Supplementary Materials

Supplementary Methods

Prostate cohorts:

Seven prostate cancer cohorts included 4,213 patients (Supplementary Table S3) from: the United Kingdom RAPPER-prostate enrolled RT01 (n=219) and CHHiP (n=1,487) clinical trials; the Spanish RADIOGEN-prostate cohort (n=647); The United States Gene-PARE cohort (n=225); the Belgian UGhent cohort (n=136); the Canadian CCI-EBRT (n=151) cohort; and the multinational REQUITE-Prostate cohort (n= 1,348 from 9 centers across Europe and the United States)[9]. Details are as follows.

RAPPER-CHHiP and RAPPER-RT01 Cohorts: RAPPER (UKCRN1471) recruits patients from clinical trials and observational studies, which prospectively collect radiotherapy toxicity data[1] . All patients received radical prostate radiotherapy following neoadjuvant androgen suppression as part of the MRC RT01 trial (ISRCTN47772397) or the Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer (CHHiP) trial (ISRCTN97182923). Both were international multi-center randomized controlled trials that recruited men with localized prostate cancer (pT1b–T3aN0M0). RT01 randomized participants to standard (64 Gy) or high dose (74 Gy) radical 3D conformal radiotherapy. CHHiP randomized participants to conventional (74 Gy delivered in 37 fractions) or one of two hypofractionated schedules (60 Gy in 20 fractions or 57 Gy in 19 fractions) all delivered with intensity-modulated techniques. Participants in RT01 were given 3 months of neoadjuvant androgen suppression; participants in CHHiP were given 3–6 months of neoadjuvant and concurrent androgen suppression. RAPPER is approved by the East of England Cambridge South Research Ethics Committee (05/Q0108/365), and informed consent was obtained from all patients.

RADIOGEN-PrCa Cohort: RADIOGEN-PrCa (RADIOGEN; Study on the genomic influence in patients undergoing RT) recruited men with prostate cancer from northwest Spain (Galicia region) who were treated at the Radiation Oncology Department of the Clinical University Hospital of Santiago de Compostela (Spain) from 2006 to 2011[2]. Treatment plans were generated by seven coplanar fields to the pelvis (from the mid-abdomen to 3 cm below the ischial tuberosities), by use of 15-MV photon beams. Patients treated with salvage

radiotherapy or with adjuvant radiotherapy received a unique planning target volume (PTV) in the ranges of 66–70 Gy and 60–66 Gy, respectively. The total dose for radical radiotherapy for PTV I ranged between 70 and 76 Gy. Intermediate-risk patients also received 56 Gy for PTV II, whereas high-risk patients included for a third PTV received 46 Gy. Written informed consent was obtained for each subject, according to the protocols approved by the ethics review board of the Galician Ethical Committee for Clinical Research.

GenePARE Cohort: Participants recruited from Mount Sinai Medical Center were treated with definitive radiation for biopsy-proven adenocarcinoma of the prostate between 1991 and 2011. Radiation consisted of brachytherapy alone with a full ^{125}Iodine implant prescribed to 160 Gy (TG43), a partial ^{103}Palladium implant prescribed to 100 Gy followed in 6-8 weeks by external beam irradiation (3-dimensional conformal or image-guided, intensity modulated radiation therapy [IMRT]) to 24-50 Gy (median 45 Gy), or EBRT alone to 66.6-81 Gy (IMRT). GenePARE was approved by the Institutional Review Board of each study site, and all patients provided informed consent.

UGhent-PrCa Cohort: UGhent-PrCa recruited participants from the Ghent University Hospital[3]. All patients had localized or locally advanced prostate cancer (T1–T4, N0M0) and received IMRT with 18 MV photons between 1998 and 2002. Prescription doses ranged from 72Gy to 78Gy in 36 to 38 fractions. A subset of patients received hormonal therapy 3 months prior to radiotherapy and up to 3 years after radiotherapy. UGhent-PrCa was approved by the Ghent University Hospital ethics committee, and all patients provided informed consent.

CCI-EBRT Cohort: Participants in CCI-EBRT were recruited from the Cross Cancer Institute and the Tom Baker Cancer Centre in Canada[4] between 2000 and 2007 .All participants received IMRT with either standard fractionation consisting of 72–82 Gy delivered in 1.8–2 Gy per fraction of hypofraction consisting of 68 Gy in 25 fractions or 55 Gy in 16 fractions. A subset of patients received neoadjuvant hormonal therapy. CCI-EBRT was approved by the Health Research Ethics Board of Alberta, and all patients provided informed consent.

REQUITE-PrCa Cohort: REQUITE is an international multi-center, prospective observational cohort study of radiotherapy toxicity[5]. Participants were recruited from 26 hospitals in eight countries (Belgium, France, Germany, Italy, the Netherlands, Spain, UK, the USA). REQUITE-PrCa recruited adult prostate cancer patients prior to radiotherapy between 2014 and 2016. Conventional and hypofractionated radiotherapy, with or

without prior prostatectomy and/or hormonal therapy was prescribed according to local standard-of-care regimens. The study was approved by local ethics committees (registered at www.controlled-trials.com ISRCTN98496463), and all patients gave written informed consent.

HNC cohorts:

Seven HNC cohorts included 4,042 patients (Supplementary Table S2): Dutch UMCG-HANS (n=1,279), Danish DAHANCA (n=1,183), Spanish RADIOGEN-HNC (n=178), Belgian Ghent-HNC (n=273), and UK RAPPER-HNC study (n=187), NIMRAD (n=270) and Head and Neck 5000 (n=672).

DAHANCA Cohorts: DAHANCA cohorts comprised patients treated within The Danish Head and Neck Cancer Group (DAHANCA) protocols in Denmark for head and neck squamous cell carcinoma in the period of 2000-2011 and were eligible by the following criteria: Histologically verified pharyngeal or laryngeal squamous cell carcinomas T1-4N0-3M0. Curative intent treatment regimen, consisting of primary RT +/- concomitant treatment, > 600 days recurrence free (curative single lymph node extirpation on the neck was accepted) and available biological tissue with germline DNA. Patients were excluded by death of any cause or switch to palliative treatment regimen during primary RT. Patients were censored by recurrence date in case of recurrence after 600 days. RT doses were 66, 68 (accelerated 6 fx/week regime) or 70 Gy (standard 5 fx/week regime). Fractionation doses were 2 Gy/fx. Concomitant treatment included weekly cisplatin and Nimorazole. Cisplatin was offered to patients with N1-3 disease from 2007, dosage 40 mg/m^2 once weekly during RT. Nimorazole was administered to all patients except patients with glottic laryngeal cancers T1N0M0. RT technique was IMRT from 2006. Before this, 3D-Conformal RT was applied. The 1,183 patients included were from the following cohorts:

DAHANCA10, (Aarhus University Hospital cohort): In a randomized phase III study, the effect of Darbepoetin-alfa in anemic patients (haemoglobin < 14.5 g/dl for men and < 13.5 g/dl for women) was analyzed with loco-regional failure as the primary endpoint. Patients were eligible by the following criteria: Squamous cell carcinoma of the larynx, oropharynx, hypopharynx, or oral cavity T1-4N0-3M0 (excluding stage I glottic

carcinomas), WHO performance score 0–2, age ≥ 18 years. The study was interrupted after interim analysis showing inferiority of the Darbepoetin-alfa arm [6].

DAHANCA19: In a randomized, open-label phase III trial in 2007-2012, the effect of zalutumumab, an EGFR-inhibitor, was analyzed with loco-regional failure as the primary endpoint. Patients were eligible by histologically verified squamous cell carcinoma of the oral cavity, larynx, oropharynx or hypopharynx, stage T1-4N0-3M0 (excluding stage I + II glottic carcinomas), WHO performance score 0–2, age ≥ 18 years [7].

DAHANCA Prospective biobank protocol, Aarhus University Hospital cohort: Consecutive patients with available biobank material, age ≥ 18 years, treated according to standardized national DAHANCA guidelines. Follow-up data was prospectively registered weekly during RT and after completion of RT course, at 2 weeks and at 3, 6, 12, 24, 36, 48 and 60 months. Acute and late endpoints were registered ordinally according to standardized DAHANCA forms, which are comparable with LENT-SOMA scales[8].

UMCG-HANS Cohorts: University Medical Center Groningen Head and Neck cancer Study (UMCG-HANS) cohort consisted of patients treated with primary or postoperative RT either or not combined with chemotherapy (CH-RT) from 2007 to 2020 at the department of Radiation Oncology of the UMCG[9]. All patients were included in the UMCG-HNC prospective data registration program (NCT02435576, clinicaltrials.gov) in which baseline patient-, tumour-, and treatment-characteristics were determined before starting the RT. Additionally, radiation-induced toxicity and patient-rated outcome measures (PROM) were prospectively assessed weekly during RT and after completion of RT course, up to 6 weeks for acute toxicity, and at 6, 12, 18, 24, 36, 48 and 60 month for late toxicity [10].The prospective data registration program has been reviewed by the medical ethical committee and is considered standard of care. Additional written informed consent was obtained for the genetic study (NCT02489084)**.** Eligibility criteria included histologically proven primary HNC, originating in the oral cavity, oropharynx, hypopharynx, nasopharynx, paranasal sinuses, and/or salivary glands; being treated with curative intent with definitive or postoperative radiotherapy either or not combined with systemic treatment; no history of prior radiation (in the head and neck area); having a northern European ethnicity; willing and able to comply with the study prescriptions; aged ≥ 18 years; signing informed consent, and good level of understanding of the Dutch language. Patients that were not eligible according to the

abovementioned criteria, were excluded. During follow-up, physician-rated acute toxicities were registered according to the Common Toxicity Criteria of Adverse Events (version 4.0)[11]. Patient-rated HNC symptoms were assessed using the EORTC QLQ-H&N35 questionnaire in addition to the EORTC-QLQ-C30[12].

Ghent-HNC Cohort: The Ghent University Hospital cohort consists of patients with oral cavity, larynx, oropharynx and hypopharynx squamous cell carcinoma receiving primary or adjuvant radiotherapy (combined or not combined with concomitant chemotherapy) treated between 2003-2014. All patients signed informed consent for several studies involving radiogenomics. All patients were followed up prospectively before and weekly during therapy using Common Toxicity Criteria of Adverse Events (version 2.0). After therapy all patients were routinely seen at following time points: months 1-3-6-9-12-16-20-24, thereafter 6-monthly until 5 years of follow-up and thereafter yearly. Toxicity data using LENT-SOMA scale was routinely performed for, amongst others, dysphagia, xerostomia, mucosal integrity and neck fibrosis. Depending on the study, some patients also prospectively filled in the EORTC QLQ-H&N35 questionnaire in addition to the EORTC-QLQ-C30. Standard dose prescriptions were 32 x 2,16 Gy for primary tumour and positive lymph nodes and 32 x 1,75 Gy for the prophylactically irradiated neck in the primary setting or in case of positive section margins after surgery, and 33 x 2 Gy in the postoperative setting to the operative bed with 33 x 1,70 Gy for the prophylactically irradiated neck[13].

RADIOGEN-HNC Cohort: RADIOGEN-HNC (Study on the genomic influence in patients undergoing RT) include patients with a diagnosis of head and neck cancer, regardless of tumor location, histological type and clinical stage, recruited prospectively at the Radiation Oncology Service of the Hospital Clínico Universitario de Santiago de Compostela, Spain, from 2011 to 2017. Dosimetric, epidemiological and clinical data were collected using a case report form. The radiation toxicity were scored by physicians according to the Common Toxicity Criteria of Adverse Events (CTCAE v.4.0)[11]. All patients were treated using three-dimensional conformal technique (3D-CRT) delivered with a linear accelerator using 6 MV or 15 MV photon beams with curative intent. The patients underwent primary or adjuvant radiotherapy (combined or not combined with chemotherapy based on cisplatin/Cetuximab). The target dose was 60-70 Gy in 30-35 fractions at 2 Gy per fraction. The patients were followed up weekly during RT, monthly from the end of RT to 6 months, then every

six months until the five-year follow-up, and annually from then; when the radiotherapy oncologist considered it necessary and in those patients with moderate to severe toxicity, they were followed up more often. Written informed consent was obtained from each subject according to the protocols approved by the ethics review board of the Galician Ethical Committee for Clinical Research.

Head and Neck 5000: (headandneck5000.org.uk) is a prospective clinical cohort of people diagnosed with head and neck cancer. The study has been described in detail elsewhere[14,15]. Briefly, 5,511 participants were recruited from 76 centres across the UK between 7th April 2011 and 31st December 2014. All people aged 16 or over with a new diagnosis of head and neck cancer were eligible to join the study and the response rate was 49%. Clinical information on diagnosis and treatment was collected using data capture forms completed by research staff at the study centres. Health and lifestyle information including information on treatment side-effects was obtained using self-completed questionnaires. Ethical approval for this study was given by the South West – Frenchay Regional Ethics Committee (ref: 10/H0107/57).

For this study, oral, pharyngeal (oropharyngeal, nasopharyngeal, hypopharyngeal) and laryngeal cancer patients who received primary or post-operative radiotherapy as part of their cancer treatment were included (N=3,467). The radiotherapy treatment protocol was decided by the local oncologist based on the current guidance. Linkage to the NatCanSat dataset, a national database of radiotherapy information, provided patient level data on radiotherapy dose and fractionation. Self-reported toxicity relating to dysphagia and xerostomia was recorded at cancer diagnosis and at 4-months following diagnosis. At 12-months and 36-months, patients who had undergone radiotherapy were invited to complete a toxicity specific questionnaire based on the LENT-SOMA questionnaire[16]. For baseline toxicity, the collection closest to but preceding the start of radiotherapy was used. To identify acute toxicity to radiotherapy only individuals with self-reported toxicity data less than 90 days after the start of their radiotherapy were included.

A score for dysphagia and xerostomia was assigned to patients who had completed the toxicity questionnaires based on the severity of their symptoms: Dysphagia: 0 = regular diet; 1 = soft diet only; 2 = liquids only; 3 = feeding tube. Xerostomia (based on: Do you have a dry mouth?): 0 = none; 1 = A little; 2 = Quite a lot; 3 = very much.

RAPPER-HNC Cohorts: The RAPPER study (Ethics Ref: 05/Q0108/365) HNC patients have been recruited from the VoxTox study (CRUK, Cambridge) and ART DECO study (The Institute of Cancer Research, London). The timepoints, cohort criteria, and patient numbers that are relevant to each study, are detailed below. Other data may have also been collected as part of each sub-cohort. As well as their own studies, patients in each cohort are required to meet the RAPPER inclusion criteria as follows: patients receiving, or have received, radiotherapy for cancer, can obtain patient consent, patients able to provide venous blood sample, no other malignancy prior to treatment for specified tumor types (expect basal cell, squamous cell carcinoma or in situ carcinoma) and, for patients < 18 years, an absolute neutrophil count of >1000 cells /µl. Patients that were not eligible according to the abovementioned criteria were not included in the study.

VoxTox Cohort: VoxTox is a single-center, non-randomized longitudinal cohort study. VoxTox recruited 85 HNC patients to the RAPPER study. VoxTox patients had their acute toxicity assessed every week for 6 weeks from the start of RT, then at 4 and 8 weeks after RT. Late toxicity assessed after RT at 3 months and 6 months, then every 12 months until 5 years since RT. Eligibility criteria for the study includes: age > 18 years, malignant or benign tumor of the head and neck, already treated with, or suitable for treatment with, radical radiotherapy (RT) with daily image guidance using TomoTherapy or equivalent technology, suitable for the 5 year follow up schedule, adequate cognitive ability to participate in the interviews and complete the forms and questionnaires and written informed consent. Patients that were not eligible according to the abovementioned criteria, or had earlier RT to the area being treated, were excluded.

ART DECO Cohort: ART DECO[17] is a phase III, multicentre, randomized controlled trial to determine the potential of dose escalated intensity-modulated radiotherapy (IMRT) to improve locoregional failure free rate and laryngeal preservation in patients with locally advanced laryngeal and hypopharyngeal cancers, without increasing the incidence of severe acute and late toxicities to unacceptable levels. ART DECO recruited 166 patients to the RAPPER study. ART DECO patients received either dose escalated IMRT or standard dose IMRT. Dose escalated IMRT delivered 67.2 Gee in 28 fractions to the involved site and nodal groups, and 56 Gy in 28 fractions to nodal areas at risk of harboring microscopic disease. Standard dose IMRT delivered 65Gy in 30 fractions to the involved site and nodal groups and 54Gy in 30 fractions to nodal areas at risk. Acute toxicity

assessed weekly during radiotherapy and at 1, 2, 3, 4, 8 weeks post treatment. Late toxicity assessed at 3, 6, 12, 18 and 24 months post treatment and annually to 5 years, with annual follow up including recurrence for at least 5 years. Eligibility for the study includes, histologically confirmed locally advanced (stage III or IV a/b disease) squamous cell cancer of the larynx or hypopharynx, chemo-radiotherapy or induction chemotherapy, WHO performance status of 0 or 1, creatinine clearance of >50ml/min, adequate cognitive ability suitable for long term follow-up and informed consent. Exclusion criteria includes previous RT to the head and neck, metastatic disease, previous or concurrent illness, pre-existing previous speech or swallowing problems unrelated to cancer diagnosis or a large primary tumour, where organ preservation is unrealistic.

NIMRAD Cohort: NIMRAD study is independent of the recruitment to the RAPPER cohort. NIMRAD is a randomized placebo-controlled trial of synchronous NIMorazole versus RADiotherapy alone in patients with locally advanced head and neck squamous cell carcinoma not suitable for synchronous chemotherapy or cetuximab. 338 patients were genotyped for GWAS. 30 fractions of radiotherapy (RT), each of 2.17 Gy given once a day, 5 days a week, for 6 weeks, totaling 65 Gy. Acute toxicity was reported for all patients at baseline, week 1-6, and at 6 weeks and 12 weeks post treatment. Late toxicity was assessed for all patient's baseline, month 6, 12, 18, 24, 36 of follow up. Eligibility for the study includes, histologically confirmed (newly diagnosed) head and neck squamous cell carcinoma at the following primary sites – oropharynx, hypopharynx and larynx, no evidence of distant metastasis, Stage T3/T4 N0; any node +ve case including T1 node +ve; T2N0 base of tongue/hypopharynx, >18 years of age and available for follow up within the UK. Exclusion criteria includes: T1N0 tumors or those within the nasopharynx, nasal cavity or sinus, oral cavity; T2N0 larynx and tonsil, any prior chemotherapy in the last 6 months or RT within the planned radiation field, presence of any life-threatening illness, patient unable to give informed consent or complete questionaries, any malabsorption syndrome, patients who are breastfeeding, previous malignancy within the last 5 years and previous definitive surgery to the primary site.

Breast Cohorts:

Two breast cancer cohorts included 2,966 patients (Supplementary Table S5): United Kingdom RAPPER-breast (n=907) and multinational REQUITE-breast (n=2,059). Details are as follows.

RAPPER Cohort: Women with operable unilateral histological-confirmed breast cancer (T1–3, N0–1, M0 at presentation) or DCIS requiring radiotherapy after complete macroscopic excision of the tumour by breast conserving surgery (no implants) were eligible for the IMRT trial[18]. All patients underwent conservative surgery followed by adjuvant radiotherapy with doses of 40 Gy in 15 fractions over three weeks. Patients were randomised to standard breast radioterhapy (control arm) or a simple, manual forward-planned intensity-modulated radiotherapy (IMRT) technique (interventional arm). Blood samples were collected as part of the trial and patients provided consent for their DNA to be used in future radiogenomics studies. RAPPER[19] performed all DNA extraction and genotyping. The primary endpoint of the IMRT trial was photographic assessment of late cosmetic effects. Acute skin toxicity was recorded prospectively at 3 weeks using the RTOG scale.

REQUITE Cohort: The multicentre REQUITE breast cancer patient cohort was recruited prospectively in seven European countries and the USA between 2014 and 2016 with standardised prospective data collection[20]. Patient baseline characteristics and methodology have been described in detail elsewhere[5]. All enrolled patients had unilateral invasive or in situ breast cancer and were treated with breast-conserving surgery followed by EBRT according to local protocol. Approximately half were treated with IMRT, with a lower proportion in France and no IMRT at Italian or US centres. The majority of patients received a tumour-bed boost (64 %), ranging from less than 20 % at the French, Italian and Spanish centres to over 80 % at the Belgian centres, given either simultaneously (n=257) or sequentially (n=1,138). Patients with invasive breast cancer in Belgium and the UK were treated using the START-B hypo-fractionated regimen. Although late toxicity was the main endpoint in REQUITE, data collected at the end of radiation treatment was used to document acute toxicity. All patients gave written informed consent. The study was approved by local ethics committees in participating countries (UK NRES Approval 14/NW/0035) and registered at www.controlled-trials.com (ISRCTN98496463).

Lung cohorts:

Three lung cancer cohorts included 821 patients (Supplementary Table S4): Spanish RADIOGEN-Lung cohort (n=154), the multinational REQUITE-lung cohort (n=467), and the European-Canadian CONVERT trial (n=200). Details are as follows.

RADIOGEN-Lung Cohort: The RADIOGEN (Study on the genomic influence in patients undergoing RT) lung cohort[21] consists of patients with a diagnosis of non-small cell lung cancer stages I-III, eligible for receiving three-dimensional conformal radiotherapy with curative intent. The target dose was 60-66 Gy in 30-37 fractions at 1.8 to 2 Gy per fraction. Patients recruited at the Radiation Oncology Department of the Clinical University Hospital of Santiago de Compostela, Spain, between 2008 and 2015. Written informed consent was obtained from each subject according to the protocols approved by the ethics review board of the Galician Ethical Committee for Clinical Research.

REQUITE-Lung Cohort: This cohort consists of the set of patients diagnosed with lung cancer from the REQUITE project[5]. Lung cancer participants were recruited from 16 hospitals in seven countries (Belgium, France, Italy, the Netherlands, Spain, UK, the USA) between 2014 and 2017. Patients with a confirmed diagnosis of primary lung cancer, eligible for radical radiotherapy, sequential or concurrent chemoradiotherapy, or stereotactic body radiotherapy, without other neoplasms before treatment or evidence of distant metastases, were included. All patients gave written informed consent. The study was approved by local ethics committees and registered at www.controlled-trials.com (ISRCTN98496463).

CONVERT Cohort: Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT)[22] was an open-label, phase 3, randomized superiority trial, registered with ClinicalTrials.gov (NCT00433563) and on the International Standardized Randomised Controlled Trial Registry (ISRCTN91927162). Patients with cytological or histological confirmation of limited-stage small-cell lung cancer were recruited from 2008 to 2013 on 73 centres in eight countries. Patients were randomized to receive concurrent twice-daily radiotherapy (45Gy in 30 twice-daily fractions) or concurrent once-daily radiotherapy (66Gy in 33 once-daily fractions) starting on day 22 of cycle 1 of chemotherapy. The mandatory radiotherapy technique was 3D conformal RT, although it was allowed to include patients with intensity-modulated RT and planning with PET/CT. Elective lymph node irradiation was not allowed. The trial was reviewed in the UK by

the National Research Ethics Service Committee North West–Greater Manchester Central, which granted ethics approval for the study (07/H1008/229). The protocol was also approved by the institutional review board or research ethics committee in each country and at each study centre.

Assessment of acute RIT

To achieve a composite score describing overall acute RIT, we used the standardized total average toxicity (STAT) method as described previously[23]. $STAT_{acute}$ scores were calculated as follows:

$$Z_{k,i} = (s_{k,i} - Mean_i) / Standard\ Deviation_i$$

$$STAT_k = mean\ Z_{k,i}$$

where s = toxicity score for a given endpoint, i, in each individual, k. Mean and standard deviation were taken over all cases in the study population. STATacute was calculated using toxicity assessments collected within 90 days from start of RT. When more than one assessment was available within this timeframe, the worst score was used. Different endpoints were used for calculating STATacute in each cancer type (Supplementary Tables S6-S9). Patients with high baseline toxicity were excluded (Supplementary Table S10).

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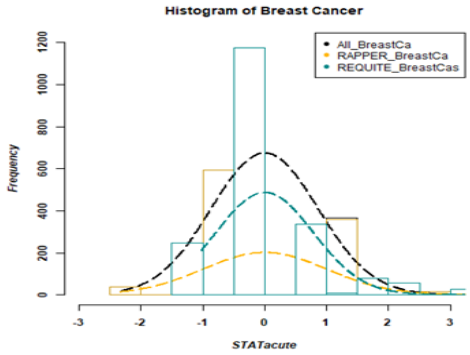
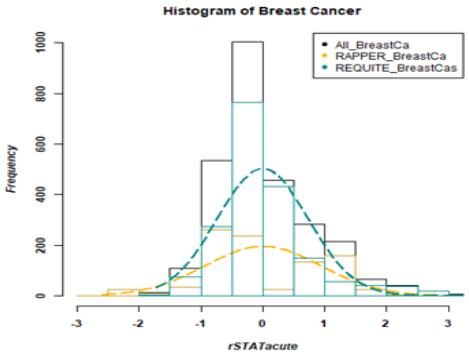
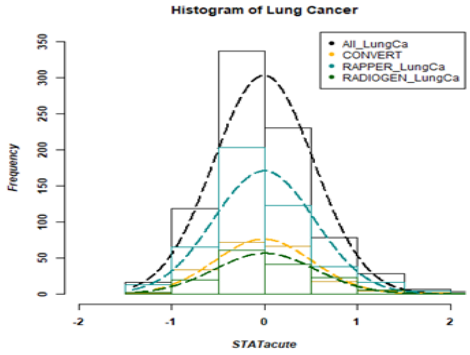
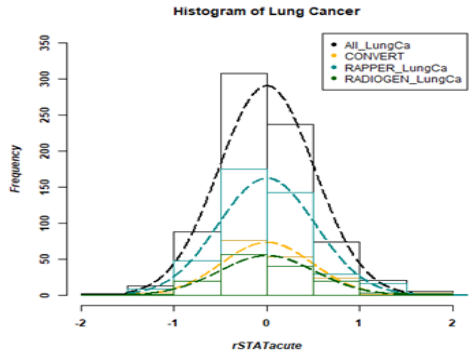
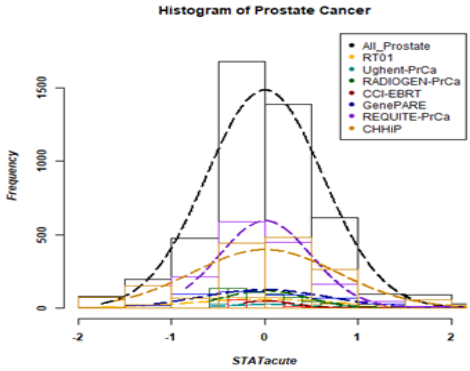
Supplementary Figure 1: Cancer type specific histograms of $STAT_{acute}$ and $rSTAT_{acute}$ and curve of normal-log distribution.

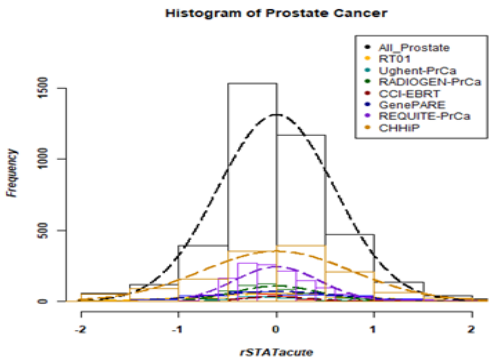


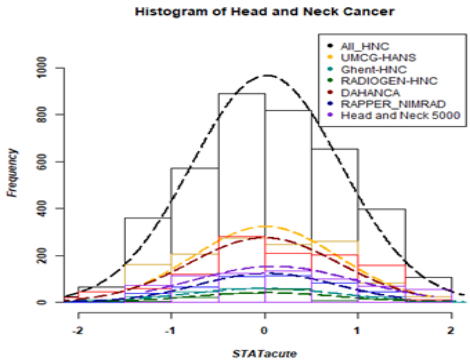


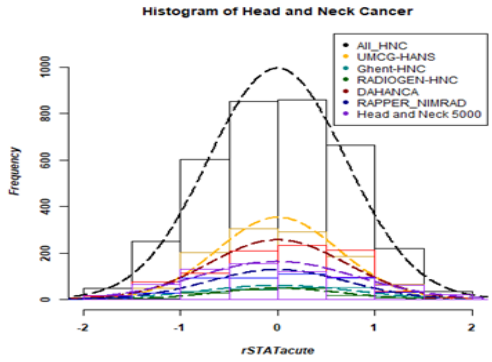




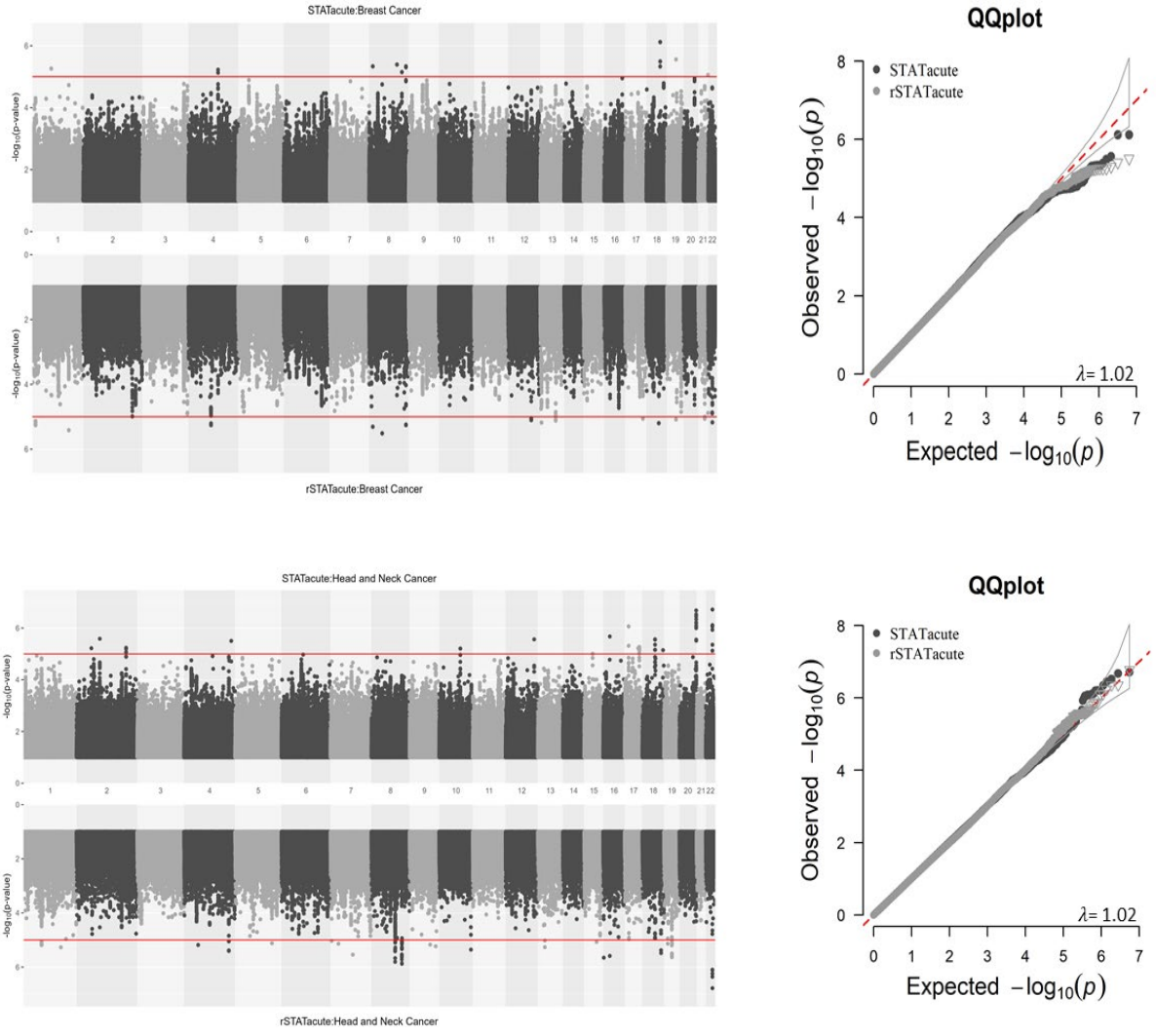


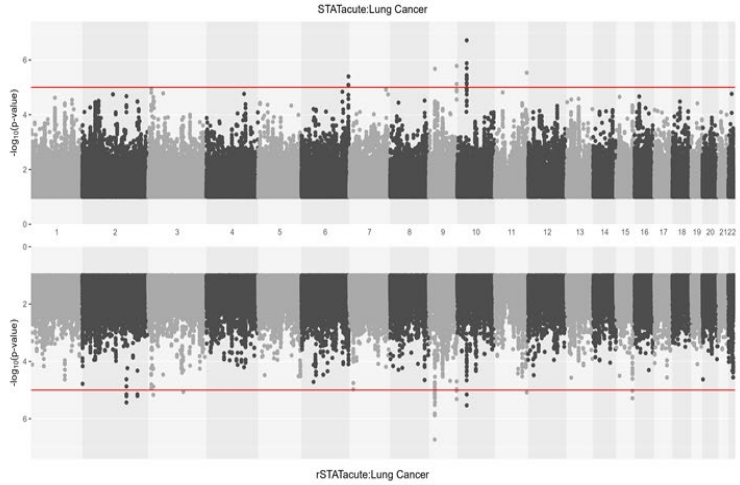


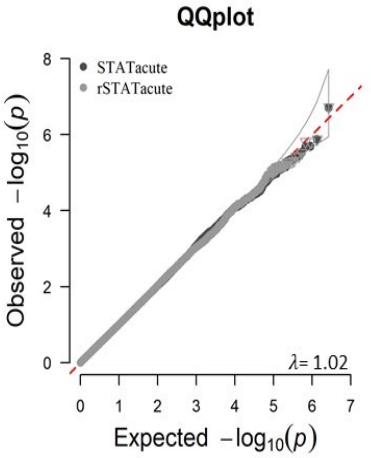


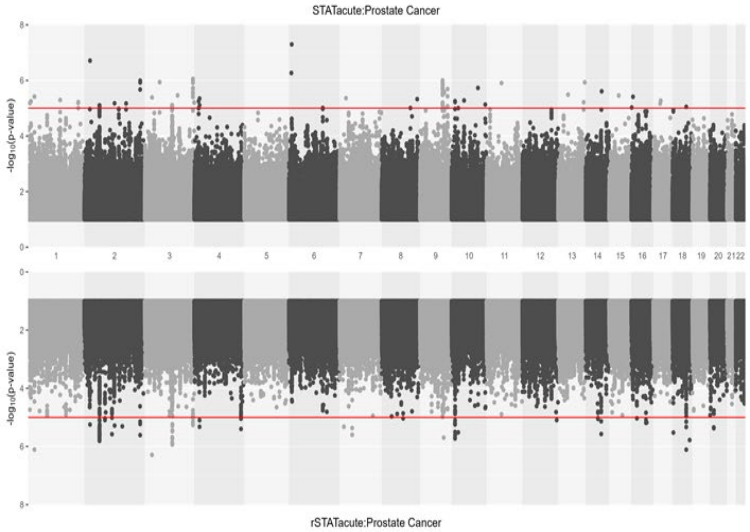


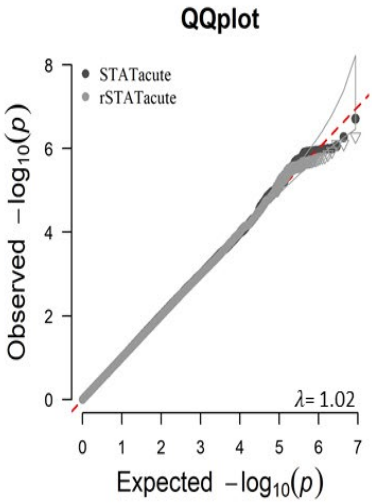
Supplementary Figure 2: Manhattan (left) and QQ (right) plots of meta-analysis for $STAT_{acute}$ and $rSTAT_{acute}$ in four cancer type. Manhattan plots: GWAS results of $STAT_{acute}$ and $rSTAT_{acute}$ are shown in the upper and the lower panel, respectively, of the Manhattan plots. The *X* axis shows location in the genome. Each SNP is plotted as a dot. The *Y* axis shows $-\log_{10}$ P-values for the association of each of the SNPs to the desired outcome. The red line shows the threshold for genome-wide suggestive ($P\text{-}value<1\times10^{-5}$). QQ plots: The *Y* axis shows observed $-\log_{10}$ P-values, and the *X* axis shows the expected $-\log_{10}$ P-values. Each SNP is plotted as a dot, and the red line indicates null hypothesis of no true association. Deviation from the expected P-value distribution is evident only in the tail area, and along with the estimated lambda coefficients, suggesting that population stratification was adequately controlled.



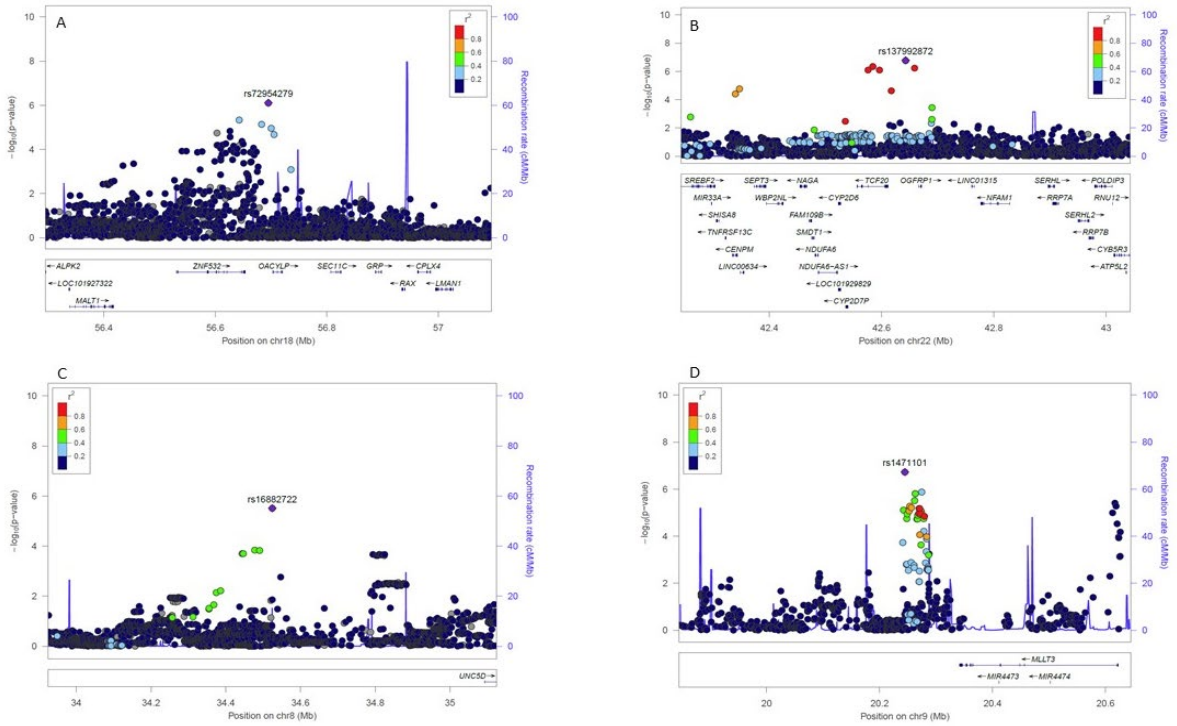

STATacute:Lung Cancer
rSTATacute:Lung Cancer


QQplot
STATacute
rSTATacute
λ= 1.02
Observed −log10(p)
Expected −log10(p)

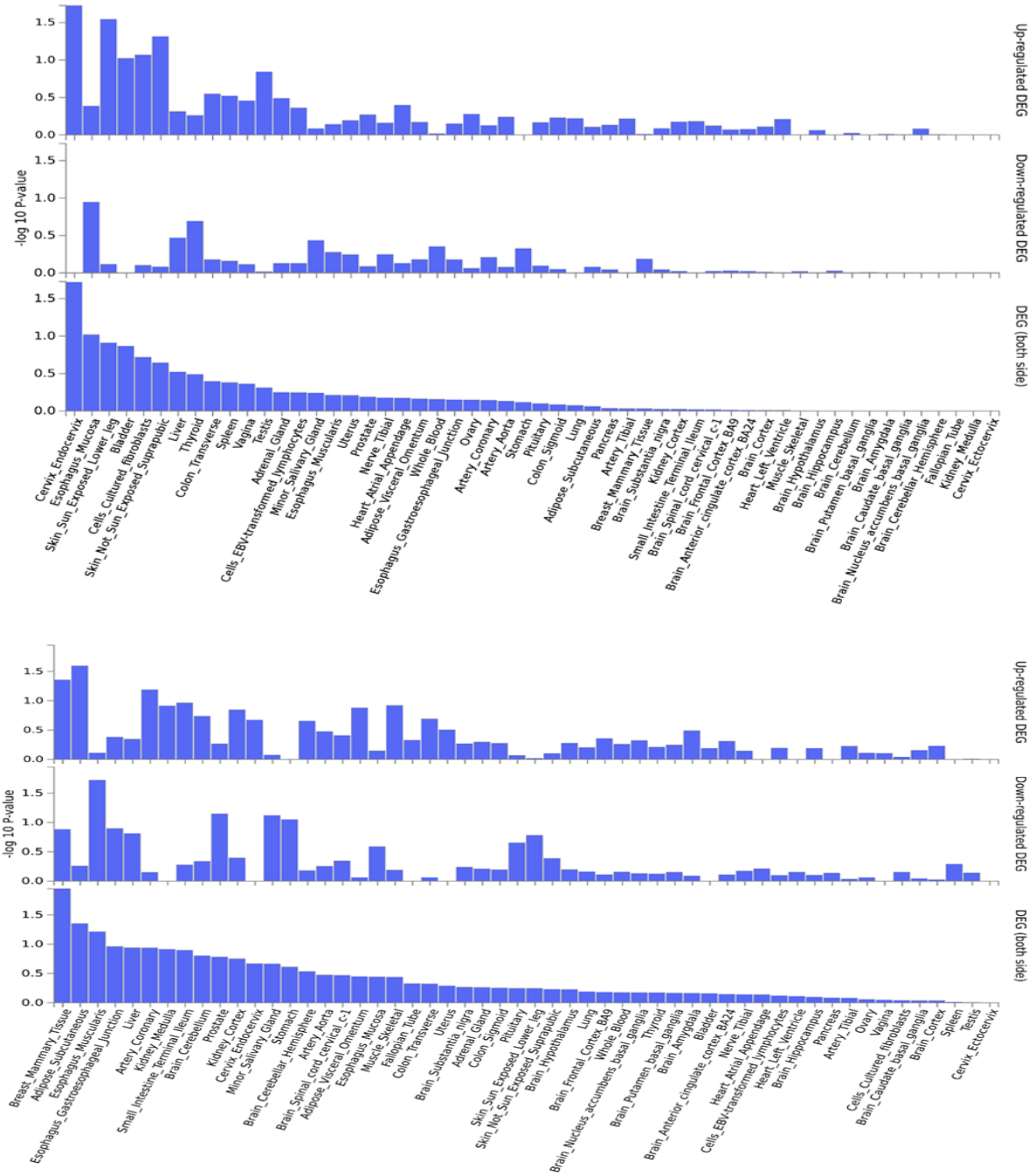

STATacute:Prostate Cancer
rSTATacute:Prostate Cancer

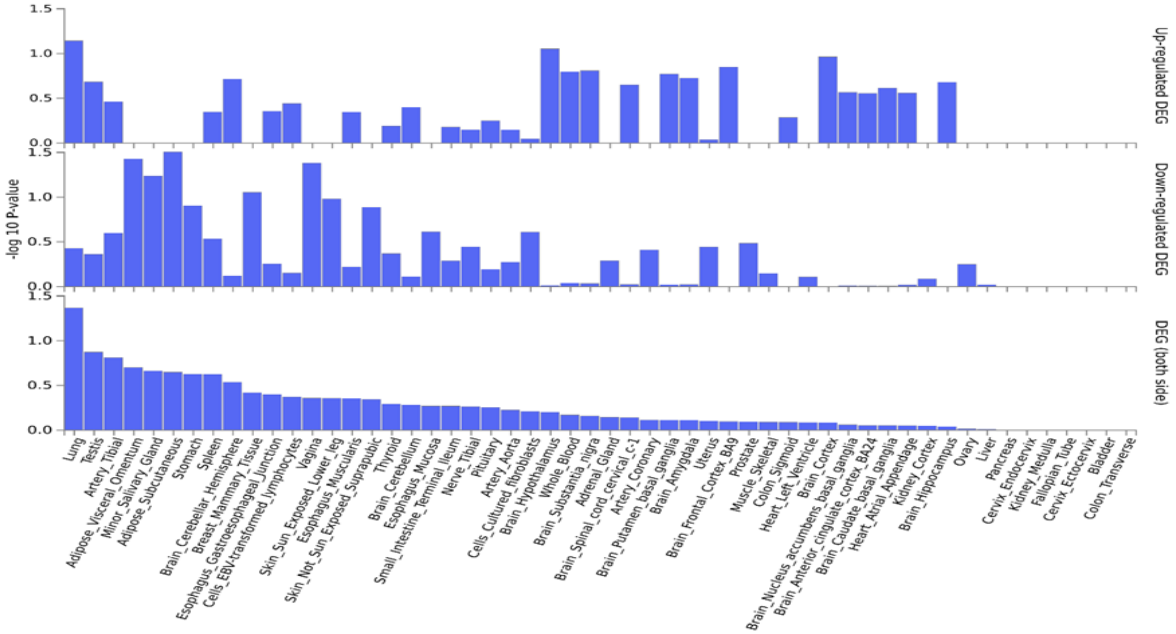

QQplot
STATacute
rSTATacute
λ= 1.02
Observed −log10(p)
Expected −log10(p)

Supplementary Figure 3: Locus Zoom plot for top locus associated with $rSTAT_{acute}$; A: prostate, B: HNC, C: breast, and D: lung cancer. Purple diamond shows the top SNP in each plot and variants are colored according to linkage disequilibrium with the top SNP. The *Y* axis shows observed $-\log_{10}$ P-values, and the *X* axis shows the position across the genome with genes mapped there. In the prostate cancer cohorts (**panel A**), rs72954279 showed the strongest association with $rSTAT_{acute}$ (effect size of 0.020, P-value =7.76e-7) near *OACYLP*, which encodes the O-acyltransferase like pseudogene. In the HNC cohorts (**panel B**), rs137992872 showed the strongest association with both $rSTAT_{acute}$ (effect size 0.038; p-value =1.66e-7) and $STAT_{acute}$ (effect size of 0.211, p-value =1.93e-7). The nearest gene to rs137992872 was *TCF20*, which encodes a transcription factor for the platelet-derived growth factor-responsive element in the matrix metalloproteinase 3 promoter. In the breast cancer cohorts (**panel C**), rs16882722 was the top associated SNP (effect size 0.158; p-value =3.09e-6) located near *UNC5D,* encoding a protein involved in neuronal cell guidance and cell-cell adhesion. In the lung cancer cohorts (**panel D**), rs1471101, near *MLLT3*, part of the transcription elongation factor complex, was the most stronly associated SNP (effect size 0.031; p-value =1.88e-7).



Supplementary Figure 4. Gene expression plot in 53 tissue types for genes related to $rSTAT_{acute}$ per cancer type; A: prostate, B: HNC, C: breast, and D: lung cancer. Tissue expression analysis testing the positive relationship between all annotated genes using the full distribution of SNPs p-values and the average expression of genes per tissue type based on GTEx RNA-seq data.




-log 10 P-value
Up-regulated DEG
Down-regulated DEG
DEG (both side)
1.5
1.0
0.5
0.0
Lung
Testis
Artery_Tibial
Adipose_Visceral_Omentum
Minor_Salivary_Gland
Adipose_Subcutaneous
Stomach
Spleen
Brain_Cerebellar_Hemisphere
Breast_Mammary_Tissue
Esophagus_Gastroesophageal_Junction
Cells_EBV-transformed_lymphocytes
Skin_Sun_Exposed_Lower_leg
Vagina
Esophagus_Muscularis
Skin_Not_Sun_Exposed_Suprapubic
Thyroid
Brain_Cerebellum
Esophagus_Mucosa
Small_Intestine_Terminal_Ileum
Nerve_Tibial
Pituitary
Artery_Aorta
Cells_Cultured_fibroblasts
Brain_Hypothalamus
Whole_Blood
Brain_Substantia_nigra
Adrenal_Gland
Brain_Spinal_cord_cervical_c-1
Artery_Coronary
Brain_Putamen_basal_ganglia
Brain_Amygdala
Uterus
Brain_Frontal_Cortex_BA9
Prostate
Muscle_Skeletal
Colon_Sigmoid
Heart_Left_Ventricle
Brain_Cortex
Brain_Nucleus_accumbens_basal_ganglia
Brain_Anterior_cingulate_cortex_BA24
Brain_Caudate_basal_ganglia
Heart_Atrial_Appendage
Kidney_Cortex
Brain_Hippocampus
Ovary
Liver
Pancreas
Cervix_Endocervix
Kidney_Medulla
Fallopian_Tube
Cervix_Ectocervix
Bladder
Colon_Transverse