substudy to undergo RNA sequencing if they were on anti-retroviral treatment (ART), had viral load <200 copies per mL, and completed measures of sexual minority stress.

At the baseline visit, enrolled participants completed a battery of psychosocial measures, provided an additional urine sample

for on-site toxicology testing to index recent (~72 h) stimulant use, and provided a peripheral venous blood sample collected in two 2.5 mL PAXgene® vacutainers (Qiagen, Inc.) for gene expression analyses and in vacutainers containing the preservative EDTA to measure HIV disease markers and for specimen banking. This study was approved by the Institutional Review Boards for the University of California, San Francisco, University of Miami, and Northwestern University. A certificate of confidentiality was obtained from the National Institute on Drug Abuse.

### 2.1. Measures

#### 2.1.1. Demographics, health and psychiatric status, and HIV markers.

Participants completed a demographic questionnaire assessing age, race, ethnicity, and health-related factors such as current HIV medication regimen. The Addiction Severity Index (ASI) was used to measure severity of drug and alcohol use (McLellan et al., 1992). The 20-item Centers for Epidemologic Studies Depression Scale (CES-D) measured depression (Radloff, 1977). Possible Post Traumatic Stress Disorder (PTSD) was assessed using the PTSD Checklist-Civilian Version (PCL-C; Wilkins et al., 2011). The Abbott Real Time HIV-1 assay (Abbott Molecular, Inc.; Des Plaines, IL), with a lower limit of detection of 40 copies/mL was used to assess HIV viral load. CD4 + T-cell count was assessed by Quest Diagnostics using a clinical assay.

#### 2.1.2. Sexual minority Stress.

Sexual minority stress was measured using the five-item sexual minority stress subscale of the Cultural Assessment of Risk for Suicide (CARS) scale (Chu et al., 2013), which is validated for use with sexual minority people. This subscale captures distress related to sexual minority stress, and includes items that reference constructs of concealment, internalized stigma, and rejection from others. For example one item on this scale referencing concealment is "The decision to hide or reveal my sexual or gender orientation to others causes me significant distress," while an item referencing rejection and stigma is "I was rejected by a family member or friend after telling him/her my sexual or gender orientation." Each item of the CARS is rated on a scale from 1 to 6, ranging from "strongly disagree" to "strongly agree." Scores were calculated as specified within the CARS manual by summing the five items, with one item reverse coded (Chu et al., 2013b). The sexual minority stress subscale of the CARS was validated in the context of the relationship between minority stress and suicidality (Chu et al., 2013), and cutoff scores were created to determine the level of clinical concern based on responses to the CARS items (Chu et al., 2013b). Cutoff scores were derived based on the relationships between these cutoff scores and increased risk of suicidal ideation, suicide attempts, and hopelessness (Chu et al., 2013b). Within this sample, internal consistency of this scale was 0.71. Participants were divided into low and high sexual minority stress groups using cutoff scores deemed to be of clinical concern according to the CARS manual: $\leq$13, corresponding to "minimal stress" and $\geq$14, corresponding to "moderate" or "severe" stress (Chu et al., 2013b).

#### 2.1.3. On-site urine screening.

On-site toxicology screening using iCup (Redwood Biotech, Inc., Santa Rosa, CA) was conducted on urine samples. This was used to identify individuals who had used methamphetamine or cocaine in the previous ~72 h.

#### 2.1.4. Pro-inflammatory cytokines in plasma.

Plasma levels of tumor necrosis factor-alpha (TNF-α) and IL-6 were examined within this study. IL-6 was selected due to its relationship with stress and mortality (Papanicolaou, 1998), and because IL-6 is associated with mortality specifically among persons living with HIV (Kuller et al., 2008). TNF-α was selected because both TNF-α and IL-6 monocyte expression can be altered by stimulant (i.e., cocaine) use (Irwin et al., 2007). TNF-α and IL-6 levels were obtained via undiluted plasma samples using the Human Quantikine Immunoassay (R&D Systems, Minneapolis, MN). Results were $\log_{10}$ transformed prior to use in analysis.

### 2.2. RNA sample preparation, sequencing, and analysis

#### 2.2.1. Sample preparation and sequencing.

Total RNA was isolated from samples in PAXgene tubes using the PAXgene blood miRNA kit (Qiagen). Library preparation and sequencing was done by a Core Facility, the Vincent J. Coates Genomics Sequencing Laboratory at the University of California, Berkeley. Ribosomal RNA was reduced using Ribo-Zero (Illumina Inc., San Diego, CA). RNAs were then prepared for Illumina sequencing on an Apollo 324™ with PrepX™ RNAseq Library Prep reagents (WaferGen Biosystems, Fremont, CA) following the manufacturer's protocol. Thirteen cycles of PCR amplification were used for single 6 base pair index addition and library fragment enrichment. Prepared libraries were then quantified on a Roche LightCycler 480II (Roche Diagnostics Corp., Indianapolis, IN) using KAPA Illumina library quantitative PCR reagents (Roche Diagnostics Corp., Indianapolis, IN). Sequencing was done on an Illumina HiSeq 4000 apparatus (Illumina Inc., San Diego, CA). RNA-sequencing as a methodology has been validated against other methodologies in multiple studies (see Fang and Cui, 2011 for a discussion or Marioni et al., 2008 for previous validation).

In total, 72 samples were sequenced across 8 lanes, including 10 technical replicates, for a total of 62 unique samples from 62 different participants. Of these 62 participants, 39 had completed measures of minority stress, with 38 of these eligible for inclusion in the analyses in this study. Nine samples were multiplexed per lane for 100 cycles of paired end reads with a 1% PhiX v3 control library spike in (Illumina Inc., San Diego, CA). Post-sequencing basecall files (bclfiles) were demultiplexed and converted into FASTQ file format using the bcl2fastq v2.17 software (Illumina Inc., San Diego, CA). Specific data processing procedures are outlined in Supplemental Materials (S1). One sample from each replicate pair was excluded using a coin-flip. Data exploration was performed with multi-dimensional scaling (MDS) plots for all samples, and was used to identify potential batch effects due to technical artifacts (e.g., RNA quality, processing laboratory, technician, sequencing lane).

RNA-sequencing measurement of gene expression has been found to be a reliable and reproducible technology, with the measurement of relative expression levels in high agreement with qPCR and microarrays (Su et al., 2014). To evaluate the reproducibility of our measurements (Allison et al., 2006), the 10 technical replicates were generated from independent library preparations and sequenced in different lanes (Fang and Cui, 2011). The reliability of the sequencing data was evaluated through alignment performance and MDS plots between replicate pairs. The reproducibility of replicate count estimates was evaluated by Pearson correlation.

### 2.3. Statistical analyses

Chi-square analyses and t-tests were used to examine differences in demographic and clinical characteristics between low and high sexual minority stress groups, including: age, time since HIV diagnosis, CD4+ T-cell count, number of days in the past 30 that methamphetamine was used, severity of drug use, severity of alcohol use, depression (both continuous and using cutoff scores of $\geq$16 consistent with a widely used clinical cutoff for depression,

Vilagut et al., 2016), PTSD symptoms, sexual orientation, race, proportion on different ART regimens, proportion with undetectable HIV viral load (<40 copies/mL), and toxicology that was positive or negative for stimulants. Differences in these demographic and clinical characteristics were also examined between participants who had RNA sequenced who had received minority stress measures and those who had participated in the study before these measures were integrated into the protocol. T-tests were used to examine differences in $\log_{10}$ transformed plasma levels of TNF-α and IL-6 by low and high sexual minority stress. Levels of TNF-α and IL-6 are reported here to identify if results of gene expression assays that pertain to inflammation are also observed in plasma. Differential expression was examined using a variance modeling strategy in edgeR to address the over-dispersion observed in gene expression count data (Landau and Liu, 2013), which performs well relative to other strategies (Rapaport et al., 2013; Soneson and Delorenzi, 2013). Our workflow for this project was based on best practices previously described in detail elsewhere (Anders et al., 2013; Love et al., 2015). General linear models were used to estimate overall, gene-wise, and tag-wise dispersion, using the Cox-Reid-adjusted likelihood method (Cox and Reid, 1987; McCarthy et al., 2012). Negative-binomial generalized linear models (GLMs) were fit for each gene examining differences by high and low minority stress groups, and accounting for urine toxicology positive or negative for stimulants. Gene identifiers were annotated with Entrez gene IDs and names were annotated using the HUGO Gene Nomenclature Committee database ("HGNC database of human gene names | HUGO Gene Nomenclature Committee," n. d.). Surrogate variable analysis was used to capture unspecified heterogeneity (Leek et al., 2012), and surrogate variables were retained unless highly correlated with the sexual minority stress phenotype ($p < .10$). Likelihood ratio tests were used to test differences between the high and low minority stress groups. The Benjamini-Hochberg procedure was used to estimate the false discovery rate (FDR) with an FDR cut-off of 0.10.

Gene set or pathway analyses, examining differences in perturbations among groups of genes were completed using Generally Applicable Gene-set Enrichment (GAGE, Luo et al., 2009b), using a competitive method to identify if a given pathway of interest is differentially expressed more often between high and low minority stress groups when compared to a complementary set of genes (Emmert-Streib and Glazko, 2011; Goeman and Bühlmann, 2007) using an FDR cutoff of 0.10. Additional gene set analyses were conducted using signaling pathway impact analysis (SPIA, Tarca et al., 2009) to identify purturbations in a biological pathway considering both the level of differential expression of individual genes as well as the topology of the pathway. The Kyoto Encyclopedia of Genes and Genomes (Kanehisa et al., 2011; KEGG: Kyoto Encyclopedia of Genes and Genomes, n.d.) database was used to define gene sets.

Once results were obtained, existing research on each of the differentially expressed genes was reviewed for relevance to the hypothesized mechanisms of inflammation, immune function, cancer, or cardiovascular function. Pathways were categorized for potential relationships to each of these hypothesized mechanisms.

## 3. Results

### 3.1. Participants

Thirty-eight of 62 participants met all eligibility criteria and had RNA sequencing data available for analysis. The current study utilized data from the 39 participants who completed minority stress measures; the 23 participants lacking minority stress measures were enrolled prior to the integration of these measures into the study protocol. There were no differences in demographic or clinical characteristics among those who underwent RNA sequencing who received or did not receive minority stress measures, with the exception that participants who received minority stress measures were more likely to have a higher CD4+ T-cell count ($M$ = 730) than those who did not ($M$ = 474, $p < .001$). One additional sample was removed from the 39 who had sequencing data because the participant's viral load was greater that 200 copies per mL, thus they did not meet our inclusion criteria, for a total of 38 participants within this study. Of the 38 participants, 20 were designated low sexual minority stress and 18 were designated high sexual minority stress. There were no differences between low versus high minority stress groups on age, time since HIV diagnosis, CD4+ T-cell count, number of days within the past 30 that methamphetamine was used, drug or alcohol use severity, depression, PTSD symptoms, sexual orientation, race/ethnicity, proportion with undetectable viral load, proportion on different ART regimens, or proportion with a positive urine toxicology screen for stimulants. There were no differences in plasma levels of TNF-α and IL-6 in the low versus high minority stress groups. Participant demographic information and $p$-values of chi-square analyses and t-tests of demographic and clinical variables by low and high minority stress groups are found in Table 1.

### 3.2. Gene expression results

Mean RNA integrity numbers were 7.2 (range 6.3–9.1). High replicability was supported with clustering of technical replicates in MDS plots and with mean within-replicate Pearson correlations coefficients of 0.999 between technical replicates across different lanes. After filtering out genes that were lowly expressed within the sample (<1 count per million in 10 of the samples), 19,541 genes remained for consideration. Mean library size was 14,020,862 after filtering. Eight surrogate variables were found, 7 were used in modeling, with the remaining 1 removed from models due to high correlation with sexual minority stress groupings.

### 3.3. Differential gene expression

In total, 90 genes were differentially expressed at an FDR of 0.10. Of these 90 genes, 69 were upregulated and 21 were downregulated. Genes differentially expressed at an FDR of 0.10 with suspected relevance to inflammation or the biological functions that were shown to be previously related to sexual minority stress (i.e., immune function, cancer, or cardiovascular function; 41 genes in total), are listed in Table 2. The complete list of genes is available within Supplementary Materials (S2).

### 3.4. Pathway analysis

In GAGE analysis, there were 138 two-directional perturbed gene sets. A comprehensive list of two-directional perturbed pathways is included as a Supplementary Material (S3). Selected 2 directional pathways that are related to inflammation or previously observed relationships between sexual minority stress and biological function (i.e., immune function, cancer, cardiovascular) are listed in Table 3. Of note, as can be seen in Supplementary Materials, metabolic pathways from the KEGG database emerged frequently in two directional perturbation gene set analyses. SPIA analysis found one significant pathway: the neuroactive ligand-receptor interaction (KEGG ID: 04080), which was activated in the high sexual minority stress group ($p_{GFDR} = 0.008$). The significance of this pathway was driven by perturbation ($p_{pert} = 0.000005$), and not an enrichment of the number of differentially expressed genes ($p_{NDE} = 0.97$). This pathway was also detected in 2 dimensional perturbation analyses using GAGE ($q = 0.0000007$).

**Table 1**
Demographic information and clinical characteristics of 38 sexual minority men living with HIV by low and high minority stress.

| | Low sexual minority stress ($n$ = 20) | High sexual minority stress ($n$ = 18) | Difference, $p$ |
|---|---|---|---|
| | *M (SD)* | *M (SD)* | |
| Age | 41.6 (8.2) | 46.0 (5.3) | 0.06 |
| Time since HIV diagnosis | 13.8 (8.4) | 12.9 (8.2) | 0.73 |
| CD4+ T-cell count (cells/mm$^3$) | 708.3 (273.6) | 780.4 (280.3) | 0.43 |
| Methamphetamine use days (past 30 days) | 5.0 (6.5) | 8.1 (8.8) | 0.22 |
| ASI drug score | 0.1 (0.1) | 0.2 (0.1) | 0.10 |
| ASI alcohol score | 0.1 (0.1) | 0.2 (0.1) | 0.48 |
| CES-D depression | 22.6 (13.7) | 28.7 (11.8) | 0.15 |
| PCL-C PTSD | 48.4 (15.0) | 52.2 (13.0) | 0.41 |
| $Log_{10}$ interleukin-6 (IL-6) | 0.3 (0.3) | 0.4 (0.3) | 0.29 |
| $Log_{10}$ tumor necrosis factor – alpha (TNF-$\alpha$) | 1.7 (0.2) | 1.7 (0.2) | 0.96 |
| | *n* (%) | *n* (%) | |
| Sexual orientation | | | 0.40 |
| Gay | 17 (85.0%) | 14 (77.8%) | |
| Bisexual | 2 (10.0%) | 4 (22.2%) | |
| Heterosexual | 1 (5.0%) | 0 (0.0%) | |
| Race/ethnicity | | | 0.32 |
| Asian | 0 (0.0%) | 1 (5.6%) | |
| African American/ Black | 2 (10.0%) | 2 (11.1%) | |
| Hispanic/Latino | 3 (15.0%) | 6 (33.3%) | |
| Multiracial | 2 (10.0%) | 3 (16.7%) | |
| White | 13 (65.0%) | 6 (33.3%) | |
| ART Regimen | | | 0.06 |
| INSTI & NRTI | 3 (15.8%) | 8 (50.0%) | |
| Boosted PI & NRTI | 6 (31.6%) | 2 (12.5%) | |
| NNRTI & NRTI | 5 (26.3%) | 6 (37.5%) | |
| Other HAART | 4 (21.0%) | 0 (0.0%) | |
| No HAART | 1 (5.3%) | 0 (0.0%) | |
| Undetectable HIV viral load (<40 copies/mL) | 16 (80.0%) | 14 (77.8%) | 0.87 |
| Urine positive for stimulants | 8 (40.0%) | 12 (66.7%) | 0.10 |

*Abbreviations:* ART = antiretroviral therapy; ASI = Addiction Severity Index; CES-D = Center for the Epidemiologic Study -Depression Scale; HAART = highly active antiretroviral therapy; INSTI = integrase strand transfer inhibitor; M = mean; NNRTI = non-nucleoside reverse transcriptase inhibitor; NRTI = nucleoside reverse transcriptase inhibitor; PCL-C = PTSD Checklist – Civilian Version; PI = protease inhibitor; PTSD = post traumatic stress disorder; SD = standard deviation.

## 4. Discussion

This study found that sexual minority stress is related to differential expression of individual genes and pathways in leukocytes that are implicated in inflammation, immune function, cancer, and cardiovascular function. In total, 90 single genes were differentially expressed at an FDR of <0.10, of which 41 are related to hypothesized mechanisms underlying minority stress: inflammation, immune function, cancer, and cardiovascular function. Notably, these relationships between minority stress and differential gene expression were observed after controlling for recent stimulant use. Furthermore, 138 pathways evidenced 2-directional perturbation, 35 of which are related to hypothesized mechanisms. The neuroactive ligand receptor interaction pathway was identified through both enrichment pathway analysis and perturbation analysis, driven by multiple genes evidencing perturbation on this pathway. These results add to the emerging body of research that has identified relationships between minority stress and biological functioning (e.g., Cole et al., 1996a,b; Frost et al., 2015; Huebner

**Table 2**
Selected differentially expressed genes (FDR < 0.10) between low and high sexual minority stress groups (N = 38 sexual minority men living with HIV) grouped by potential biological relevance to inflammation, immune function, cancer, or cardiovascular function, and including citations that suggested this biological relevance.

| Function | Gene[a] | Log fold difference | FDR adjusted p value |
|---|---|---|---|
| Inflammation | | | |
| | BTLA (Bekiaris et al., 2013; Otsuki et al., 2006) | 0.582 | 0.062 |
| | PLCB2 (Mao et al., 2016) | −0.357 | 0.076 |
| Immune | | | |
| | GZMA (Müllbacher et al., 1999) | 0.828 | 0.050 |
| | CD69 (Sancho et al., 2005) | 0.798 | 0.072 |
| | CLEC4E (Behler-Janbeck et al., 2016; Kottom et al., 2017) | −0.576 | 0.083 |
| | KLRB1 (Llibre et al., 2016) | 0.569 | 0.098 |
| | PPP1R12C (Dutheil et al., 2014) | −0.384 | 0.088 |
| Cancer | | | |
| | ZNF426 (Yang et al., 2009; Yang and Wood, 2007) | 0.480 | 0.006 |
| | RPS15A (Chen et al., 2016; Yao et al., 2016) | 1.011 | 0.050 |
| | CACNA1E (Natrajan et al., 2006) | −1.056 | 0.050 |
| | TRIM2 (Chen et al., 2015; Panaccione et al., 2017) | 1.230 | 0.050 |
| | RPL9 (Baik et al., 2016) | 1.305 | 0.050 |
| | ERH (Schmitt et al., 1999; Weng and Luo, 2013) | 0.676 | 0.053 |
| | SKIL (Annala et al., 2015; Hagerstrand et al., 2013; Shinozuka et al., 2013; Zhu et al., 2016) | 0.476 | 0.053 |
| | RPS21 (Arthurs et al., 2017) | 0.763 | 0.053 |
| | PRR14 (Yang et al., 2016) | −0.584 | 0.057 |
| | BIRC3 (Wang et al., 2016, 2017; Yamato et al., 2015) | 0.602 | 0.062 |
| | RPS7 (Zhang et al., 2016) | 1.028 | 0.062 |
| | RPL35A (Oliver et al., 2017) | 0.578 | 0.064 |
| | JDP2 (Chen et al., 2017; Yuanhong et al., 2010) | −0.493 | 0.076 |
| | SNRPF (Sun et al., 2016) | 0.761 | 0.076 |
| | RPL23 (Wu et al., 2012) | 0.897 | 0.076 |
| | EIF5A2 (Li et al., 2014a; Luo et al., 2009a; Meng et al., 2015) | 0.694 | 0.076 |
| | ANKRD46 (Cheng et al., 2012) | 0.498 | 0.076 |
| | ANXA2R (D'Souza et al., 2012; Shiozawa et al., 2008) | 0.450 | 0.076 |
| | CA1 (Zheng et al., 2015) | 0.727 | 0.076 |
| | SP2 (Phan et al., 2004; Zhao et al., 2014) | −0.939 | 0.076 |
| | PSMD10 (Fu et al., 2002; Meng et al., 2010; Qin et al., 2016) | 0.435 | 0.077 |
| | MAPKAPK5-AS1 (Zhang et al., 2015) | 0.500 | 0.083 |
| | RPS14 (Ebert et al., 2008; Wang et al., 2014) | 0.589 | 0.083 |
| | EIF3E (Grzmil et al., 2010; Li et al., 2014a,b) | 0.474 | 0.083 |
| | RPL31 (Maruyama et al., 2014) | 1.077 | 0.083 |
| | UGCG (Liu et al., 2011a,b) | 0.345 | 0.083 |
| | ZDHHC2 (Peng et al., 2014; Yan et al., 2013) | 0.420 | 0.083 |
| | USP45 (Perez-Oliva et al., 2015) | 0.393 | 0.083 |
| | NUDCD1(Jin et al., 2008; Rao et al., 2014) | 0.643 | 0.087 |
| | RPS20 (De Bortoli et al., 2006; Yong et al., 2015) | 0.545 | 0.089 |
| | PHF14 (Zhang et al., 2017) | 0.367 | 0.089 |
| | FANCM (Alix-Panabières et al., 2017; Matta et al., 2013) | 0.449 | 0.089 |
| Cardiovascular | | | |
| | AKAP7 (O'Connell et al., 2017) | 0.599 | 0.077 |
| | ZNF260 (Komati et al., 2011) | 0.677 | 0.083 |

[a] Gene name is accompanied by references relating it to this biological process or function. References were included irrespective of tissue or direction of relationship with biological process or function.

**Table 3**
Selected gene sets identified in GAGE analysis to have 2 dimensional perturbation below an FDR < 0.10 between low and high sexual minority stress groups in 38 sexual minority men living with HIV with potential relevance to inflammation or observed health disparities among sexual minority people or biological outcomes previously related to minority stress (e.g., cardiovascular risk, inflammation, HIV progression, cancer, or infection/immune).

| Function | Database and ID | Name | q value |
|---|---|---|---|
| Inflammation | | | |
| | KEGG 04060 | Cytokine-cytokine receptor interaction | $9.87^{-07}$ |
| | KEGG 04062 | Chemokine signaling pathway | $2.36^{-05}$ |
| | KEGG 05322 | Systemic lupus erythematosus | 0.0008 |
| | KEGG 04610 | Complement and coagulation cascades | 0.001 |
| | KEGG 04514 | Cell adhesion molecules | 0.004 |
| | KEGG 04620 | Toll-like receptor signaling pathway | 0.006 |
| | KEGG 04940 | Type I diabetes mellitus | 0.006 |
| | KEGG 05310 | Asthma | 0.010 |
| | KEGG 05332 | Graft-versus-host disease | 0.010 |
| | KEGG 05145 | Toxoplasmosis | 0.013 |
| | KEGG 04145 | Phagosome | 0.019 |
| | KEGG 04664 | Fc epsilon RI signaling pathway | 0.021 |
| | KEGG 04670 | Leukocyte transenothelial migration | 0.025 |
| Immune | | | |
| | KEGG 04650 | Natural killer cell mediated cytotoxicity | $5.57^{-05}$ |
| | KEGG 05150 | Staphylococcus aureus infection | 0.003 |
| | KEGG 04660 | T cell receptor signaling pathway | 0.015 |
| Cancer | | | |
| | KEGG 04080 | Neuroactive ligand-receptor interaction | $6.58^{-07}$ |
| | KEGG 05200 | Pathways in cancer | $1.50^{-05}$ |
| | KEGG 05211 | Renal cell carcinoma | 0.005 |
| | KEGG 05219 | Bladder cancer | 0.013 |
| | KEGG 05221 | Acute myeloid leukemia | 0.016 |
| | KEGG 05222 | Small cell lung cancer | 0.016 |
| | KEGG 05223 | Non-small cell lung cancer | 0.017 |
| | KEGG 05212 | Pancreatic cancer | 0.037 |
| Cardiovascular | | | |
| | KEGG 04260 | Cardiac muscle contraction | 0.0003 |
| | KEGG 04270 | Vascular smooth muscle contraction | 0.005 |
| | KEGG 04614 | Renin-angiotensin system | 0.013 |
| | KEGG 05414 | Dilated cardiomyopathy | 0.013 |

and Davis, 2005) and suggest that continued investigation of these relationships is warranted. In this study, the approach employed to assess differential gene expression and pathway analysis builds on prior studies, which examined the relationship between sexual minority stress and HIV progression and mortality, cancer or infection, and cortisol. This study provides a first step in exploring the biological processes whereby sexual minority stress may influence the health of sexual minority people.

Relevant to the health and immune function of individuals living with HIV, this study found that 7 genes and 16 pathways related to inflammation or immune functioning were differentially expressed between low and high minority stress groups. For example, the differentially expressed genes include *BTLA*, whose proteins are associated with homeostasis of inflammatory responses within cells (Bekiaris et al., 2013), *KLRB1*, which inhibits natural killer cell cytotoxicity, and *CD69*, which has a role in the regulation of immune function and inflammation (Sancho et al., 2005). Interestingly, although we found differential perturbation in the cytokine-cytokine receptor interaction pathway (KEGG 04060) of which *TNF* and *IL-6* are members, and that TNF-α and IL-6 are common inflammatory markers, we did not see a difference between groups in the levels of either in plasma or in gene expression. The relationship between circulating cytokines and gene expression is not always consistent, as some studies have observed differences in circulating cytokines when no difference was observed in gene expression (Moldoveanu et al., 2000), while other studies have, similar to the study reported here, found evidence for differences in gene expression related to inflammation when no differences were observed in circulating cytokines such as IL-6 (Creswell et al., 2012; Miller et al., 2009; Murphy et al., 2012). Moreover, *de novo* gene expression is but one of several means of regulation (e.g., sequestration of proteins in complexes such as inflammaosomes) and thus differences in gene expression may not immediately result in differences in protein levels and vice versa. Finally, given that circulating cytokines can be impacted by multiple factors (e.g., co-occurring mental illness, Hoge et al., 2009; Schiepers et al., 2005, or viral infection, Yu et al., 2011), a larger sample size may be required to detect differences in circulating cytokines in relation to minority stress. This supports the hypothesis that although immune function and inflammation are associated with minority stress, a broader set of biomarkers should be investigated in future studies. While these results corroborate previous research that has found a relationship between minority stress and HIV related outcomes such as faster progression to AIDS, AIDS mortality, and lower CD4 T-cell count (Cole et al., 1997; Pala et al., 2015), more research is needed to elucidate the specific mechanisms by which minority stress may be related to poorer HIV outcomes. Our results suggest that dysregulation of the immune and inflammatory systems could be a potential area for further investigation.

This study found that between low and high sexual minority stress groups, 32 differentially expressed genes and 8 perturbed pathways were related to cancer. These results corroborate work which previously found a relationship between minority stress and development of cancer (Cole et al., 1996a). To appropriately contextualize these results, it is important to note that we included genes related to cancer irrespective of their tissue of origin or the directionality of this relationship. Furthermore these results may in part be biased by the amount of cancer research that is reflected in the literature; while many genes are being documented as related to cancer development (e.g., cell survival and proliferation, biological functions which exist outside of cancer), their roles are likely more complex than solely based on their contribution to cancer pathogenesis. In time our understanding of the complex networks of cancer development will have greater specificity. In the meantime, we observed differential expression of genes related to cancer development of viral origins, such as *ZNF426* (Yang et al., 2009; Yang and Wood, 2007), which is important to the replication of Kaposi's sarcoma associated herpes virus, and those that have been shown to be related to cancer development (e.g., *SKIL*, Annala et al., 2015; Hagerstrand et al., 2013; Shinozuka et al., 2013; Zhu et al., 2016) or aggressiveness (e.g. *EIF5A2*, Li et al., 2014a,b; Luo et al., 2009a,b; Meng et al., 2015). Notably, the relationship observed in this study between minority stress and differential expression of *ZNF426* support prior research that illustrated the role of autonomic nervous system activity in the reactivation of Kaposi's sarcoma associated herpes virus (Chang et al., 2005). The neuroactive-ligand receptor interaction (KEGG ID: 04080) also appears to be associated with cancer (e.g., Fang et al., 2013; Liu et al., 2015; Wei et al., 2015; Wei et al., 2012), though this pathway has also been associated with other phenomena (e.g., chronic fatigue syndrome as in Fang et al., 2006, or viral infection as in Huang et al., 2008). Of note, the measure of minority stress that we used within this study likely detects persistent minority stress, as opposed to acute minority stress (e.g., exposure to a single instance of discrimination), and it is likewise expected that greater cancer risk would be conferred over time rather than through acute exposure. More research is needed to understand the specific cascade of biological events that may result after acute exposure to sexual minority stressors, through prolonged exposure to minority stressors, and to understand if those responses can be modified through interventions.

The genes and pathways documented here in relationship to minority stress warrant replication in order to further refine which genes would be most useful as outcomes in future studies examining minority stress or interventions to reduce the impacts of this unique, pernicious form of stress. Future research is needed to validate the candidate genes identified in this study in an independent sample of participants. The genes and pathways identified here and in replication studies could function as outcomes within studies examining the efficacy of cognitive or behavioral interventions intended to reduce the deleterious impacts of minority stress. These genes or pathways may even be considered as measures that could enable titration or adjustment of these interventions (e.g., changes in the expression of these genes would indicate efficacy, while lack of change would warrant adjustment of the intervention).

While unable to examine it here, the complex paths by which sexual minority stress and its relationship with gene expression may interact with psychological processes such as rumination, hopelessness, or self-schemas (i.e., expansion of work by Hatzenbuehler, 2009) is an important area of future research. Within this model, it is anticipated that gene expression, as an active biological process responsible for the biological behavior of the organism, may both be impacted by and reciprocally impact these psychological processes. In addition to psychological processes, behavioral processes associated with sexual minority stress (e.g., smoking or substance use, Livingston et al., 2017) are important to consider. Additionally, social processes which may impact biological functioning (e.g., childhood adversity, Miller and Cole, 2012, or social isolation, Cole et al., 2007) and may have reciprocal relationships with minority stress (e.g., the higher rates of childhood victimization reported among sexual minority people, Friedman et al., 2011) will also be important to consider within this model. Identifying ways in which the response to sexual minority stressors may impact subsequent biological functioning will be an important area for future research. Sexual minority stress was considered here while controlling for recent stimulant use. As sexual minority stress is predictive of substance use (Hatzenbuehler et al., 2008; Livingston et al., 2017), additional studies with larger samples are needed to examine whether or not there is a mediating or moderating effect for substance use in the relationship between sexual minority stress and expression of genes on these pathways. Of note, none of the differentially expressed genes reported here overlapped with those found to be related to stimulant use in a companion paper resulting from this project, which suggests that the relationship between sexual minority stress and gene expression may be unique and not a direct result of stimulant use. Future research is also needed to examine if these same candidate genes or pathways are responsive to stress in general, and sexual minority stress in particular, and whether or not these patterns of gene expression may be modified through intervention, either through modification of health behaviors or by targeting the stress directly.

There are limitations to consider in contextualizing these results and considering future directions for research. First, this study was within individuals who had used methamphetamine recently, though not all participants had used methamphetamine or other stimulants in the days preceding the study visit. Stimulant use that had occurred in the days just prior to the study visit was biologically confirmed via urinalysis within this sample, and we controlled for this variable within analysis to control for the effects of stimulants. This study was also conducted among sexual minority men living with HIV, and the effects among people living with HIV may be more robust than effects among persons who are living without a co-occurring disease process. Much of the literature to date that has documented a relationship between minority stress and biological functioning appears to be among individuals with HIV, and it remains unknown if that is because people living with HIV are generally more studied, or if it is because the same relationships have not been observed among individuals who do not have HIV.

This study did not account for important medical comorbidities that could be occurring among people living with HIV, though the lack of observed differences in CD4 T cell count and IL-6 levels suggests relatively comparable health status of the high and low minority stress groups. Comorbidities can be particularly deleterious for health among those living with HIV and are linked to greater risk of morbidity (Lohse et al., 2011; Rodriguez-Penney et al., 2013). These comorbidities should be accounted for in subsequent research. Given the modest size of the sample, it is likely that additional differences in gene expression and circulating cytokines were not identified (i.e., false negatives). This study consisted only of men who were assigned birth sex of male; future work should examine the relationship between minority stress and expression of genes among sexual minority women and gender minority people. For example, sexual minority women are at greater risk for being overweight or obese (Boehmer et al., 2007) suggesting that biological pathways between stress related to sexual minority status and health may be different (e.g., metabolic) among this population. This study also focused solely on minority stress, while future work should explore the complex relationships between minority stress and other psychosocial factors that may be related to both gene expression and minority stress such as childhood adversity and social isolation. This study included sexual minority men irrespective of their sexual identity. Sexual minority stressors may be uniquely experienced by sexual minority men who identify as heterosexual (as one did in this study).

In conclusion, our study is among the first to observe a relationship between sexual minority stress and differential expression of single genes as well as sets of genes that are functionally related to inflammation, immune function, cancer, and cardiovascular function. Our results suggest several potential biological pathways for future work investigating the relationship between sexual minority stress and health.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bbi.2018.03.016.

## References

Alix-Panabières, C., Cayrefourcq, L., Mazard, T., Maudelonde, T., Assenat, E., Assou, S., 2017. Molecular Portrait of Metastasis-Competent Circulating Tumor Cells in

Colon Cancer Reveals the Crucial Role of Genes Regulating Energy Metabolism and DNA Repair. Clin. Chem. 63 (3), 700–713. https://doi.org/10.1373/clinchem.2016.263582.
Allison, D.B., Cui, X., Page, G.P., Sabripour, M., 2006. Microarray data analysis: from disarray to consolidation and consensus. Nat. Rev. Genet. 7 (1), 55.
Anders, S., McCarthy, D.J., Chen, Y., Okoniewski, M., Smyth, G.K., Huber, W., Robinson, M.D., 2013. Count-based differential expression analysis of RNA sequencing data using R and Bioconductor. ArXiv Preprint ArXiv:1302.3685. Retrieved from https://arxiv.org/abs/1302.3685
Annala, M., Kivinummi, K., Tuominen, J., Karakurt, S., Granberg, K., Latonen, L., et al., 2015. Recurrent SKIL-activating rearrangements in ETS-negative prostate cancer. Oncotarget 6 (8), 6235–6250. https://doi.org/10.18632/oncotarget.3359.
Antoni, M.H., Lutgendorf, S.K., Blomberg, B., Carver, C.S., Lechner, S., Diaz, A., et al., 2012. Cognitive-behavioral stress management reverses anxiety-related leukocyte transcriptional dynamics. Biol. Psychiatry 71 (4), 366–372.
Arthurs, C., Murtaza, B.N., Thomson, C., Dickens, K., Henrique, R., Patel, H.R.H., et al., 2017. Expression of ribosomal proteins in normal and cancerous human prostate tissue. PloS One 12 (10), e0186047. https://doi.org/10.1371/journal.pone.0186047.
Baik, I.H., Jo, G.-H., Seo, D., Ko, M.J., Cho, C.H., Lee, M.G., Lee, Y.-H., 2016. Knockdown of RPL9 expression inhibits colorectal carcinoma growth via the inactivation of Id-1/NF-κB signaling axis. Int. J. Oncol. 49 (5), 1953–1962. https://doi.org/10.3892/ijo.2016.3688.
Behler-Janbeck, F., Takano, T., Maus, R., Stolper, J., Jonigk, D., Tort Tarrés, M., et al., 2016. C-type Lectin Mincle Recognizes Glucosyl-diacylglycerol of Streptococcus pneumoniae and Plays a Protective Role in Pneumococcal Pneumonia. PLoS Pathog. 12 (12), e1006038. https://doi.org/10.1371/journal.ppat.1006038.
Bekiaris, V., Šedý, J.R., Macauley, M.G., Rhode-Kurnow, A., Ware, C.F., 2013. The inhibitory receptor BTLA controls γδ T cell homeostasis and inflammatory responses. Immunity 39 (6), 1082–1094. https://doi.org/10.1016/j.immuni.2013.10.017.
Black, D.S., Cole, S.W., Irwin, M.R., Breen, E., Cyr, N.M.S., Nazarian, N., et al., 2013. Yogic meditation reverses NF-κB and IRF-related transcriptome dynamics in leukocytes of family dementia caregivers in a randomized controlled trial. Psychoneuroendocrinology 38 (3), 348–355.
Boehmer, U., Bowen, D.J., Bauer, G.R., 2007. Overweight and obesity in sexual-minority women: evidence from population-based data. Am. J. Public Health 97 (6), 1134–1140. https://doi.org/10.2105/AJPH.2006.088419.
Cabral, G.A., 2006. Drugs of abuse, immune modulation, and AIDS. J. Neuroimmune Pharmacol. 1 (3), 280–295. https://doi.org/10.1007/s11481-006-9023-5.
Carrico, A.W., Johnson, M.O., Morin, S.F., Remien, R.H., Riley, E.D., Hecht, F.M., Fuchs, D., 2008. Stimulant use is associated with immune activation and depleted tryptophan among HIV-positive persons on anti-retroviral therapy. Brain Behav. Immun. 22 (8), 1257–1262.
Chae, C.U., Lee, R.T., Rifai, N., Ridker, P.M., 2001. Blood Pressure and Inflammation in Apparently Healthy Men. Hypertension 38 (3), 399–403. https://doi.org/10.1161/01.HYP.38.3.399.
Chang, M., Brown, H.J., Collado-Hidalgo, A., Arevalo, J.M., Galic, Z., Symensma, T.L., et al., 2005. β-Adrenoreceptors Reactivate Kaposi's Sarcoma-Associated Herpesvirus Lytic Replication via PKA-Dependent Control of Viral RTA. J. Virol. 79 (21), 13538–13547. https://doi.org/10.1128/JVI.79.21.13538-13547.2005.
Chen, J., Wei, Y., Feng, Q., Ren, L., He, G., Chang, W., et al., 2016. Ribosomal protein S15A promotes malignant transformation and predicts poor outcome in colorectal cancer through misregulation of p53 signaling pathway. Int. J. Oncol. 48 (4), 1628–1638. https://doi.org/10.3892/ijo.2016.3366.
Chen, X., Dong, C., Law, P.T.Y., Chan, M.T.V., Su, Z., Wang, S., et al., 2015. MicroRNA-145 targets TRIM2 and exerts tumor-suppressing functions in epithelial ovarian cancer. Gynecol. Oncol. 139 (3), 513–519. https://doi.org/10.1016/j.ygyno.2015.10.008.
Chen, Y.-L., Chan, S.-H., Lin, P.-Y., Chu, P.-Y., 2017. The expression of a tumor suppressor gene JDP2 and its prognostic value in hepatocellular carcinoma patients. Hum. Pathol. 63, 212–216. https://doi.org/10.1016/j.humpath.2017.03.003.
Cheng, L., Wang, P., Yang, S., Yang, Y., Zhang, Q., Zhang, W., et al., 2012. Identification of genes with a correlation between copy number and expression in gastric cancer. BMC Med. Genomics 5, 14. https://doi.org/10.1186/1755-8794-5-14.
Chu, J., Floyd, R., Diep, H., Pardo, S., Goldblum, P., Bongar, B., 2013. A tool for the culturally competent assessment of suicide: The Cultural Assessment of Risk for Suicide (CARS) Measure. Psychol. Assess. 25 (2), 424.
Chu, J., Floyd, R., Diep, H., Pardo, S., Goldblum, P., Bongar, B., 2013b. A tool for the culturally competent assessment of suicide: The Cultural Assessment of Risk for Suicide (CARS) Measure Manual. Retrieved from http://psycnet.apa.org/journals/pas/25/2/424/.
Cochran, S.D., Ackerman, D., Mays, V.M., Ross, M.W., 2004. Prevalence of non-medical drug use and dependence among homosexually active men and women in the US population. Addiction 99 (8), 989–998.
Cochran, S.D., Keenan, C., Schober, C., Mays, V.M., 2000. Estimates of alcohol use and clinical treatment needs among homosexually active men and women in the US population. J. Consult. Clin. Psychol. 68 (6), 1062.
Cochran, S.D., Mays, V.M., 2007. Physical health complaints among lesbians, gay men, and bisexual and homosexually experienced heterosexual individuals: results from the California Quality of Life Survey. Am. J. Public Health 97 (11), 2048–2055.
Cochran, S.D., Sullivan, J.G., Mays, V.M., 2003. Prevalence of mental disorders, psychological distress, and mental health services use among lesbian, gay, and bisexual adults in the United States. J. Consult. Clin. Psychol. 71 (1), 53.
Cohen, S., Janicki-Deverts, D., Doyle, W.J., Miller, G.E., Frank, E., Rabin, B.S., Turner, R.B., 2012. Chronic stress, glucocorticoid receptor resistance, inflammation, and disease risk. Proc. Natl. Acad. Sci. 109 (16), 5995–5999.
Cole, S.W., Hawkley, L.C., Arevalo, J.M., Cacioppo, J.T., 2011. Transcript origin analysis identifies antigen-presenting cells as primary targets of socially regulated gene expression in leukocytes. Proc. Natl. Acad. Sci. 108 (7), 3080–3085.
Cole, S.W., Hawkley, L.C., Arevalo, J.M., Sung, C.Y., Rose, R.M., Cacioppo, J.T., 2007. Social regulation of gene expression in human leukocytes. Genome Biol 8 (9), R189.
Cole, S.W., Kemeny, M.E., Taylor, S.E., 1997. Social identity and physical health: Accelerated HIV progression in rejection-sensitive gay men. J. Pers. Soc. Psychol. 72 (2), 320–335. https://doi.org/10.1037/0022-3514.72.2.320.
Cole, S.W., Kemeny, M.E., Taylor, S.E., Visscher, B.R., 1996a. Elevated physical health risk among gay men who conceal their homosexual identity. Health Psychol. 15 (4), 243.
Cole, S.W., Kemeny, M.E., Taylor, S.E., Visscher, B.R., Fahey, J.L., 1996b. Accelerated course of human immunodeficiency virus infection in gay men who conceal their homosexual identity. Psychosom. Med. 58 (3), 219–231.
Cole, S.W., Korin, Y.D., Fahey, J.L., Zack, J.A., 1998. Norepinephrine accelerates HIV replication via protein kinase A-dependent effects on cytokine production. J. Immunol. 161 (2), 610–616.
Conron, K.J., Mimiaga, M.J., Landers, S.J., 2010. A population-based study of sexual orientation identity and gender differences in adult health. Am. J. Public Health 100 (10), 1953–1960.
Cox, D.R., Reid, N., 1987. Parameter Orthogonality and Approximate Conditional Inference. J. Roy. Stat. Soc.: Ser. B (Methodol.) 49 (1), 1–39.
Creswell, J.D., Irwin, M.R., Burklund, L.J., Lieberman, M.D., Arevalo, J.M., Ma, J., et al., 2012. Mindfulness-based stress reduction training reduces loneliness and pro-inflammatory gene expression in older adults: a small randomized controlled trial. Brain Behav. Immun. 26 (7), 1095–1101.
Darke, S., Kaye, S., McKetin, R., Duflou, J., 2008. Major physical and psychological harms of methamphetamine use. Drug Alcohol Rev. 27 (3), 253–262.
Sancho, David, Gomez, Manual, Sanchez-Madrid, Francisco, 2005. CD69 is an immunoregulatory molecule induced following activation. Trends Immunol. 26 (3), 136–140. https://doi.org/10.1016/j.it.2004.12.006.
De Bortoli, M., Castellino, R.C., Lu, X.-Y., Deyo, J., Sturla, L.M., Adesina, A.M., et al., 2006. Medulloblastoma outcome is adversely associated with overexpression of EEF1D, RPL30, and RPS20 on the long arm of chromosome 8. BMC Cancer 6, 223. https://doi.org/10.1186/1471-2407-6-223.
D'Souza, S., Kurihara, N., Shiozawa, Y., Joseph, J., Taichman, R., Galson, D.L., Roodman, G.D., 2012. Annexin II interactions with the annexin II receptor enhance multiple myeloma cell adhesion and growth in the bone marrow microenvironment. Blood 119 (8), 1888–1896. https://doi.org/10.1182/blood-2011-11-393348.
Dutheil, N., Smith, S.C., Agúndez, L., Vincent-Mistiaen, Z.I., Escalante, C.R., Linden, R.M., Henckaerts, E., 2014. Adeno-associated virus Rep represses the human integration site promoter by two pathways that are similar to those required for the regulation of the viral p5 promoter. J. Virol. 88 (15), 8227–8241. https://doi.org/10.1128/JVI.00412-14.
Ebert, B.L., Pretz, J., Bosco, J., Chang, C.Y., Tamayo, P., Galili, N., et al., 2008. Identification of RPS14 as a 5q- syndrome gene by RNA interference screen. Nature 451 (7176), 335–339. https://doi.org/10.1038/nature06494.
Emmert-Streib, F., Glazko, G.V., 2011. Pathway Analysis of Expression Data: Deciphering Functional Building Blocks of Complex Diseases. PLOS Comput. Biol. 7 (5), e1002053. https://doi.org/10.1371/journal.pcbi.1002053.
Everett, B., Mollborn, S., 2013. Differences in Hypertension by Sexual Orientation Among U.S. Young Adults. J. Community Health 38 (3), 588–596. https://doi.org/10.1007/s10900-013-9655-3.
Fang, H., Xie, Q., Boneva, R., Fostel, J., Perkins, R., Tong, W., 2006. Gene expression profile exploration of a large dataset on chronic fatigue syndrome. Pharmacogenomics 7 (3), 429–440. https://doi.org/10.2217/14622416.7.3.429.
Fang, Z., Cui, X., 2011. Design and validation issues in RNA-seq experiments. Briefings Bioinf. 12 (3), 280–287. https://doi.org/10.1093/bib/bbr004.
Fang, Z.-Q., Zang, W.-D., Chen, R., Ye, B.-W., Wang, X.-W., Yi, S.-H., et al., 2013. Gene expression profile and enrichment pathways in different stages of bladder cancer. Genetics Mol. Res. GMR 12 (2), 1479–1489. https://doi.org/10.4238/2013.May.6.1.
Fredriksen-Goldsen, K.I., Kim, H.-J., Barkan, S.E., Muraco, A., Hoy-Ellis, C.P., 2013. Health Disparities Among Lesbian, Gay, and Bisexual Older Adults: Results From a Population-Based Study. Am. J. Public Health 103 (10), 1802–1809. https://doi.org/10.2105/AJPH.2012.301110.
Friedman, M.S., Marshal, M.P., Guadamuz, T.E., Wei, C., Wong, C.F., Saewyc, E.M., Stall, R., 2011. A meta-analysis of disparities in childhood sexual abuse, parental physical abuse, and peer victimization among sexual minority and sexual nonminority individuals. Am. J. Public Health 101 (8), 1481–1494. https://doi.org/10.2105/AJPH.2009.190009.
Frost, D.M., Lehavot, K., Meyer, I.H., 2015. Minority stress and physical health among sexual minority individuals. J. Behav. Med. 38 (1), 1–8.
Fu, X.-Y., Wang, H.-Y., Tan, L., Liu, S.-Q., Cao, H.-F., Wu, M.-C., 2002. Overexpression of p28/gankyrin in human hepatocellular carcinoma and its clinical significance. World J. Gastroenterol. 8 (4), 638–643.

Goeman, J.J., Bühlmann, P., 2007. Analyzing gene expression data in terms of gene sets: methodological issues. Bioinformatics 23 (8), 980–987. https://doi.org/10.1093/bioinformatics/btm051.

Grzmil, M., Rzymski, T., Milani, M., Harris, A.L., Capper, R.G., Saunders, N.J., et al., 2010. An oncogenic role of eIF3e/INT6 in human breast cancer. Oncogene 29 (28), 4080–4089. https://doi.org/10.1038/onc.2010.152.

Hagerstrand, D., Tong, A., Schumacher, S.E., Ilic, N., Shen, R.R., Cheung, H.W., et al., 2013. Systematic interrogation of 3q26 identifies TLOC1 and SKIL as cancer drivers. Cancer Discovery 3 (9), 1044–1057. https://doi.org/10.1158/2159-8290.CD-12-0592.

Hatzenbuehler, M.L., 2009. How does sexual minority stigma "get under the skin"? A psychological mediation framework. Psychol. Bull. 135 (5), 707.

Hatzenbuehler, M.L., McLaughlin, K.A., 2014. Structural stigma and hypothalamic–pituitary–adrenocortical axis reactivity in lesbian, gay, and bisexual young adults. Ann. Behav. Med. 47 (1), 39–47.

Hatzenbuehler, M.L., McLaughlin, K.A., Slopen, N., 2013. Sexual orientation disparities in cardiovascular biomarkers among young adults. Am. J. Prev. Med. 44 (6), 612–621.

Hatzenbuehler, M.L., Nolen-Hoeksema, S., Erickson, S.J., 2008. Minority stress predictors of HIV risk behavior, substance use, and depressive symptoms: results from a prospective study of bereaved gay men. Health Psychol. 27 (4), 455.

HGNC database of human gene names | HUGO Gene Nomenclature Committee. (n.d.). Retrieved September 20, 2017, from http://www.genenames.org/.

Hoge, E.A., Brandstetter, K., Moshier, S., Pollack, M.H., Wong, K.K., Simon, N.M., 2009. Broad spectrum of cytokine abnormalities in panic disorder and posttraumatic stress disorder. Depression Anxiety 26 (5), 447–455. https://doi.org/10.1002/da.20564.

Huang, Y.-C.T., Li, Z., Hyseni, X., Schmitt, M., Devlin, R.B., Karoly, E.D., Soukup, J.M., 2008. Identification of gene biomarkers for respiratory syncytial virus infection in a bronchial epithelial cell line. Genomic Med. 2 (3–4), 113–125. https://doi.org/10.1007/s11568-009-9080-y.

Huebner, D.M., Davis, M.C., 2005. Gay and bisexual men who disclose their sexual orientations in the workplace have higher workday levels of salivary cortisol and negative affect. Ann. Behav. Med. 30 (3), 260–267.

Hughes, T.L., Eliason, M., 2002. Substance use and abuse in lesbian, gay, bisexual and transgender populations. J. Primary Prevention 22 (3), 263–298.

Institute of Medicine, 2011. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. The National Academies Press, Washington, D.C..

Irwin, M.R., Olmos, L., Wang, M., Valladares, E.M., Motivala, S.J., Fong, T., et al., 2007. Cocaine dependence and acute cocaine induce decreases of monocyte proinflammatory cytokine expression across the diurnal period: autonomic mechanisms. J. Pharmacol. Exp. Ther. 320 (2), 507–515.

Jin, S., Wang, Y., Zhang, Y., Zhang, H.-Z., Wang, S.-J., Tang, J.-Q., et al., 2008. Humoral immune responses against tumor-associated antigen OVA66 originally defined by serological analysis of recombinant cDNA expression libraries and its potentiality in cellular immunity. Cancer Sci. 99 (8), 1670–1678. https://doi.org/10.1111/j.1349-7006.2008.00860.x.

Kabagambe, E.K., Judd, S.E., Howard, V.J., Zakai, N.A., Jenny, N.S., Hsieh, M., et al., 2011. Inflammation biomarkers and risk of all-cause mortality in the reasons for geographic and racial differences in stroke cohort. Am. J. Epidemiol. kwr085.

Kanehisa, M., Goto, S., Sato, Y., Furumichi, M., Tanabe, M., 2011. KEGG for integration and interpretation of large-scale molecular data sets. Nucleic Acids Res. 40 (D1), D109–D114.

KEGG: Kyoto Encyclopedia of Genes and Genomes. (n.d.). Retrieved September 20, 2017, from http://www.genome.jp/kegg/.

King, M., Semlyen, J., Tai, S.S., Killaspy, H., Osborn, D., Popelyuk, D., Nazareth, I., 2008. A systematic review of mental disorder, suicide, and deliberate self harm in lesbian, gay and bisexual people. BMC Psychiatry 8 (1), 70.

Komati, H., Maharsy, W., Beauregard, J., Hayek, S., Nemer, M., 2011. ZFP260 Is an Inducer of Cardiac Hypertrophy and a Nuclear Mediator of Endothelin-1 Signaling. J. Biol. Chem. 286 (2), 1508–1516. https://doi.org/10.1074/jbc.M110.162966.

Kottom, T.J., Hebrink, D.M., Jenson, P.E., Nandakumar, V., Wüthrich, M., Wang, H., et al., 2017. The interaction of pneumocystis with the C-type lectin receptor mincle exerts a significant role in host defense against infection. J. Immunol. (Baltimore, Md.: 1950) 198 (9), 3515–3525. https://doi.org/10.4049/jimmunol.1600744.

Kuller, L.H., Tracy, R., Belloso, W., De Wit, S., Drummond, F., Lane, H.C., et al., 2008. Inflammatory and coagulation biomarkers and mortality in patients with HIV infection. PLoS Med. 5 (10), e203.

Landau, W.M., Liu, P., 2013. Dispersion Estimation and Its Effect on Test Performance in RNA-seq Data Analysis: A Simulation-Based Comparison of Methods. PLOS ONE 8 (12), e81415. https://doi.org/10.1371/journal.pone.0081415.

Lange, R.A., Hillis, L.D., 2001. Cardiovascular Complications of Cocaine Use. N. Engl. J. Med. 345 (5), 351–358. https://doi.org/10.1056/NEJM200108023450507.

Lederman, M.M., Funderburg, N.T., Sekaly, R.P., Klatt, N.R., Hunt, P.W., 2013. Residual immune dysregulation syndrome in treated HIV infection. Adv. Immunol. 119, 51–83. https://doi.org/10.1016/B978-0-12-407707-2.00002-3.

Leek, J.T., Johnson, W.E., Parker, H.S., Jaffe, A.E., Storey, J.D., 2012. The sva package for removing batch effects and other unwanted variation in high-throughput experiments. Bioinformatics 28 (6), 882–883.

Li, Y., Fu, L., Li, J.-B., Qin, Y., Zeng, T., Zhou, J., et al., 2014a. Increased expression of EIF5A2, via hypoxia or gene amplification, contributes to metastasis and angiogenesis of esophageal squamous cell carcinoma. Gastroenterology 146 (7). https://doi.org/10.1053/j.gastro.2014.02.029.

Li, Z., Lin, S., Jiang, T., Wang, J., Lu, H., Tang, H., et al., 2014b. Overexpression of eIF3e is correlated with colon tumor development and poor prognosis. Int. J. Clin. Exp. Path. 7 (10), 6462–6474.

Liu, X., Wang, J., Sun, G., 2015. Identification of key genes and pathways in renal cell carcinoma through expression profiling data. Kidney Blood Pressure Res. 40 (3), 288–297. https://doi.org/10.1159/000368504.

Liu, Y.-Y., Patwardhan, G.A., Bhinge, K., Gupta, V., Gu, X., Jazwinski, S.M., 2011a. Suppression of glucosylceramide synthase restores p53-dependent apoptosis in mutant p53 cancer cells. Cancer Res. 71 (6), 2276–2285. https://doi.org/10.1158/0008-5472.CAN-10-3107.

Liu, Y.-Y., Patwardhan, G.A., Xie, P., Gu, X., Giuliano, A.E., Cabot, M.C., 2011b. Glucosylceramide synthase, a factor in modulating drug resistance, is overexpressed in metastatic breast carcinoma. Int. J. Oncol. 39 (2), 425–431. https://doi.org/10.3892/ijo.2011.1052.

Livingston, N., Flentje, A., Heck, N.C., Szalda-Petree, A., Cochran, B.N., 2017. Ecological momentary assessment of daily prejudice experiences and nicotine, alcohol, and drug use among sexual and gender minority individuals. J. Consult. Clin. Psychol. 85 (12), 1131–1143.

Llibre, A., López-Macías, C., Marafioti, T., Mehta, H., Partridge, A., Kanzig, C., et al., 2016. LLT1 and CD161 expression in human germinal centers promotes B cell activation and CXCR4 downregulation. J. Immunol. (Baltimore, Md.: 1950) 196 (5), 2085–2094. https://doi.org/10.4049/jimmunol.1502462.

Lohse, N., Gerstoft, J., Kronborg, G., Larsen, C.S., Pedersen, C., Pedersen, G., et al., 2011. Comorbidity acquired before HIV diagnosis and mortality in persons infected and uninfected With HIV: a Danish population-based cohort study. JAIDS J. Acquired Immune Deficiency Syndromes 57 (4), 334. https://doi.org/10.1097/QAI.0b013e31821d34ed.

Love, M. I., Anders, S., Kim, V., Huber, W., 2015. RNA-Seq workflow: gene-level exploratory analysis and differential expression. F1000Research, 4. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4670015.1/.

Luo, J.-H., Hua, W.-F., Rao, H.-L., Liao, Y.-J., Kung, H.-F., Zeng, Y.-X., et al., 2009a. Overexpression of EIF-5A2 predicts tumor recurrence and progression in pTa/pT1 urothelial carcinoma of the bladder. Cancer Sci. 100 (5), 896–902. https://doi.org/10.1111/j.1349-7006.2009.01126.x.

Luo, W., Friedman, M.S., Shedden, K., Hankenson, K.D., Woolf, P.J., 2009b. GAGE: generally applicable gene set enrichment for pathway analysis. BMC Bioinf. 10 (1), 161.

Mao, G., Jin, J., Kunapuli, S.P., Rao, A.K., 2016. Nuclear factor-κB regulates expression of platelet phospholipase C-β2 (PLCB2). Thromb. Haemost. 116 (5), 931–940. https://doi.org/10.1160/TH15-09-0749.

Marioni, J.C., Mason, C.E., Mane, S.M., Stephens, M., Gilad, Y., 2008. RNA-seq: an assessment of technical reproducibility and comparison with gene expression arrays. Genome Res. 18 (9), 1509–1517. https://doi.org/10.1101/gr.079558.108.

Maruyama, Y., Miyazaki, T., Ikeda, K., Okumura, T., Sato, W., Horie-Inoue, K., et al., 2014. Short hairpin RNA library-based functional screening identified ribosomal protein L31 that modulates prostate cancer cell growth via p53 pathway. PloS One 9 (10), e108743. https://doi.org/10.1371/journal.pone.0108743.

Matta, J., Morales, L., Dutil, J., Bayona, M., Alvarez, C., Suarez, E., 2013. Differential expression of DNA repair genes in Hispanic women with breast cancer. Mol. Cancer Biol. 1 (1), 54. https://doi.org/10.9777/mcb.2013.10006.

McCabe, S.E., Bostwick, W.B., Hughes, T.L., West, B.T., Boyd, C.J., 2010. The relationship between discrimination and substance use disorders among lesbian, gay, and bisexual adults in the United States. Am. J. Public Health 100 (10), 1946–1952.

McCabe, S.E., Boyd, C., Hughes, T.L., d'Arcy, H., 2003. Sexual identity and substance use among undergraduate students. Substance Abuse 24 (2), 77–91.

McCarthy, D.J., Chen, Y., Smyth, G.K., 2012. Differential expression analysis of multifactor RNA-Seq experiments with respect to biological variation. Nucleic Acids Res. 40 (10), 4288–4297.

McLellan, A.T., Kushner, H., Metzger, D., Peters, R., Smith, I., Grissom, G., et al., 1992. The fifth edition of the Addiction Severity Index. J. Subst. Abuse Treat. 9 (3), 199–213.

Meng, Q.-B., Kang, W.-M., Yu, J.-C., Liu, Y.-Q., Ma, Z.-Q., Zhou, L., et al., 2015. Overexpression of eukaryotic translation initiation factor 5A2 (EIF5A2) correlates with cell aggressiveness and poor survival in gastric cancer. PloS One 10 (3), e0119229. https://doi.org/10.1371/journal.pone.0119229.

Meng, Y., He, L., Guo, X., Tang, S., Zhao, X., Du, R., et al., 2010. Gankyrin promotes the proliferation of human pancreatic cancer. Cancer Lett. 297 (1), 9–17. https://doi.org/10.1016/j.canlet.2010.04.019.

Meyer, I.H., 2003. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol. Bull. 129 (5), 674.

Miller, G.E., Cole, S.W., 2012. Clustering of depression and inflammation in adolescents previously exposed to childhood adversity. Biol. Psychiatry 72 (1), 34–40.

Miller, G., Rohleder, N., Cole, S.W., 2009. Chronic interpersonal stress predicts activation of pro-and anti-inflammatory signaling pathways six months later. Psychosom. Med. 71 (1), 57.

Moldoveanu, A.I., Shephard, R.J., Shek, P.N., 2000. Exercise elevates plasma levels but not gene expression of IL-1β, IL-6, and TNF-α in blood mononuclear cells. J. Appl. Physiol. 89 (4), 1499–1504. https://doi.org/10.1152/jappl.2000.89.4.1499.

Müllbacher, A., Waring, P., Tha Hla, R., Tran, T., Chin, S., Stehle, T., et al., 1999. Granzymes are the essential downstream effector molecules for the control of primary virus infections by cytolytic leukocytes. PNAS 96 (24), 13950–13955.

Murphy, M.L., Slavich, G.M., Rohleder, N., Miller, G.E., 2012. Targeted rejection triggers differential pro-and anti-inflammatory gene expression in adolescents as a function of social status. Clin. Psychol. Sci. 2167702612455743.

Natrajan, R., Little, S.E., Reis-Filho, J.S., Hing, L., Messahel, B., Grundy, P.E., et al., 2006. Amplification and overexpression of CACNA1E correlates with relapse in favorable histology Wilms' tumors. Clin. Cancer Res. Official J. Am. Assoc. Cancer Res. 12 (24), 7284–7293. https://doi.org/10.1158/1078-0432.CCR-06-1567.

Norcini Pala, A., Hart, R.P., Steca, P., 2015. Minority Stress, Depression and HIV-Progression Biomarkers: An Exploratory Study on a Sample of Italian HIV-Positive Gay and Bisexual Men. J. Gay Lesbian Mental Health 19 (3), 244–260.

O'Connell, G.C., Treadway, M.B., Petrone, A.B., Tennant, C.S., Lucke-Wold, N., Chantler, P.D., Barr, T.L., 2017. Peripheral blood AKAP7 expression as an early marker for lymphocyte-mediated post-stroke blood brain barrier disruption. Sci. Rep. 7 (1), 1172. https://doi.org/10.1038/s41598-017-01178-5.

Oliver, D., Ji, H., Liu, P., Gasparian, A., Gardiner, E., Lee, S., et al., 2017. Identification of novel cancer therapeutic targets using a designed and pooled shRNA library screen. Sci. Rep. 7, 43023. https://doi.org/10.1038/srep43023.

Otsuki, N., Kamimura, Y., Hashiguchi, M., Azuma, M., 2006. Expression and function of the B and T lymphocyte attenuator (BTLA/CD272) on human T cells. Biochem. Biophys. Res. Commun. 344 (4), 1121–1127. https://doi.org/10.1016/j.bbrc.2006.03.242.

Panaccione, A., Guo, Y., Yarbrough, W.G., Ivanov, S.V., 2017. Expression profiling of clinical specimens supports the existence of neural progenitor-like stem cells in basal breast cancers. Clin. Breast Cancer 17 (4). https://doi.org/10.1016/j.clbc.2017.01.007.

Pandrea, I., Happel, K.I., Amedee, A.M., Bagby, G.J., Nelson, S., 2010. Alcohol's role in HIV transmission and disease progression. Alcohol Res. Health J. Natl. Inst. Alcohol Abuse Alcoholism 33 (3), 203–218.

Papanicolaou, D.A., 1998. The pathophysiologic roles of interleukin-6 in human disease. Ann. Intern. Med. 128 (2), 127. https://doi.org/10.7326/0003-4819-128-2-199801150-00009.

Peng, C., Zhang, Z., Wu, J., Lv, Z., Tang, J., Xie, H., et al., 2014. A critical role for ZDHHC2 in metastasis and recurrence in human hepatocellular carcinoma. BioMed Res. Int. 2014, 832712. https://doi.org/10.1155/2014/832712.

Perez-Oliva, A.B., Lachaud, C., Szyniarowski, P., Muñoz, I., Macartney, T., Hickson, I., et al., 2015. USP45 deubiquitylase controls ERCC1–XPF endonuclease-mediated DNA damage responses. The EMBO J. 34 (3), 326–343. https://doi.org/10.15252/embj.201489184.

Phan, D., Cheng, C.-J., Galfione, M., Vakar-Lopez, F., Tunstead, J., Thompson, N.E., et al., 2004. Identification of Sp2 as a transcriptional repressor of carcinoembryonic antigen-related cell adhesion molecule 1 in tumorigenesis. Cancer Res. 64 (9), 3072–3078.

Qin, X., Wang, X., Liu, F., Morris, L.E., Wang, X., Jiang, B., Zhang, Y., 2016. Gankyrin activates mTORC1 signaling by accelerating TSC2 degradation in colorectal cancer. Cancer Lett. 376 (1), 83–94. https://doi.org/10.1016/j.canlet.2016.03.013.

Radloff, L.S., 1977. The CES-D scale: a self-report depression scale for research in the general population. Appl. Psychol. Meas. 1 (3), 385–401.

Rao, W., Xie, G., Zhang, Y., Wang, S., Wang, Y., Zhang, H., et al., 2014. OVA66, a tumor associated protein, induces oncogenic transformation of NIH3T3 cells. PloS One 9 (3), e85705. https://doi.org/10.1371/journal.pone.0085705.

Rapaport, F., Khanin, R., Liang, Y., Pirun, M., Krek, A., Zumbo, P., et al., 2013. Comprehensive evaluation of differential gene expression analysis methods for RNA-seq data. Genome Biol. 14, 3158. https://doi.org/10.1186/gb-2013-14-9-r95.

Rodriguez-Penney, A.T., Iudicello, J.E., Riggs, P.K., Doyle, K., Ellis, R.J., Letendre, S.L., et al., 2013. Co-morbidities in persons infected with HIV: increased burden with older age and negative effects on health-related quality of life. AIDS Patient Care STDs 27 (1), 5–16. https://doi.org/10.1089/apc.2012.0329.

Sacerdote, P., Franchi, S., Panerai, E., A., 2012. Non-analgesic effects of opioids: mechanisms and potential clinical relevance of opioid-induced immunodepression. Curr. Pharm. Des. 18 (37), 6034–6042. https://doi.org/10.2174/138161212803582496.

Schiepers, O.J.G., Wichers, M.C., Maes, M., 2005. Cytokines and major depression. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 29 (2), 201–217. https://doi.org/10.1016/j.pnpbp.2004.11.003.

Schmitt, A.O., Specht, T., Beckmann, G., Dahl, E., Pilarsky, C.P., Hinzmann, B., Rosenthal, A., 1999. Exhaustive mining of EST libraries for genes differentially expressed in normal and tumour tissues. Nucleic Acids Res. 27 (21), 4251–4260.

Sell, R.L., Holliday, M.L., 2014. Sexual orientation data collection policy in the United States: public health malpractice. Am. J. Public Health 104 (6), 967–969. https://doi.org/10.2105/AJPH.2013.301814.

Shinozuka, E., Miyashita, M., Mizuguchi, Y., Akagi, I., Kikuchi, K., Makino, H., et al., 2013. SnoN/SKIL modulates proliferation through control of hsa-miR-720 transcription in esophageal cancer cells. Biochem. Biophys. Res. Commun. 430 (1), 101–106. https://doi.org/10.1016/j.bbrc.2012.11.005.

Shiozawa, Y., Havens, A.M., Jung, Y., Ziegler, A.M., Pedersen, E.A., Wang, J., et al., 2008. Annexin II/annexin II receptor axis regulates adhesion, migration, homing, and growth of prostate cancer. J. Cell. Biochem. 105 (2), 370–380. https://doi.org/10.1002/jcb.21835.

Slavich, G.M., Cole, S.W., 2013. The emerging field of human social genomics. Clin. Psychol. Sci. 2167702613478594.

Soneson, C., Delorenzi, M., 2013. A comparison of methods for differential expression analysis of RNA-seq data. BMC Bioinf. 14 (1), 91.

Stall, R., Paul, J.P., Greenwood, G., Pollack, L.M., Bein, E., Crosby, G.M., et al., 2001. Alcohol use, drug use and alcohol-related problems among men who have sex with men: the Urban Men's Health Study. Addiction 96 (11), 1589–1601.

Su, Z., Labaj, P.P., Li, S., Thierry-Mieg, J., Thierry-Mieg, D., Shi, W., et al., 2014. A comprehensive assessment of RNA-seq accuracy, reproducibility and information content by the Sequencing Quality Control Consortium. Nat. Biotechnol. 32 (9), 903.

Sun, X., Zhang, H., Luo, L., Zhong, K., Ma, Y., Fan, L., et al., 2016. Comparative proteomic profiling identifies potential prognostic factors for human clear cell renal cell carcinoma. Oncol. Rep. 36 (6), 3131–3138. https://doi.org/10.3892/or.2016.5159.

Tarca, A.L., Draghici, S., Khatri, P., Hassan, S.S., Mittal, P., Kim, J., et al., 2009. A novel signaling pathway impact analysis. Bioinformatics 25 (1), 75–82. https://doi.org/10.1093/bioinformatics/btn577.

Tien, P.C., Choi, A.I., Zolopa, A.R., Benson, C., Scherzer, R., Bacchetti, P., et al., 2010. Inflammation and mortality in HIV-infected adults: analysis of the FRAM study cohort. J. Acquired Immune Deficiency Syndromes (1999) 55 (3), 316.

Vilagut, G., Forero, C.G., Barbaglia, G., Alonso, J., 2016. Screening for depression in the general population with the center for epidemiologic studies depression (CES-D): a systematic review with meta-analysis. Plos One 11 (5), e0155431. https://doi.org/10.1371/journal.pone.0155431.

Wang, D., Berglund, A.E., Kenchappa, R.S., MacAulay, R.J., Mulé, J.J., Etame, A.B., 2017. BIRC3 is a biomarker of mesenchymal habitat of glioblastoma, and a mediator of survival adaptation in hypoxia-driven glioblastoma habitats. Sci. Rep. 7 (1), 9350. https://doi.org/10.1038/s41598-017-09503-8.

Wang, D., Berglund, A., Kenchappa, R.S., Forsyth, P.A., Mulé, J.J., Etame, A.B., 2016. BIRC3 is a novel driver of therapeutic resistance in Glioblastoma. Sci. Rep. 6, 21710. https://doi.org/10.1038/srep21710.

Wang, L., Luo, J., Nian, Q., Xiao, Q., Yang, Z., Liu, L., 2014. Ribosomal protein S14 silencing inhibits growth of acute myeloid leukemia transformed from myelodysplastic syndromes via activating p53. Hematology (Amsterdam, Netherlands) 19 (4), 225–231. https://doi.org/10.1179/1607845413Y.0000000127.

Wei, B., Wang, L., Du, C., Hu, G., Wang, L., Jin, Y., Kong, D., 2015. Identification of differentially expressed genes regulated by transcription factors in glioblastomas by bioinformatics analysis. Mol. Med. Rep. 11 (4), 2548–2554. https://doi.org/10.3892/mmr.2014.3094.

Wei, P., Tang, H., Li, D., 2012. Insights into pancreatic cancer etiology from pathway analysis of genome-wide association study data. PloS One 7 (10), e46887. https://doi.org/10.1371/journal.pone.0046887.

Weng, M.-T., Luo, J., 2013. The enigmatic ERH protein: its role in cell cycle, RNA splicing and cancer. Protein Cell 4 (11), 807–812. https://doi.org/10.1007/s13238-013-3056-3.

Wilkins, K.C., Lang, A.J., Norman, S.B., 2011. Synthesis of the psychometric properties of the PTSD checklist (PCL) military, civilian, and specific versions. Depression Anxiety 28 (7), 596–606.

Wu, L., Li, X., Xu, F., Chang, C., He, Q., Zhang, Z., Zhang, Y., 2012. Over-expression of RPL23 in myelodysplastic syndromes is associated with apoptosis resistance of CD34+ cells and predicts poor prognosis and distinct response to CHG chemotherapy or decitabine. Ann. Hematol. 91 (10), 1547–1554. https://doi.org/10.1007/s00277-012-1486-2.

Yamato, A., Soda, M., Ueno, T., Kojima, S., Sonehara, K., Kawazu, M., et al., 2015. Oncogenic activity of BIRC2 and BIRC3 mutants independent of nuclear factor-κB-activating potential. Cancer Sci. 106 (9), 1137–1142. https://doi.org/10.1111/cas.12726.

Yan, S.-M., Tang, J.-J., Huang, C.-Y., Xi, S.-Y., Huang, M.-Y., Liang, J.-Z., et al., 2013. Reduced expression of ZDHHC2 is associated with lymph node metastasis and poor prognosis in gastric adenocarcinoma. PloS One 8 (2), e56366. https://doi.org/10.1371/journal.pone.0056366.

Yang, M., Lewinska, M., Fan, X., Zhu, J., Yuan, Z.-M., 2016. PRR14 is a novel activator of the PI3K pathway promoting lung carcinogenesis. Oncogene 35 (42), 5527–5538. https://doi.org/10.1038/onc.2016.93.

Yang, Z., Wen, H.-J., Minhas, V., Wood, C., 2009. The zinc finger DNA-binding domain of K-RBP plays an important role in regulating Kaposi's sarcoma-associated herpesvirus RTA-mediated gene expression. Virology 391 (2), 221–231. https://doi.org/10.1016/j.virol.2009.06.014.

Yang, Z., Wood, C., 2007. The transcriptional repressor K-RBP modulates RTA-mediated transactivation and lytic replication of Kaposi's sarcoma-associated herpesvirus. J. Virol. 81 (12), 6294–6306. https://doi.org/10.1128/JVI.02648-06.

Yao, Y., Liu, Y., Lv, X., Dong, B., Wang, F., Li, J., et al., 2016. Down-regulation of ribosomal protein S15A inhibits proliferation of human glioblastoma cells in vivo and in vitro via AKT pathway. Tumour Biol. J. Int. Soc. Oncodev. Biol. Med. 37 (4), 4979–4990. https://doi.org/10.1007/s13277-015-4323-0.

Yong, W.H., Shabihkhani, M., Telesca, D., Yang, S., Tso, J.L., Menjivar, J.C., et al., 2015. Ribosomal proteins RPS11 and RPS20, two stress-response markers of glioblastoma stem cells, are novel predictors of poor prognosis in glioblastoma patients. PloS One 10 (10), e0141334. https://doi.org/10.1371/journal.pone.0141334.

Yu, X., Zhang, X., Zhao, B., Wang, J., Zhu, Z., Teng, Z., Wu, F., 2011. Intensive cytokine induction in pandemic H1N1 influenza virus infection accompanied by robust production of IL-10 and IL-6. PLOS ONE 6 (12), e28680. https://doi.org/10.1371/journal.pone.0028680.

Yuanhong, X., Feng, X., Qingchang, L., Jianpeng, F., Zhe, L., Kejian, G., 2010. Downregulation of AP-1 repressor JDP2 is associated with tumor metastasis and poor prognosis in patients with pancreatic carcinoma. Int. J. Biol. Markers 25 (3), 136–140.

Zhang, J., Fan, D., Jian, Z., Chen, G.G., Lai, P.B.S., 2015. Cancer Specific Long Noncoding RNAs Show Differential Expression Patterns and Competing Endogenous RNA Potential in Hepatocellular Carcinoma. PLoS ONE 10 (10). https://doi.org/10.1371/journal.pone.0141042.

Zhang, L., Huang, Q., Lou, J., Zou, L., Wang, Y., Zhang, P., et al., 2017. A novel PHD-finger protein 14/KIF4A complex overexpressed in lung cancer is involved in cell mitosis regulation and tumorigenesis. Oncotarget 8 (12), 19684–19698. https://doi.org/10.18632/oncotarget.14962.

Zhang, W., Tong, D., Liu, F., Li, D., Li, J., Cheng, X., Wang, Z., 2016. RPS7 inhibits colorectal cancer growth via decreasing HIF-1α-mediated glycolysis. Oncotarget 7 (5), 5800–5814. https://doi.org/10.18632/oncotarget.6807.

Zhao, L.Y., Yao, Y., Han, J., Yang, J., Wang, X.F., Tong, D.D., et al., 2014. miR-638 suppresses cell proliferation in gastric cancer by targeting Sp2. Dig. Dis. Sci. 59 (8), 1743–1753. https://doi.org/10.1007/s10620-014-3087-5.

Zheng, Y., Xu, B., Zhao, Y., Gu, H., Li, C., Wang, Y., Chang, X., 2015. CA1 contributes to microcalcification and tumourigenesis in breast cancer. BMC Cancer 15, 679. https://doi.org/10.1186/s12885-015-1707-x.

Zhu, Q., Le Scolan, E., Jahchan, N., Ji, X., Xu, A., Luo, K., 2016. SnoN Antagonizes the hippo kinase complex to promote TAZ signaling during breast carcinogenesis. Dev. Cell 37 (5), 399–412. https://doi.org/10.1016/j.devcel.2016.05.002.