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Personalised Pathway Analysis Reveals Association between DNA Repair Pathway Dysregulation and Chromosomal Instability in Sporadic Breast Cancer

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Abstract

The Homologous Recombination (HR) pathway is crucial for the repair of DNA double-strand breaks (DSBs) generated during DNA replication. Defects in HR repair have been linked to the initiation and development of a wide variety of human malignancies, and exploited in chemical, radiological and targeted therapies. In this study, we performed a personalised pathway analysis independently for four large sporadic breast cancer cohorts to investigate the status of HR pathway dysregulation in individual sporadic breast tumours, its association with HR repair deficiency and its impact on tumour characteristics. Specifically, we first manually curated a list of HR genes according to our recent review on this pathway (Liu et al., 2014), and then applied a personalised pathway analysis method named Pathifier (Drier et al., 2013) on the expression levels of the curated genes to obtain an *HR* score quantifying HR pathway dysregulation in individual tumours. Based on the score, we observed a great diversity in HR dysregulation between and within gene expression-based breast cancer subtypes, and by using two published HR-defect signatures, we found HR pathway dysregulation reflects HR repair deficiency. Furthermore, we identified a novel association between HR pathway dysregulation and chromosomal instability (CIN) in sporadic breast cancer. Although CIN has long been considered as a hallmark of most solid tumours, with recent extensive studies highlighting its importance in tumour evolution and drug resistance, the molecular basis of CIN in sporadic cancers remains poorly understood. Our results imply that HR pathway dysregulation might contribute to CIN in sporadic breast cancer.

Keywords: *DNA repair*; *homologous recombination*; *breast cancer*; *chromosomal instability*; *pathway analysis*

Introduction

Chromosomal instability (CIN), defined as an increased rate of gain or loss of whole chromosomes or large chromosomal fragments, is a hallmark of most solid tumours. CIN is the primary form of genomic instability that is thought to be the major cause of genetic heterogeneity in cancer (Burrell et al., 2013b), and is thus strongly implicated in tumour evolution. CIN also has important clinical implications, as it has been linked to poor prognosis e.g. by conferring intrinsic multidrug resistance (Lee et al., 2011). The molecular basis of CIN in hereditary cancer is relatively clear, which has been attributed to mutations in DNA repair genes (Negrini et al., 2010); however, the underlying mechanisms of CIN in various sporadic cancers remain poorly understood. Carter and colleagues developed a gene expression-based CIN signature, termed CIN25, based on 25 genes that are most overexpressed in tumours with CIN (Carter et al., 2006). A considerable number of genes involved in *replication* and *cell cycle* contribute to this signature, suggesting an important link between these cellular processes and CIN. This was further corroborated by Negrini et al. (2010), who proposed a *replication stress* model to explain CIN in sporadic tumours; this model was recently validated in colorectal cancer (Burrell et al., 2013a).

Highly proliferative cancer cells undergo considerable replication stress that results in the stalling of replication forks. These stalled forks are usually stabilised and restarted after the source of stress is removed via a complex replication stress response pathway (Zeman and Cimprich, 2014). Lack of stabilisation and/or the prolonged persistence of a stalled fork can generate DNA double-strand breaks (DSBs), which are subsequently repaired by DSB repair machinery to restart the forks. However, in the absence of such a DSB repair machinery the DSBs will develop into chromosomal breaks, resulting in CIN. *Homologous recombination* (HR) is a crucial pathway responsible for repairing DSBs during replication. Using homologous sister chromatid as templates, HR presents a high-fidelity repair mechanism that is crucial for error-free DNA replication.

The core components of HR are fairly well established for their specific roles i.e. monitoring, signalling and repairing of DSBs (Liu et al., 2014), and HR defects can be detected by investigating the loss-of-function mutations in these genes. However, the dysfunction of HR can also be caused by numerous other mechanisms. For example, changes or defects in chromatin remodelling (Price and D'Andrea, 2013; van Attikum and Gasser, 2009), microRNAs (Chowdhury et al., 2013; d'Adda di Fagagna, 2014; Sharma and Misteli, 2013), post-translational modifications such as ubiquitination and sumoylation (Bekker-

Jensen and Mailand, 2011; Dou et al., 2011; Ulrich, 2012), and inappropriate expression of certain genes that are not directly involved in HR (Y. Peng et al., 2015; Watkins et al., 2015) can considerably affect HR components, thereby causing aberrant HR function. As a consequence, single-gene approaches or approaches focusing on one mechanism yield only an incomplete picture of abnormal HR in a given tumour. On the other hand, HR-deficient cells may compensate for the defect in a given HR gene by altering the expression level of other HR genes (Pitroda et al., 2014). The most notable example is the overexpression of DNA repair protein RAD51 homolog 1 (*RAD51*), which is observed when breast cancer susceptibility gene 1 (*BRCA1*) (Martin et al., 2007), breast cancer susceptibility gene 2 (*BRCA2*) (Brown and Holt, 2009) or other key HR genes (Takata et al., 2001) are defective. It is therefore of interest to determine a measure of HR *pathway* dysregulation, aggregating the expression of all HR genes, which may reflect HR repair deficiency in tumours regardless of the mechanism that has led to the deficiency.

The vast majority of breast tumours are sporadic, which accounts for 90%-95% of all diagnosed breast cancer cases (Davis, 2011) and are characterised by their great heterogeneity in biological property and patient outcome. To dissect this heterogeneity, estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) have been used as standardised diagnostic markers in clinical practice to guide the choice of treatment. Gene expression profiling has defined five intrinsic subtypes (also known as PAM50 subtypes) with clinical relevance: Luminal A, Luminal B, Basal-like, HER2 and Normal-like (Hu et al., 2006; Parker et al., 2009; Perou et al., 2000; Sørlie et al., 2001). More-recent genomic studies, notably from the Cancer Genome Atlas (TCGA) and Molecular Taxonomy of Breast Cancer International Consortium (METABRIC), have uncovered substantial heterogeneities within these receptor- or gene expression-based subtypes, resulting in the definition of up to ten subtypes (Ciriello et al., 2013; Curtis et al., 2012; Koboldt et al., 2012; Lehmann et al., 2011; Yanagawa et al., 2012). However, it is likely that heterogeneity exists even within these newly established subtypes. In the coming age of personalised medicine, each tumour may be analysed individually.

Pathway analysis has become the first choice to gain functional insights from expression data, beyond the detection of differential genes. Numerous pathway analysis tools have been developed, however, most of them are designed for providing pathway dysregulation information at population level instead of tumour level. Among the recently proposed methods for personalised pathways analysis (Ahn et al., 2014; Drier et al., 2013; Vaske et al., 2010; Wang et al., 2015a; 2015b), Pathifier (Drier et al., 2013) has proven to be

particularly robust. It has been successfully applied to provide a pathway-based classification of breast cancer (Livshits et al., 2015), and when combined with Cox regression and L1 penalised estimation, has achieved better prognosis prediction compared with gene-based models (Huang et al., 2014).

In this study, we sought to perform a personalised pathway analysis to obtain a comprehensive understanding of the status of HR pathway dysregulation in individual sporadic breast tumours, its association with HR repair deficiency and its impact on tumour characteristics (CIN in this case). To this end, we calculated for each breast tumour an *HR* score that quantified the extent of HR pathway dysregulation in that tumour. Base on the score, we observed a great diversity in HR dysregulation between and within the PAM50 subtypes, and by using two published HR-defect signatures, we found HR pathway dysregulation reflects HR repair deficiency. More importantly, we uncovered a novel association between HR dysregulation and CIN, which indicates that dysregulated HR might contribute to replication stress-induced CIN in breast cancer. This knowledge may help future studies to identify the causative factors of CIN in sporadic breast cancer as well as in other cancer types.

Materials and Methods

1. Genomic data

Whole-genome gene expression data, DNA copy-number data, gene mutation data (only available for the TCGA samples) and related clinical data for four breast cancer cohorts (Table 1) were obtained from METABRIC (Curtis et al., 2012) and TCGA (Koboldt et al., 2012).

Table 1 Breast cancer cohorts analysed in this study

Cohort	No. of tumour samples						No. of normal breast tissues
	All	Basal-like	HER2	LumA	LumB	Normal-like	
METABRIC Discovery	997	118	87	466	268	58	144
METABRIC Validation	995	213	153	255	224	144	144
TCGA RNA-seq	1068	188	80	549	213	38	113
TCGA Microarray	522	98	58	231	127	8	22

Gene-expression data and chromosomal-level DNA copy-number data from the METABRIC project (Genome-phenome Archive accession number EGAS00000000083) were made available upon request, and had already been preprocessed as described by Curtis

et al. (Curtis et al., 2012). Gene-expression data from this project were based on the Illumina HT-12 v3 Expression Beadchip (Illumina, San Diego, CA, USA). The probe-level transcription estimates were mapped to gene-level estimates using the HT-12 v3 annotation file downloaded from the Illumina website (http://www.illumina.com/). Where two or more probes represented the same gene, the probe with the largest variation was chosen as the gene representative. DNA copy-number data from METABRIC had been generated using Affymetrix SNP 6.0 arrays (Affymetrix, Santa Clara, CA, USA). The corresponding PAM50 subtype assignment and clinical outcome were obtained from (Curtis et al., 2012).

The preprocessed gene-expression and DNA copy-number data (both chromosome-level and gene-level) for the TCGA RNA-seq cohort were downloaded via the UCSC Cancer Genomics Browser (https://genome-cancer.ucsc.edu/) on 13 October 2014. Gene-expression data for this cohort were measured using the Illumina HiSeq 2000 RNA Sequencing platform, and show the Expectation Maximization (RSEM)-normalised and percentile-ranked gene-level transcription estimates. DNA copy-number data for this cohort had been generated using Affymetrix SNA 6.0 arrays, with germline copy-number variation filtered out. PAM50 classifications for this cohort were obtained through personal communication with the TCGA consortium. A subset of these 1068 cases also has gene expression data obtained from microarray. The Level 3 gene-expression data for this TCGA Microarray cohort and the corresponding PAM50 classifications were downloaded from the TCGA data portal publication site (https://tcga-data.nci.nih.gov/docs/publications/brca_2012/) on 3 June 2014. These gene-expression data were based on Agilent custom 244K whole-genome microarrays and had been preprocessed as described by Koboldt et al. (Koboldt et al., 2012). DNA copy-number data for this cohort were obtained as a subset of the TCGA RNA-seq cohort, as the samples of the former cohort were covered by the later cohort.

The preprocessed gene mutation data for 982 TCGA samples, generated on an IlluminaGA system, were downloaded via the UCSC Cancer Genomics Browser (https://genome-cancer.ucsc.edu/) on 06 July 2015. Each gene had been assigned a value of 1 or 0, indicating whether a non-silent mutation was identified in the coding region of that gene (value=1) or not (value=0). These data were matched to the two TCGA cohorts respectively according to the sample ID.

2. HR pathway curation and calculation of *HR* score

Based on our recent review of the HR pathway (Liu et al., 2014), we manually curated a list of 82 genes with direct relevance to HR (Supplementary Table S1). We then

applied Pathifier (Drier et al., 2013) to the mRNA expression level of the curated HR genes to calculate an *HR* score that quantifies HR pathway dysregulation in individual breast tumours. Based on gene-expression profiles for tumours and normal breast tissues, Pathifier transforms HR gene-expression measurements into a measure of HR pathway dysregulation by fitting a principal curve (see Supplementary Figure S1 for a visualisation of the curve) that captures the maximal variability of the expression levels of the HR genes in all samples, and then projects each sample onto that curve. A sample's *HR* score is defined as its distance along the curve from the centroid of the normal tissues (Drier et al., 2013).

Not all HR genes we curated were present in the gene expression data for each of the four cohorts. We therefore calculated the *HR* score for each cohort based only on HR genes that are available for that cohort (ranges from 67 to 72, see Supplementary Table S1). No other ways for selecting HR genes were examined to minimize retrospective optimization for the correlations with CIN (see below).

3. CIN measurements calculation

The numbers of chromosomal breakpoints and the proportions of the genome affected by copy-number change (Genomic Instability Index, GII) for samples in the two METABRIC cohorts were downloaded from a recent study (Vollan et al., 2015) in which the METABRIC Group was involved. According to this study, a few samples with mismatched DNA/RNA were identified and excluded, resulting in 985 samples remaining in the Discovery cohort and 965 in the Validation cohort. To get the number of amplified/deleted genes for the same samples, we first calculated the copy number of each gene using the chromosomal-level DNA copy-number data available for the two cohorts, then applied cut-offs (≥ 0.10 for amplified genes and ≤ -0.15 for deleted genes) that are similar to those used by METABRIC to define chromosomal regions with amplifications or deletions.

For the two TCGA cohorts, we used the chromosomal-level DNA copy-number data to calculate number of breaks by counting the total number of chromosomal segments at least 1 kb in length. The calculation of GII was also based on the chromosomal-level DNA copy-number data after filtering out segments shorter than 1kb, and the same cut-offs as mentioned above (≥ 0.10 for amplification and ≤ -0.15 for deletion) were used to identify chromosomal regions with copy-number change. The number of amplified/deleted genes for each of the two TCGA cohorts was obtained from the downloaded gene-level DNA copy-number data, where +1 and +2 represent amplification and -1 and -2 represent deletion.

4. Survival analysis

Survival analysis for both of the METABRIC datasets was performed using the R package *survival* (http://cran.r-project.org/web/packages/survival/index.html). Patient follow-up time was limited to 15 years, and only breast cancer-related deaths were counted.

Results

1. An *HR* score for quantifying HR pathway dysregulation in individual breast tumours

An *HR* score was developed for each breast tumour to quantify HR pathway dysregulation in that tumour; a high *HR* score means that the expression of the HR genes as a whole in an individual tumour is very different from the situation in normal breast tissues (see Supplementary Figure S2 for HR gene expression in tumours with low to high *HR* score). To calculate this score, we first manually curated a list of 82 HR genes (Supplementary Table S1) according to our recent review on the HR pathway (Liu et al., 2014). This gene list provides more up-to-date knowledge about the content of HR compared to publicly available pathway databases; for instance, it catalogues 54 more genes than the HR pathway in the Kyoto Encyclopedia of Genes and Genomes (KEGG) database (Kanehisa and Goto, 2000). The expression profiles of the curated HR genes were then employed as input to the Pathifier method (Drier et al., 2013) to compute the score. To ensure reproducibility of the results, we performed this pathway analysis independently for four large breast cancer cohorts that also include data on normal breast tissues (Table 1). Depending on data availability, the number of HR genes for calculating the score is slightly different across the cohorts (Supplementary Table S1).

The boxplots in Figure 1 display the *HR* score distribution in each cohort with regard to the PAM50 molecular subtypes, and in normal breast tissues. We observed a consistent pattern across the four cohorts: basal-like tumours generally have the highest *HR* score, followed by HER2 and Luminal B tumours, and then Luminal A and Normal-like tumours; the normal breast tissues always have the lowest *HR* score as a consequence of being the benchmark. Similar results can be seen in Supplementary Figure S3 showing *HR* score versus the *HR* score-based rank of the tumours of different subtypes. The consistent distribution of the *HR* score by tumour subtype across the different cohorts and gene-expression profiling platforms (RNA-seq and microarray in TCGA) is strong evidence that the *HR* score is robust

and reproducible. Interestingly, we observed some variability in *HR* score within tumours of the same subtype, as highlighted by some outliers in the boxplots, suggesting some heterogeneity in HR pathway dysregulation within the subtypes.

2. The *HR* score is reflective of HR repair deficiency.

The *HR* score is gene expression-based, and measures the extent to which the HR pathway is dysregulated. To test whether there exists an association between HR pathway dysregulation and HR repair deficiency, we next asked whether the *HR* score is reflective of HR repair deficiency (i.e., whether a tumour with high *HR* score is likely to be HR-defective). We used two published HR-defect signatures, homologous recombination defect (HRD) (G. Peng et al., 2014) and Large-scale transitions (LSTs) (Popova et al., 2012), to test this hypothesis.

2.1. Comparison with the HRD signature

The HRD signature encompasses 230 genes that are differentially expressed between HR-intact and HR-deficient cells, and is intended to represent the global impact of HR defect on the transcriptome of a tumour cell (G. Peng et al., 2014). To identify tumours (or cell lines) with HR deficiency, Peng et al. performed a hierarchical clustering analysis based on the expression level of the 230 genes to divide samples into two clusters, one considered as HR-intact and the other HR-deficient (G. Peng et al., 2014).

In this study, we performed the same clustering analysis for each of the four cohorts (Figure 2A for the METABRIC discovery cohort and Supplementary Figures S4, S5 and S6 for the three remaining cohorts). As shown in Figure 2A, tumours with low HR score (upper horizontal bar, green) are mostly tumours belonging to the HR-intact cluster, whereas tumours with high HR score (upper horizontal bar, red) are mostly tumours belonging to the HR-deficient cluster. To be more precise, Figure 2B shows the distribution of the HR score in the two HRD-based clusters for each of the four cohorts, demonstrating that tumours in the HR-deficient cluster in general have significantly higher HR score compared with tumours in the HR-intact cluster (p-values $\leq$ 9.1e-63, Wilcoxon Signed-rank test). These observations indicate that tumours with high HR scores are likely to be HR-defective, as predicted by the HRD signature.

2.2. Comparison with the LST signature

LST refers to a chromosomal break whose flanking regions are at least 10 Mb in size. A tumour with a large number of LSTs indicates HR defect-related genomic scarring as a

measure of chromosomal instability (Popova et al., 2012). In this study, we estimated the number of LSTs for each tumour using the DNA copy number data, and divided each cohort into two groups according to the method and cut-offs described in (Popova et al., 2012): LST^+ ($\geq$ 20 LSTs) and LST^- (< 20 LSTs). The numbers of LST^+ and LST^- tumours identified in each cohort are summarised in Supplementary Table S2. As in the comparison with the HRD signature, we found that LST^+ tumours generally have higher HR scores compared with LST^- tumours, even in the case of the METABRIC Discovery cohort where only nine LST^+ tumours were identified (Figure 3). This observation also supports the idea that the *HR* score is indicative of HR defect.

Taken together, the results based on HRD and on LST demonstrate an association between HR pathway dysregulation, as represented by the *HR* score, and HR repair deficiency. In addition, in the two TCGA cohorts for which gene mutation data were available, we also observe that tumours with at least one non-synonymous mutation in one of six key HR genes have significantly higher *HR* score than do the tumours with no mutation in any of these genes (see Supplementary Figure S7 for more details). All these results support the existence of a compensatory mechanism through which HR-deficient cells respond to their HR defect by altering the expression level of HR genes. Interestingly, it has been proposed that melanoma cells exploit the overexpression of DNA repair genes, particular those involved in DSB repair, to increase their DNA repair capacity that is necessary for them to invade and give rise to distant metastases (Sarasin and Kauffmann, 2008). Consistent with this, overexpression of certain DNA repair genes is utilised by polyploid cells to overcome replication stress-induced senescence barriers (Zheng et al., 2012). All these results indicate that altering the expression of DNA repair genes or pathways may be a compensatory mechanism commonly exploited by tumour cells.

3. Association with CIN

Because replication stress has emerged as a common source of CIN in caner, and HR is the crucial pathway for the repair of replication stress-induced DSBs, we hypothesised that there might be a link between HR pathway dysregulation, which is indicative of HR repair deficiency as described above, and the degree of CIN in breast carcinomas. To test this hypothesis, we first examined the correlation between the *HR* score and the widely used CIN signature CIN25 (Carter et al., 2006). We then investigated the association between the *HR* score and each of the three common CIN measurements: number of chromosomal

breakpoints, fraction of the genome with copy-number alterations (genomic instability index, GII), and number of amplified/deleted genes. In particular, as data pre-processing and segregation algorithm can significantly affect the actual value of the CIN measurements, we downloaded the numbers of chromosomal breaks and GII for the two METABRIC cohorts from a recent publication (Vollan et al., 2015). We believe these measures from a third-party study provide more-objective results for our analysis.

3.1. Association with CIN25

Figure 4 displays a scatter plot between the CIN25 score, defined as the mean expression value of the CIN25 genes (Carter et al., 2006), and the *HR* score for tumours from each of the four cohorts. Each cohort showed a high correlation between the CIN25 score and the *HR* score (Spearman correlation coefficient r = 0.94 and r = 0.93 for the two METABRIC cohorts, and r = 0.85 and r = 0.96 for the two TCGA cohorts), indicating that the *HR* score is also correlated with CIN level. Moreover we found ten of the CIN25 genes (40%) to be present among the 230 genes of the HRD signature mentioned in Section 2.1, which indicates that HR defects might be one of the underlying biological mechanisms responsible for the expression change of the CIN25 genes.

Overall, these results revealed that the *HR* score correlates with the CIN25 score, and support the hypothesis that there exists an association between HR pathway dysregulation, as represented by the *HR* score, and CIN level in tumours, as predicted by the CIN25 score.

3.2. Association with three common CIN measurements

Because the CIN25 score only indirectly estimates CIN level in tumours, we also directly assessed the relationship between the *HR* score and each of the three common CIN measures (breakpoints, GII and number of amplified/deleted genes). We asked whether tumours with higher *HR* score tend to have a higher CIN level. To address this, we divided tumours into four equal-sized groups based on the *HR* score quartiles, and statistically examined the differences between adjacent groups for each of the three CIN measurements. The boxplots in Figure 5 (METABRIC discovery cohort) show a high variability in each *HR* score quartile group for each CIN measurement, indicating that other mechanisms can also affect CIN. However, we observed a clear pattern that tumours with higher *HR* score indeed tend to have higher CIN level (Wilcoxon Signed-rank test, one sided FDR p-value < 0.05), with the exception of tumours in the third and fourth quartile groups in GII. Similar results were obtained for the remaining three cohorts (Supplementary Figures S8, S9 and S10).

Overall, these results suggest an association between the extent of HR pathway dysregulation and the degree of CIN level in breast carcinomas.

As the *HR* score is based on gene expression, to ascertain whether the association observed above is due to the gene expression-based PAM50 subtypes, we performed the same analysis independently on tumours within each PAM50 subtype. In each analysis, the samples were divided into high and low *HR* score groups according to the median. The results for the METABRIC discovery cohort are summarised in Figure 6. For this cohort we consistently observed that tumours in the high *HR* score group have more breakpoints than do tumours in the low *HR* score group within the subtypes, despite the wide range of the breakpoint numbers observed for each subtype. The difference in GII between the low and high *HR* score groups was significant in Basal-like, Luminal A and Normal-like tumours, but not in HER2 and Luminal B tumours, while the difference in number of amplified/deleted genes between the two groups was significant in all subtypes except HER2. For the other cohorts (Supplementary Figures S11, S12 and S13) we observed some differences between cohorts. For example, in the METABRIC Validation cohort, all three CIN measurements are significantly different between the two *HR* score groups for all subtypes, whereas the difference is significant in fewer subtypes in the TCGA Microarray cohort. These discrepancies might be due to low sample size in the TCGA Microarray cohort (e.g. there are only eight samples in its Normal-like subtype). Apart from these possible exceptions, the above results support the hypothesis that tumours with more-deregulated HR pathway are likely to have a higher degree of CIN, and this relationship can still be detected within the gene expression-based PAM50 subtypes.

3.3. Association between the CIN measurements and other pathways

The scatter plots in Figure 5 (METABRIC discovery cohort) show that the *HR* score is moderately correlated with each of the three CIN measurements (breakpoints r = 0.60, GII r=0.39 and number of amplified/deleted genes r = 0.48). These moderate correlations are not surprising, given that we do not consider aberrant HR as the only mechanism that contributes to CIN. In this section we investigated whether there are other pathways whose dysregulation also correlates with CIN, and whether these moderate correlations are far from random.

We computed a score for each of the 186 KEGG pathways (Kanehisa and Goto, 2000) and for 674 Reactome pathways (Croft et al., 2010), using the same approach as for the *HR* score. Spearman correlation coefficients between these scores and each of the three CIN measures were recorded and compared against the respective correlations between the *HR*

score and the three CIN measurements. Figure 7 shows the results for the METABRIC Discovery cohort (KEGG pathways are in green and Reactome pathways in blue; similar results for the other three cohorts are in Supplementary Figures S14, S15 and S16). We found only a few KEGG or Reactome pathways whose dysregulation showed a similar level of correlation with CIN as did the HR pathway. For example, only four (2.2%) KEGG pathways (cell cycle, oocyte meiosis, progesterone-mediated oocyte maturation and p53 signalling) were more strongly associated with number of breakpoints than with the HR pathway (r = 0.61- 0.63 compared to r = 0.60 for the HR pathway in Figure 7). Moreover, the strong associations of the oocyte meiosis, progesterone-mediated oocyte maturation and p53 signalling pathways with number of breakpoints is mainly due to their considerable overlap in gene content with the KEGG cell cycle pathway: 37%, 34% and 36% genes from each of these three pathways are also present in the cell cycle pathway (Supplementary Table S3). In contrast, only two HR genes are present in the cell cycle pathway. After removing the overlapping genes, association levels between each of these three pathways with number of breakpoints significantly decreased (results not shown). Similarly, although there were 24 (3.6%) Reactome pathways whose dysregulation showed a similar level of correlation with CIN as did the HR pathway, 18 of these are either the cell cycle pathway or its sub-pathways (Supplementary Table S4).

As the KEGG and Reactome pathways do not cover all genes measured in the whole-genome gene expression profiling data analysed in this study, we also constructed 1000 "Random" pathways for each cohort to calculate an empirical p-value for the association between the HR score and each of the three CIN measurements. Each Random pathway is of the same length as HR but is composed of genes randomly selected from the gene-expression profiling data, excluding those from HR and cell cycle pathways. Similar to the KEGG pathways analysed above, we computed a score for each Random pathway, and compared the correlation coefficients with the three CIN measures against those for the *HR* score. As shown in Figure 7, only a few Random pathways (in pink) showed a level of association with CIN similar to that of the HR pathway, as indicated by the empirical p-values. Similar results for the other three cohorts were obtained (Supplementary Figures S14, S15 and S16).

Overall, these results indicate that the CIN level in tumours is associated with the dysregulation of only a limited number of pathways (e.g., the cell cycle pathway), and that the correlation between HR and CIN is far from being random.

4. Association with survival in ER^+ tumours

The two METABRIC cohorts are annotated with disease-specific survival data that are lacking for the two TCGA cohorts. We thus tested whether the *HR* score can predict patient survival in the two METABRIC cohorts. Figure 8 shows Kaplan-Maier plots for patients with ER^+ tumours from the METABRIC discovery (n=699; follow-up time ≤ 15 years) and validation cohorts (n=582; follow-up time ≤ 15 years). For each cohort, patients were divided into high and low *HR* score groups based on the median *HR* score. For both cohorts, we observed a significant difference in patient survival between the two *HR* score groups with ER^+ tumours (Figure 8; Cox proportional hazards regression test p-value = 8.4e-04 and 3.9e-09 for the two cohorts, respectively). However, we observed no significant difference in survival between the two *HR* score groups for patients with ER^- tumours (data not shown). As an association between CIN and prognosis in ER^+ tumours has already been documented (Przybytkowski et al., 2014; Smid et al., 2011), and after control for the number of chromosomal breaks there is no significant difference in survival between the two *HR* score-based groups (result not shown), we infer that the prognostic value of the *HR* score in ER^+ tumours is due to the association between the *HR* score and CIN.

Discussion

Multiple molecular mechanisms have been associated with the origin of CIN in cancer, including replication stress, telomere dysfunction, aberrant DNA repair and various defects in chromosome segregation (reviewed in (Abbas et al., 2013; Aguilera and García-Muse, 2013; Negrini et al., 2010; Thompson et al., 2010). Although CIN can be experimentally induced by exploiting any of these mechanisms, replication stress has been recently identified as the first recurrent genetic defect associated with CIN in colorectal cancer (Burrell et al., 2013a). In this scenario, CIN is induced during DNA replication in fast-dividing tumour cells, giving rise to frequent stalling of replication forks. Consequently, HR as the primary pathway for repair of the resultant DSBs during replication becomes overworked, and if HR is dysfunctional the frequency of replication stress-induced CIN is likely to increase dramatically. Here we have shown that HR dysregulation as measured by the *HR* score, which is indicative of aberrant HR repair, is prevalent in sporadic breast cancer and correlates with the level of CIN. We thus propose that HR dysregulation might contribute to replication stress-induced CIN at least in sporadic breast cancer. Consistent with this view,

overexpression of the key HR gene *RAD51*, which is commonly seen in breast cancer as well as other cancer types, promotes chromosomal instability (Richardson et al., 2004), and two other critical HR genes, *BRCA1* and *BRCA2*, were recently proposed as chromosome custodians mainly due to their role in HR (Venkitaraman, 2014a; 2014b).

Dysfunction of the HR pathway, although not the primary cause, may increase the level of replication stress-induced CIN in several ways. Firstly, it can cause inefficient repair of DSBs, resulting in an accumulation of chromosomal breaks. Secondly, by triggering error-prone repair pathways including canonical non-homologous end-joining (C-NHEJ) and alternative non-homologous end-joining (Alt-NHEJ, also called microhomology-mediated end joining (MMEJ)), HR dysfunction can lead to translocations, translocation-related chromosomal breaks and DNA copy-number changes. Specifically, in contrast to HR that requires homologous sequence to guide repair, C-NHEJ and Alt-NHEJ mediate the repair by a direct ligation of the break ends after more-or-less end processing, and so do not ensure that the broken DNA strands are re-joined in the correct position. These two low-fidelity pathways come to repair DSBs generated during DNA replication when HR is deficient, resulting in translocation as well as translocation-related chromosomal breaks (Alexandrov et al., 2013; Bunting and Nussenzweig, 2013; Ottaviani et al., 2014; Villarreal et al., 2012). Moreover, gene copy number changes also arise when the repair of broken replication forks switched from HR to the two NHEJs, especially Alt-NHEJ (Hastings et al., 2009);

A third way in which HR pathway dysfunction can increase replication stress-induced CIN is by affecting mitosis and the proper functioning of telomeres. HR defects and the consequent slow progression of replication forks can elicit alterations of mitosis, which highlights the importance of HR at the interface of these two processes for protection against CIN (Wilhelm et al., 2014). In addition, DSB repair is shut down during the M phase to avoid telomere fusion and as a consequence, mitosis will continue even in the presence of DSBs or fragmented chromosomes, giving rise to CIN (Orthwein et al., 2014). This emphasises the importance of DSB repair during DNA replication, especially given the presence of DSBs that result from replication stress. HR defects caused by *BRCA2* mutations could also lead to telomere dysfunction, a mechanism that has been proposed to explain, in part, the chromosomal instability observed in *BRCA2*-deficient tumours (Badie et al., 2010). Taken together, HR dysfunction can increase CIN via diverse mechanisms, and the association revealed in this study between HR dysregulation and CIN (Figures 4, 5 and 6) indicates that dysregulated HR might contribute to the CIN observed in highly replicative tumours.

The study of CIN in breast cancer has attracted immense interest in recent years following the recognition of its clinical relevance in disease heterogeneity, drug resistance and patient response (A'Hern et al., 2013; Birkbak et al., 2011; Endesfelder et al., 2014; Habermann et al., 2009; Roylance et al., 2011; Sansregret and Nepveu, 2011; Swanton et al., 2009; Vincent-Salomon et al., 2013); reviewed by (Wiechec, 2011). CIN induces evolution in tumours, providing the heterogeneity from which aggressive and/or drug-resistant tumour clones are selectively established. CIN aids tumour development by amplifying genomic regions containing oncogenes and deleting regions containing tumour-suppressor genes, thereby significantly influencing treatment response and survival in patients. Our results further strengthen this connection by associating dysregulated HR with the extent of amplified/deleted genes and regions of the chromosome, and by showing that ER^+ tumours with high HR score or CIN levels display significantly poorer prognosis (Figure 8).

A measure of HR dysregulation such as the one adopted here can be extremely valuable to guide therapeutic options. The observation that cancer cells deficient in HR are profoundly sensitive to PARP inhibitors (Bryant et al., 2005; Farmer et al., 2005) has already led to the development of targeted PARP therapies for sporadic breast and ovarian cancers with defects in core HR genes such as *BRCA1* and *BRCA2*, a condition termed as "BRCAness" (Turner et al., 2004). PARP is an important protein family whose members function in restarting stalled replication forks and diverting DSBs to HR-mediated repair. It has been proposed that accumulated chromosomal instability arising from the continued stalling of replication forks, accompanied by deficiency in repairing DSBs and thereby triggering a genomic catastrophe, may explain how PARP inhibition kills HR-deficient cancer cells (Bryant et al., 2005; Farmer et al., 2005). Although focusing on a mechanistic explanation for PARP-based cancer therapy, these models indirectly suggest an underlying relationship among replicative stress, dysfunctional HR and the accumulation of chromosomal instability.

In conclusion, we performed a personalised pathway analysis by calculating an *HR* score that quantifies HR pathway dysregulation in individual breast tumours, with the behaviour of HR in normal breast tissues serving as a benchmark. Our results are reproducible across four large breast cancer cohorts (~ 3000 tumours in total). We found HR is dysregulated to various extents between and within the gene expression-based PAM50 subtypes, which may reflects their HR repair deficiency. More importantly, we uncovered a novel association between HR dysregulation and CIN. Although HR has a well-known role in

maintaining genomic integrity, this work is the first large-scale study to assess the correlation between HR dysregulation and CIN in sporadic breast cancer. As such our results will be useful for future studies that aim to identify causative factors of CIN in sporadic breast cancer as well as in other cancer types.

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Figure 1 - Distribution of the *HR* score across the PAM50 subtypes and normal breast tissues (in green) for the four cohorts.

Figure 2 – Comparison of the *HR* score with the HRD signature. A: HRD-based hierarchical clustering of tumours from the METABRIC Discovery cohort. B: Distribution of the *HR* score in the two HRD-based clusters for each of the four cohorts. Colour represents the HRD-based cluster. P-values were obtained using a Wilcoxon signed-rank test.

Figure 3 - Distribution of the *HR* score in LST^+ tumours and LST^- tumours for each of the four cohorts. Colour represents LST status. P-values were obtained using a Wilcoxon signed-rank test.

Figure 4 - Correlations between the CIN25 score and the *HR* score for each of the four cohorts.

Figure 5 - *HR* score versus the three CIN measurements for the METABRIC Discovery cohort. Left: Boxplots of the three CIN measurements versus the four *HR* score quartile groups; stars indicate statistical significance according to a Wilcoxon signed-rank test: ns means not significant, * means $0.01 < p\text{-value} < 0.05$, ** means $0.001 < p\text{-value} < 0.01$, and *** means $p\text{-value} < 0.001$. Right: Scatter plots of the *HR* score versus each of the three CIN measurements; r represents Pearson Correlation Coefficient.

Figure 6 - *HR* score versus the three CIN measurements within PAM50 subtypes (METABRIC Discovery cohort). For each plot, the two *HR* score groups were divided according to the median *HR* score in each subtype; stars indicate the significance according to a Wilcoxon signed-rank test for each pair of groups: ns means not significant, * means $0.01 < p < 0.05$, ** means $0.001 < p < 0.01$, and *** means $p < 0.001$.

Figure 7 - Distributions of the correlations between pathway scores and the three CIN measurements (METABRIC Discovery cohort). Results for KEGG pathways are in green, Reactome pathways in blue and Random pathways in pink. Spearman correlation coefficients (r) are represented on the x-axis. Pathway score were calculated with Pathifier. The vertical dashed line in each histogram indicates the value of r between the *HR* score and each of the three CIN measurements, and p represents an empirical p-value for that value of r.

Figure 8 - Kaplan-Maier plot for disease specific survival in the METABRIC Discovery cohort (left) and Validation cohort (right). Patients with ER^+ tumour were divided into two equal-sized groups based on the median *HR* score in each cohort.

Figure S1 – Principal curve of the HR pathway for each of the four cohorts. For each cohort, the black points represent samples in that cohort. The samples are projected onto the principal curve and are coloured according to their PAM50 assignment. The data points and the principal curve are projected on the three leading principal components for visualisation.

Figure S2 – The expression of the HR genes in tumours from the METABRIC Discovery cohort. The HR genes are ranked in decreasing importance according to their contribution to the first principal component.

Figure S3 – Scatter plots of the *HR* score versus the rank of tumours according to their *HR* score, colour by the PAM50 assignment.

Figure S4 - Hierarchical clustering of tumours from the METABRIC Validation cohort based on the HRD signature.

Figure S5 - Hierarchical clustering of tumours from the TCGA RNA-seq cohort based on the HRD signature.

Figure S6 - Hierarchical clustering of tumours from the TCGA Microarray cohort based on the HRD signature.

Figure S7 - *HR* score versus HR gene mutation for the two TCGA cohorts. *Mutant* refers to tumours with at least one nonsynonymous mutation in any of the six key HR genes (*BRCA1*, *BRCA2*, *RAD51*, *PALB2*, *DNA2* and *EXO1*). *Wild type* refers to tumours with no mutations in these six genes. *Normal* refers to normal breast tissues. P-values were obtained using a Wilcoxon signed-rank test, for the comparison between wild type and mutant tumours.

Figure S8 - *HR* score versus the three CIN measurements for the METABRIC Validation cohort. Left: Boxplots of the three CIN measurements versus the four *HR* score quartile groups; stars indicate statistical significance according to a Wilcoxon signed-rank test: ns means not significant, * means 0.01< p-value < 0.05, ** means 0.001 < p-value <0.01, and *** means p-value < 0.001. Right: Scatter plots of the *HR* score versus each of the three CIN measurements; r represents Pearson Correlation Coefficient.

Figure S9 - *HR* score versus the three CIN measurements for the TCGA RNA-seq cohort. Left: Boxplots of the three CIN measurements versus the four *HR* score quartile groups; stars indicate statistical significance according to a Wilcoxon signed-rank test: ns means not significant, * means 0.01< p-value < 0.05, ** means 0.001 < p-value <0.01, and *** means p-value < 0.001. Right: Scatter plots of the *HR* score versus each of the three CIN measurements; r represents Pearson Correlation Coefficient.

Figure S10 - *HR* score versus the three CIN measurements for the TCGA Microarray cohort. Left: Boxplots of the three CIN measurements versus the four *HR* score quartile groups; stars indicate statistical significance according to a Wilcoxon signed-rank test: ns means not significant, * means 0.01< p-value < 0.05, ** means 0.001 < p-value <0.01, and *** means p-value < 0.001. Right: Scatter plots of the *HR* score versus each of the three CIN measurements; r represents Pearson Correlation Coefficient.

Figure S11 - *HR* score versus the three CIN measurements within PAM50 subtypes (METABRIC Validation cohort). For each plot, the two *HR* score groups were divided according to the median *HR* score in each subtype; stars indicate the significance according to a Wilcoxon signed-rank test for each pair of groups: ns means not significant, * means 0.01< p < 0.05, ** means 0.001 < p <0.01, and *** means p < 0.001.

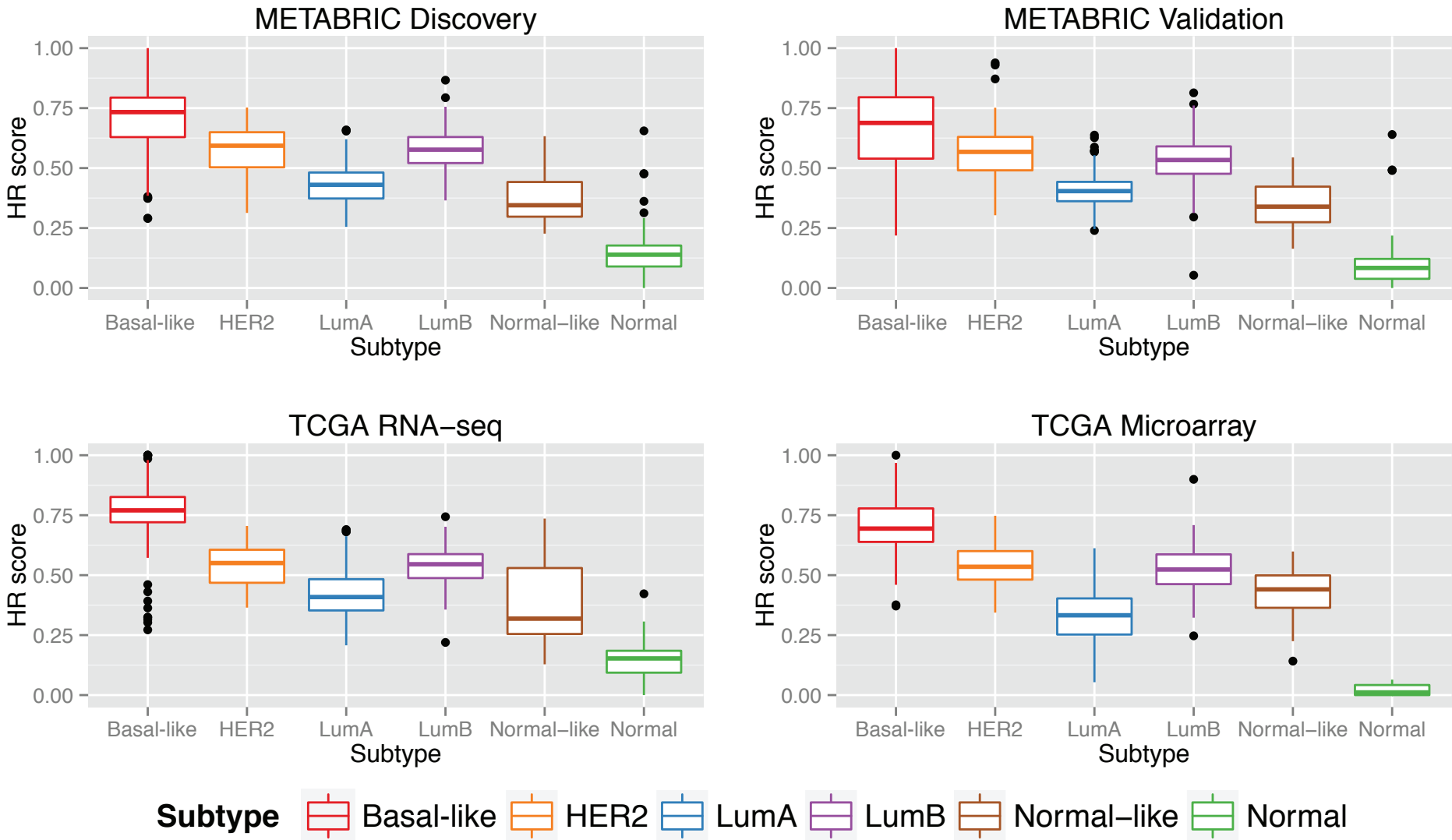
Figure S12 - *HR* score versus the three CIN measurements within PAM50 subtypes (TCGA RNA-seq cohort). For each plot, the two *HR* score groups were divided according to the median *HR* score in each subtype; stars indicate the significance according to a Wilcoxon signed-rank test for each pair of groups: ns means not significant, * means $0.01 < p < 0.05$, ** means $0.001 < p < 0.01$, and *** means $p < 0.001$.

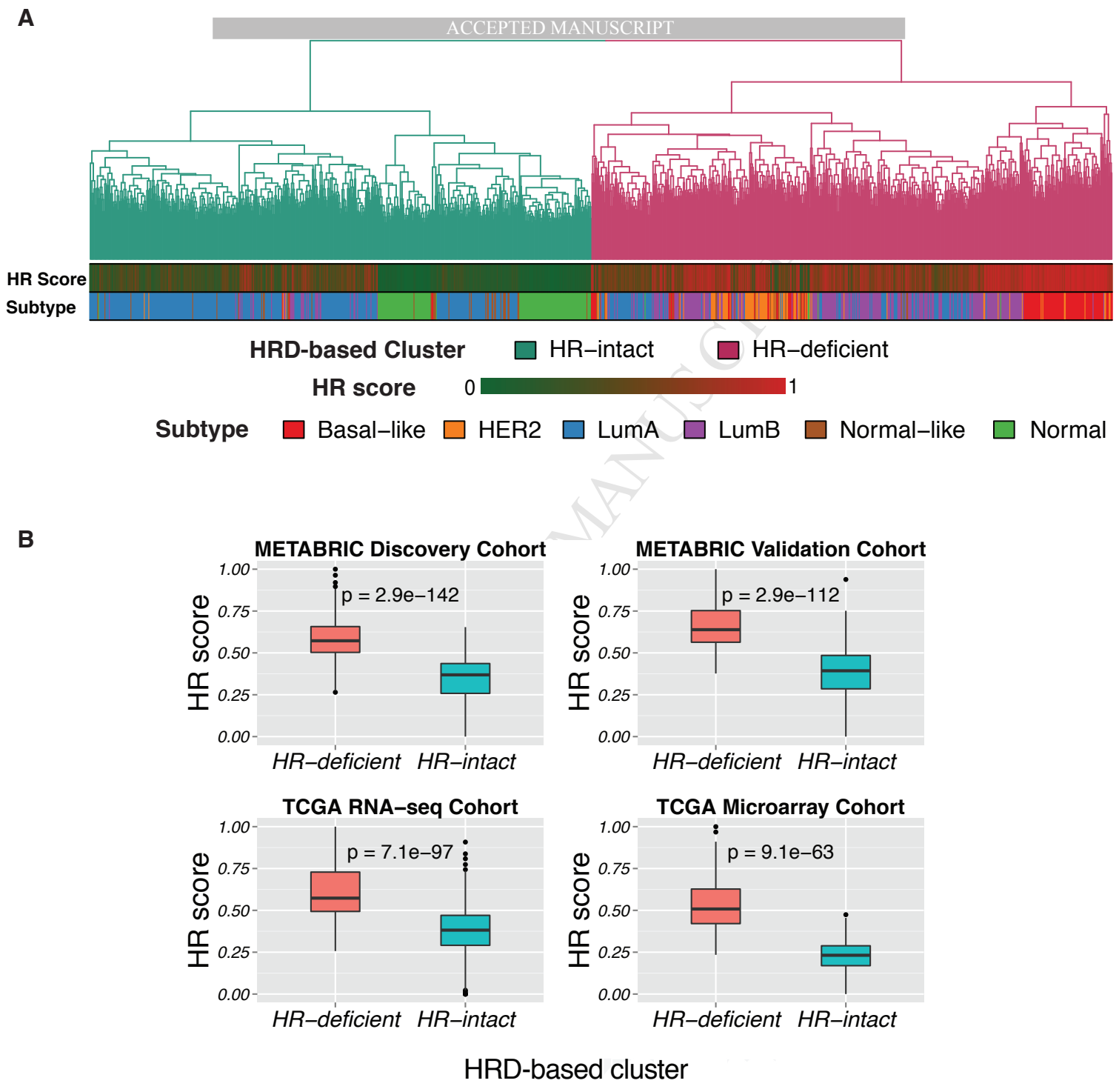
Figure S13 - *HR* score versus the three CIN measurements within PAM50 subtypes (TCGA Microarray cohort). For each plot, the two *HR* score groups were divided according to the median *HR* score in each subtype; stars indicate the significance according to a Wilcoxon signed-rank test for each pair of groups: ns means not significant, * means $0.01 < p < 0.05$, ** means $0.001 < p < 0.01$, and *** means $p < 0.001$.

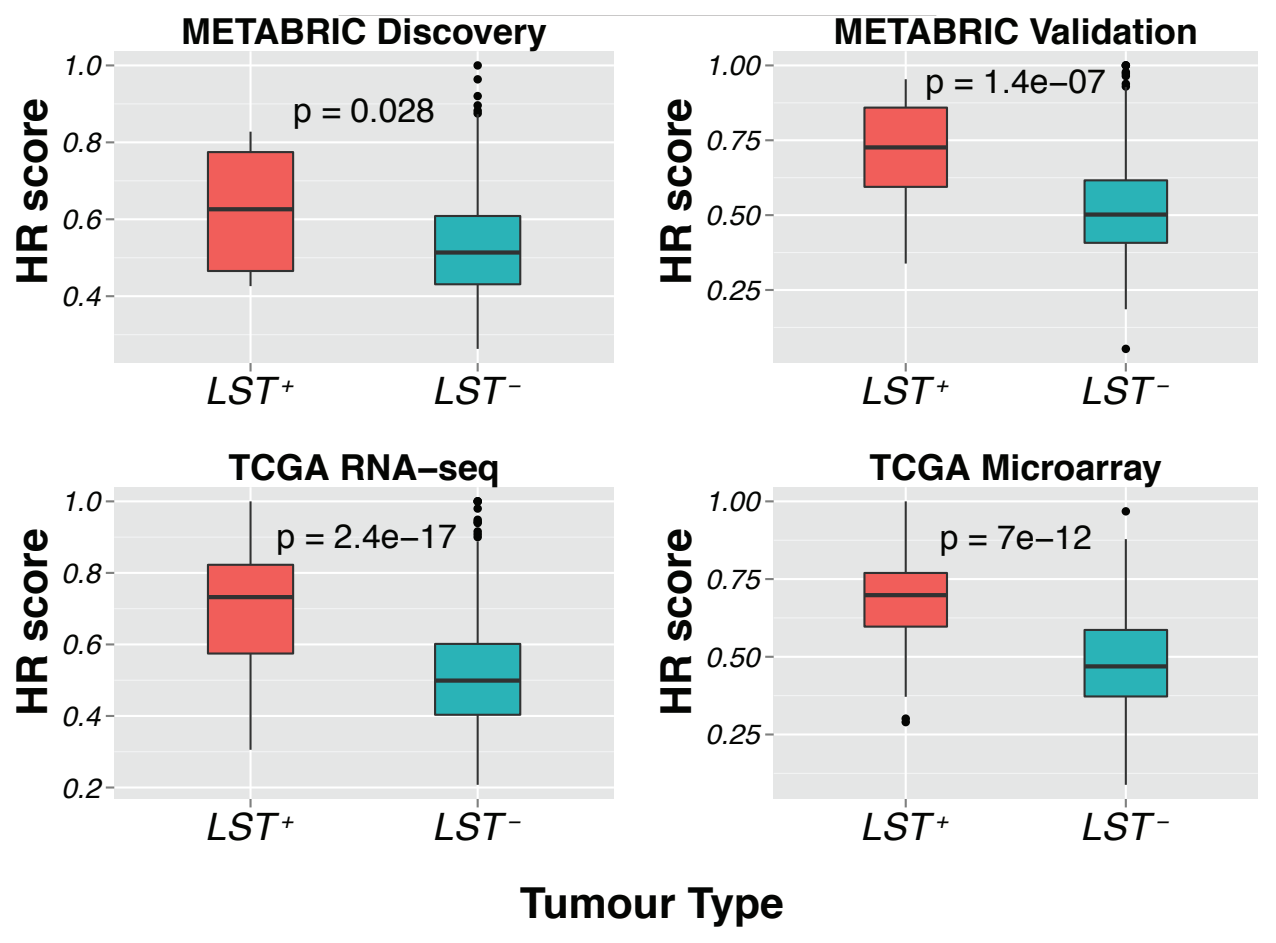
Figure S14 - Distributions of the correlations between pathway scores and the three CIN measurements (METABRIC Validation cohort). Results for KEGG pathways are in green, Reactome pathways in blue and Random pathways in pink. Spearman correlation coefficients (r) are represented on the x-axis. Pathway score were calculated with Pathifier. The vertical dashed line in each histogram indicates the value of r between the *HR* score and each of the three CIN measurements, and p represents an empirical p-value for that value of r.

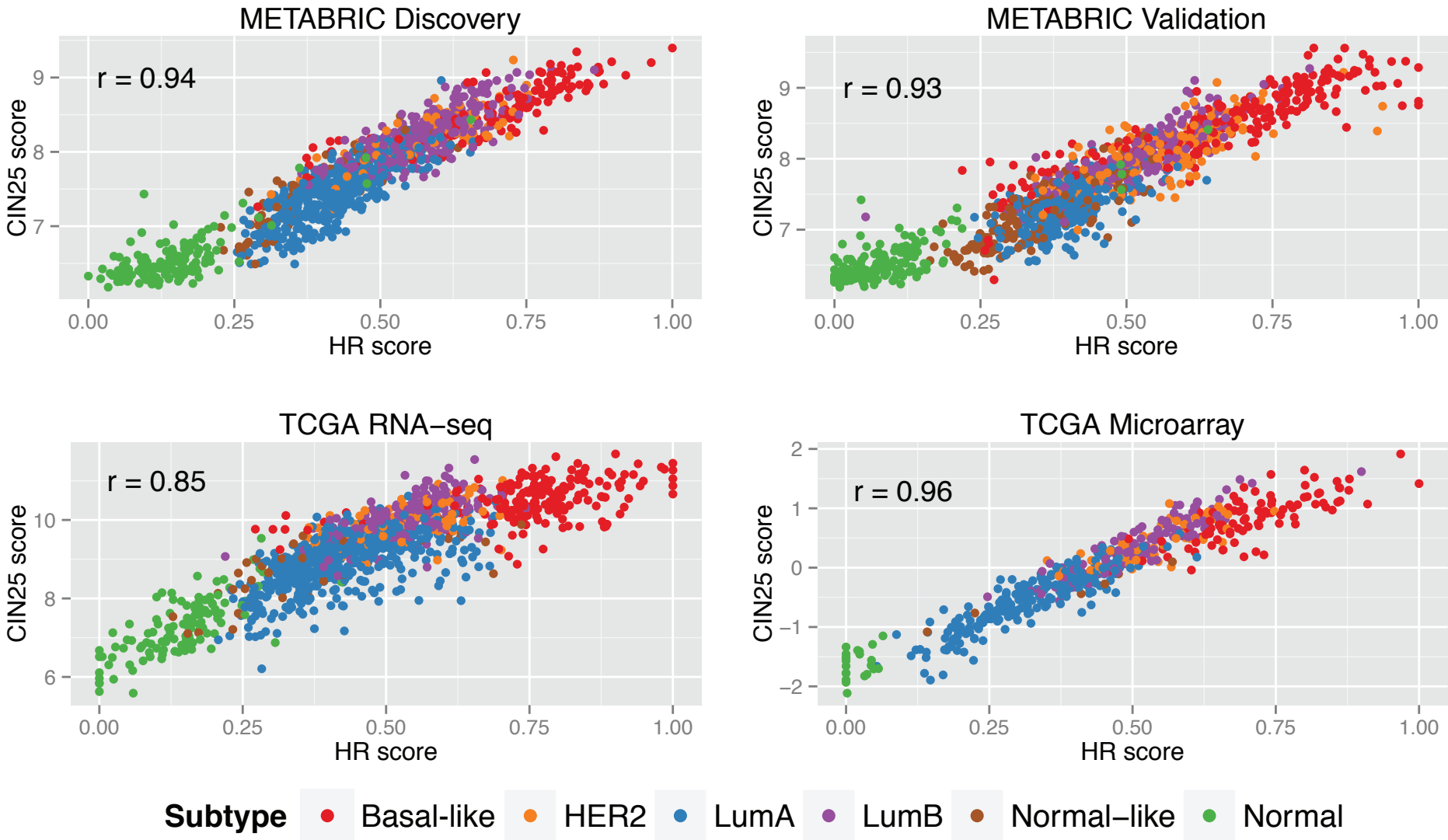
Figure S15 - Distributions of the correlations between pathway scores and the three CIN measurements (TCGA RNA-seq cohort). Results for KEGG pathways are in green, Reactome pathways in blue and Random pathways in pink. Spearman correlation coefficients (r) are represented on the x-axis. Pathway score were calculated with Pathifier. The vertical dashed line in each histogram indicates the value of r between the *HR* score and each of the three CIN measurements, and p represents an empirical p-value for that value of r.

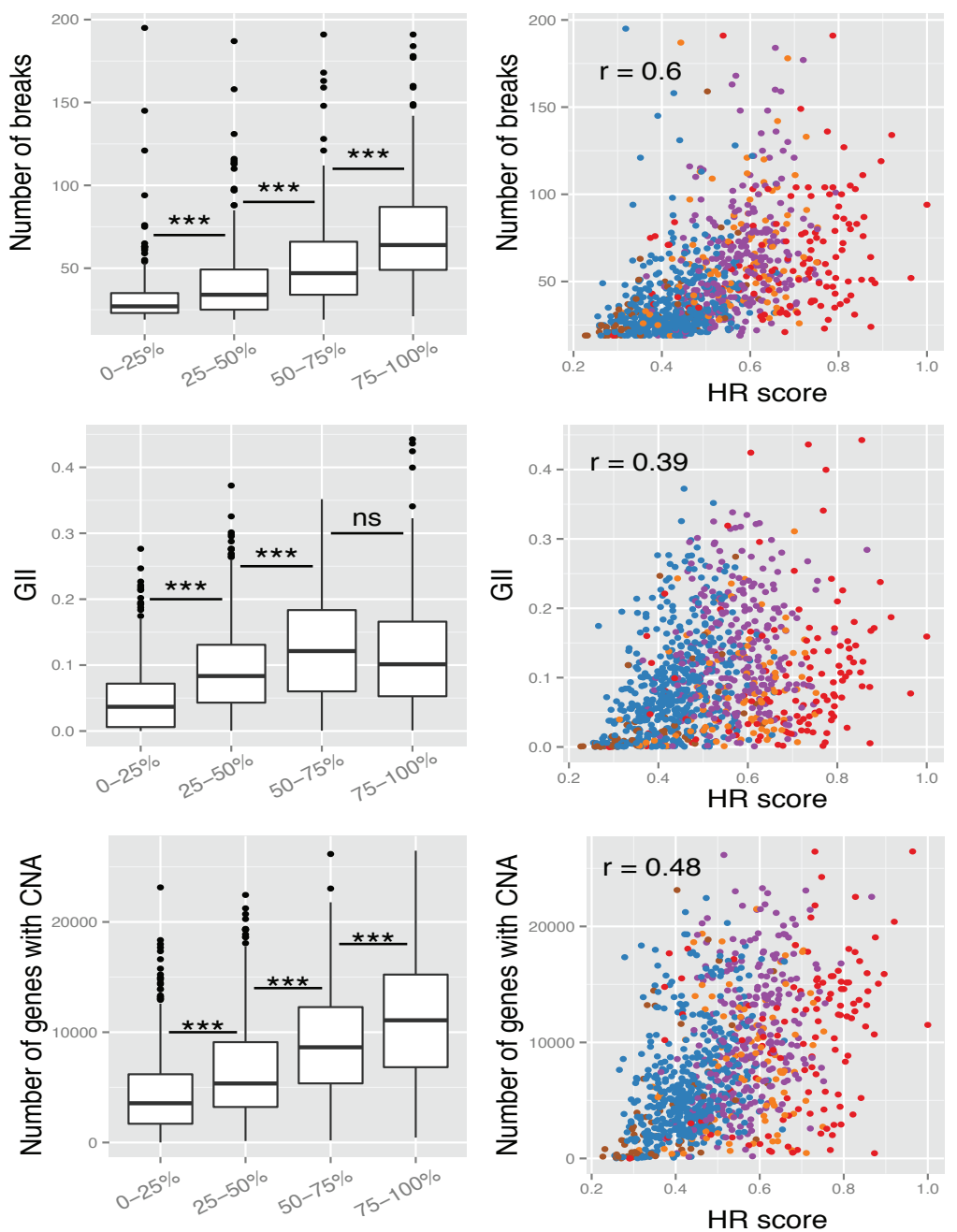
Figure S16 - Distributions of the correlations between pathway scores and the three CIN measurements (TCGA Microarray cohort). Results for KEGG pathways are in green, Reactome pathways in blue and Random pathways in pink. An additional 100 CIN-related genes were excluded prior to the construction of the Random pathways as the Pathifer method was sensitive to the addition or removal of a small number of genes in this cohort. Spearman correlation coefficients (r) are represented on the x-axis. Pathway score were calculated with Pathifier. The vertical dashed line in each histogram indicates the value of r between the *HR* score and each of the three CIN measurements, and p represents an empirical p-value for that value of r.

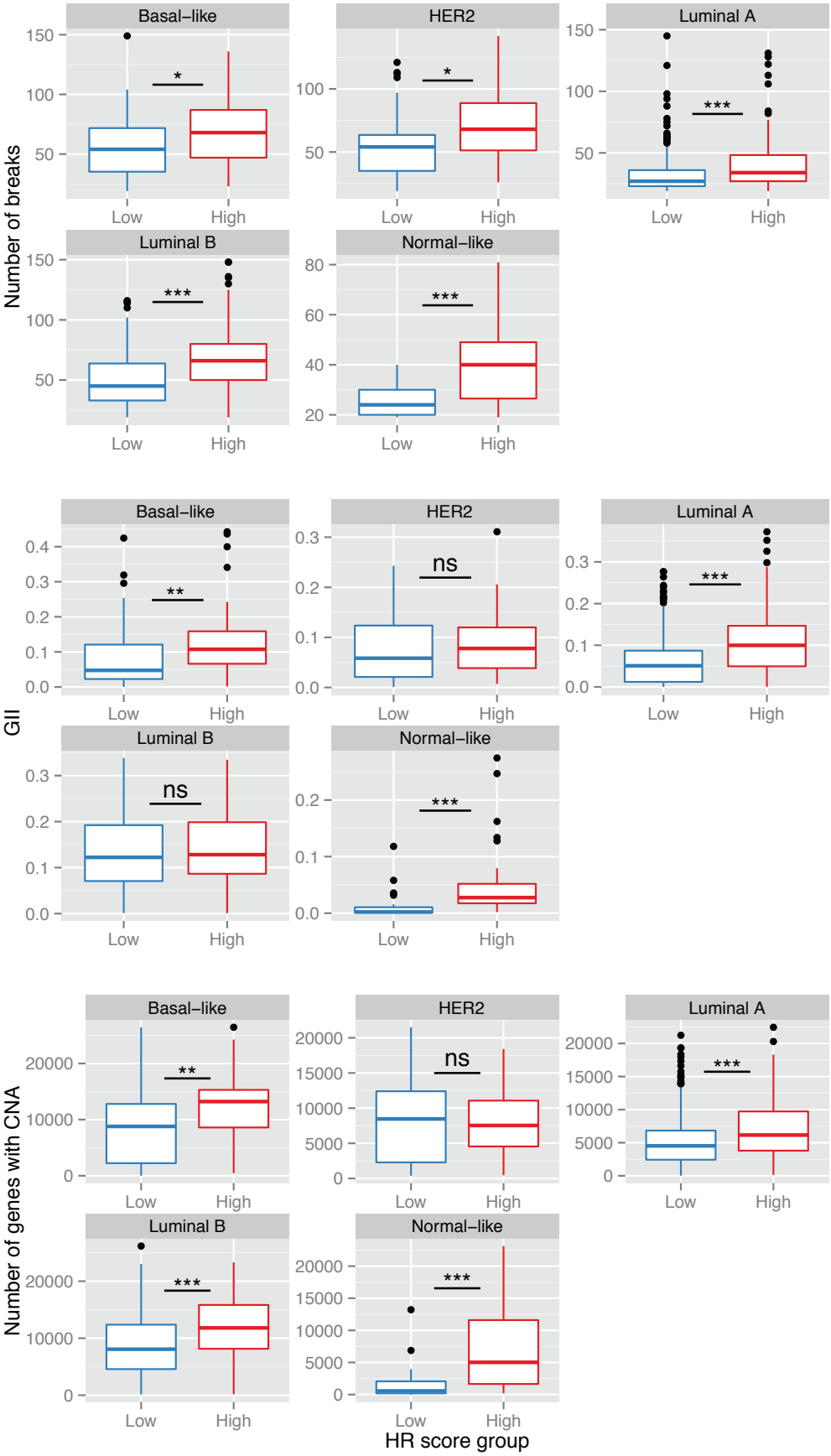

METABRIC Discovery
METABRIC Validation
TCGA RNA−seq
TCGA Microarray
HR score
1.00
0.75
0.50
0.25
0.00
Basal-like
HER2
LumA
LumB
Normal−like
Normal
Subtype
Subtype
Basal-like
HER2
LumA
LumB
Normal−like
Normal

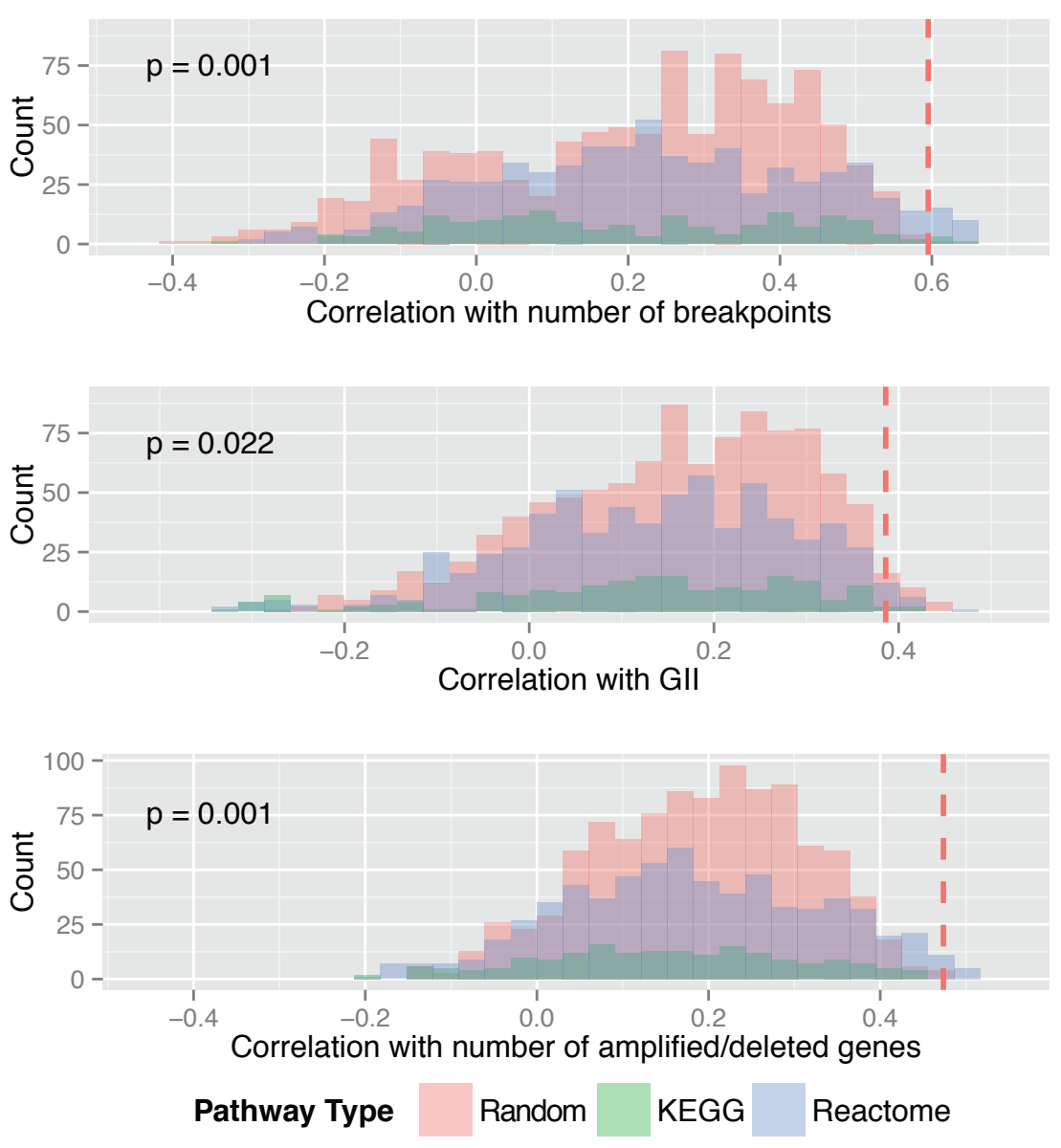


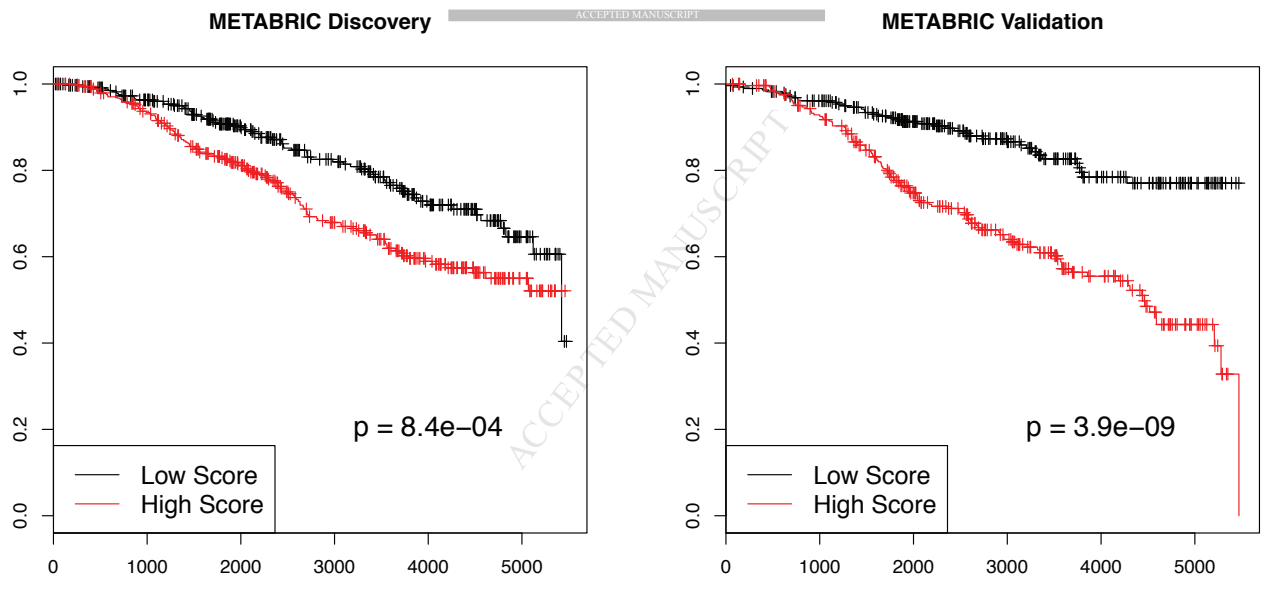

METABRIC Discovery
p = 0.028
HR score
1.0
0.8
0.6
0.4
LST+
LST−
METABRIC Validation
p = 1.4e−07
HR score
1.00
0.75
0.50
0.25
LST+
LST−
TCGA RNA−seq
p = 2.4e−17
HR score
1.0
0.8
0.6
0.4
0.2
LST+
LST−
TCGA Microarray
p = 7e−12
HR score
1.00
0.75
0.50
0.25
LST+
LST−
Tumour Type


METABRIC Discovery
r = 0.94
CIN25 score
HR score
METABRIC Validation
r = 0.93
CIN25 score
HR score
TCGA RNA−seq
r = 0.85
CIN25 score
HR score
TCGA Microarray
r = 0.96
CIN25 score
HR score
Subtype
Basal-like
HER2
LumA
LumB
Normal−like
Normal


Number of breaks
200
150
100
50
***
***
***
0–25%
25–50%
50–75%
75–100%
Number of breaks
r = 0.6
HR score
GII
0.4
0.3
0.2
0.1
0.0
***
***
ns
GII
r = 0.39
HR score
Number of genes with CNA
20000
10000
0
***
***
***
Number of genes with CNA
r = 0.48
HR score
0.2
0.4
0.6
0.8
1.0
Subtype
Basal-like
HER2
LumA
LumB
Normal-like


Basal−like
HER2
Luminal A
Luminal B
Normal−like
Number of breaks
GII
Number of genes with CNA
Low
High
HR score group
*
**
***
ns


p = 0.001
Count
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
0.6
Correlation with number of breakpoints
p = 0.022
Count
75
50
25
0
−0.2
0.0
0.2
0.4
Correlation with GII
p = 0.001
Count
100
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
Correlation with number of amplified/deleted genes
Pathway Type
Random
KEGG
Reactome



- Homologous recombination (HR) pathway dysregulation is quantified at tumour level.
- HR dysregulation is indicative of HR repair deficiency.
- An association between HR dysregulation and chromosomal instability is uncovered.
- The results are reproducible across four large breast cancer cohorts.

	Presence in Cohorts				Presence in other signatures	
In the review*	METABRIC Discovery	METABRIC Validation	TCGA RNA-seq	TCGA Microarray	CIN25	HRD
ATM	✓	✓	✓	✓	✗	✗
ATRX	✓	✓	✓	✓	✗	✗
BABAM1	✗	✗	✗	✗	✗	✗
BARD1	✓	✓	✓	✓	✗	✗
BLM	✓	✓	✓	✓	✗	✓
BRCA1	✓	✓	✓	✓	✗	✓
BRCA2	✓	✓	✓	✓	✗	✗
BRCC3	✓	✓	✓	✓	✗	✗
BRE	✓	✓	✓	✓	✗	✗
CHD4	✓	✓	✓	✓	✗	✗
CSNK2A1	✓	✓	✓	✓	✗	✗
CSNK2A2	✓	✓	✓	✓	✗	✗
CSNK2B	✓	✓	✓	✓	✗	✗
DNA2	✓	✓	✓	✗	✗	✗
EME1	✓	✓	✓	✗	✗	✗
ERCC1	✓	✓	✓	✓	✗	✗
ERCC4	✓	✓	✓	✓	✗	✗
EXO1	✓	✓	✓	✓	✗	✓
FAM175A	✗	✗	✓	✗	✗	✗
GEN1	✓	✓	✓	✗	✗	✗
H2AFX	✓	✓	✓	✓	✗	✗
HERC2	✓	✓	✓	✓	✗	✗
KAT5	✓	✓	✓	✗	✗	✗
LIG3	✓	✓	✓	✓	✗	✗
MDC1	✓	✓	✓	✓	✗	✗
MRE11A	✓	✓	✓	✓	✗	✗
MUS81	✓	✓	✓	✓	✗	✗
NBN	✓	✓	✓	✓	✗	✗
NABP1	✗	✗	✗	✗	✗	✗
NABP2	✗	✗	✗	✗	✗	✗
OTUB1	✓	✓	✓	✓	✗	✗
PALB2	✓	✓	✓	✓	✗	✗
PARPBP	✗	✗	✗	✗	✗	✗
PCNA	✓	✓	✓	✓	✓	✓
PIAS1	✓	✓	✓	✓	✗	✗
PIAS4	✓	✓	✓	✓	✗	✗
POLD1	✓	✓	✓	✓	✗	✓
POLD2	✗	✗	✓	✓	✗	✗
POLD3	✓	✓	✓	✓	✗	✗
POLD4	✓	✓	✓	✓	✗	✗
POLH	✓	✓	✓	✓	✗	✗
RAD50	✓	✓	✓	✓	✗	✗
RAD51	✓	✓	✓	✓	✗	✗
RAD51AP1	✓	✓	✓	✓	✓	✗
RAD51B	✗	✗	✗	✗	✗	✗
RAD51C	✓	✓	✓	✓	✗	✗
RAD51D	✗	✗	✗	✗	✗	✗
RAD52	✓	✓	✓	✓	✗	✗
RAD54B	✓	✓	✓	✓	✗	✓
RAD54L	✓	✓	✓	✓	✗	✓
RAD54L2	✗	✗	✓	✓	✗	✗
RBBP8	✓	✓	✓	✓	✗	✗
RMI1	✓	✓	✓	✓	✗	✗
RMI2	✗	✗	✗	✗	✗	✗
RNF168	✓	✓	✓	✓	✗	✗
RNF20	✓	✓	✓	✓	✗	✗

RNF40	✓	✓	✓	✓	✗	✗
RNF8	✓	✓	✓	✓	✗	✗
RPA1	✓	✓	✓	✓	✗	✗
RPA2	✓	✓	✓	✓	✗	✗
RPA3	✓	✓	✓	✓	✗	✗
RPA4	✓	✓	✓	✓	✗	✗
RTEL1	✓	✓	✓	✓	✗	✗
SHFM1	✓	✓	✓	✓	✗	✗
SLX1A	✗	✗	✗	✗	✗	✗
SLX1B	✗	✗	✗	✗	✗	✗
SLX4	✗	✗	✗	✗	✗	✗
TOP3A	✓	✓	✓	✓	✗	✗
TOP3B	✓	✓	✓	✓	✗	✗
TRIP12	✓	✓	✓	✓	✗	✗
UBE2N	✓	✓	✓	✓	✗	✗
UBR5	✓	✓	✓	✓	✗	✗
UIMC1	✓	✓	✓	✓	✗	✗
USP3	✓	✓	✓	✓	✗	✗
XRCC2	✓	✓	✓	✓	✗	✗
XRCC3	✓	✓	✓	✓	✗	✗
BRIP1	✓	✓	✓	✓	✗	✗
ZNF365	✓	✓	✓	✓	✗	✗
PSIP1	✓	✓	✓	✓	✗	✗
PARP1	✓	✓	✓	✓	✗	✗
TP53BP1	✓	✓	✓	✓	✗	✗
RIF1	✓	✓	✓	✓	✗	✗
Total = 82	**69 present**	**69 present**	**72 present**	**67 present**	**2 present**	**7 present**

* Chao Liu et al., NAR, 2014, 6106–6127

Cohort	LST+	LST-
METABRIC Discovery	9	976
METABRIC Validation	25	940
TCGA RNA-seq	77	820
TCGA Microarray	42	405

Correlations between the Pathifier score of each KEGG pathway and three CIN measurements in the four breast cancer cohorts

Note:

1. Overlap = length of the overlap with the CELL CYCLE pathway in KEGG

2. Percentage = percentage of the overlap with the CELL CYCLE pathway in KEGG

Pathway Name	Length	Overlap	Percentage	METABRIC Discovery Cohort			METABRIC Validation Cohort			TCGA RNA-seq Cohort			TCGA Microarray Cohort		
				No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes
OOCYTE MEIOSIS	114	42	36.84%	0.63	0.29	0.43	0.61	0.32	0.48	0.52	0.47	0.50	0.57	0.50	0.52
CELL CYCLE	128	128	100.00%	0.62	0.30	0.42	0.60	0.35	0.48	0.61	0.57	0.59	0.56	0.52	0.52
PROGESTERONE MEDIATED OOCYTE MATURATION	86	29	33.72%	0.61	0.32	0.44	0.59	0.34	0.48	0.56	0.51	0.54	0.54	0.47	0.48
P53 SIGNALING PATHWAY	69	25	36.23%	0.61	0.28	0.42	0.56	0.29	0.45	0.51	0.48	0.49	0.55	0.48	0.49
PYRIMIDINE METABOLISM	98	0	0.00%	0.58	0.30	0.43	-0.05	0.19	0.04	0.38	0.36	0.36	0.52	0.48	0.48
SMALL CELL LUNG CANCER	84	15	17.86%	0.57	0.23	0.39	0.50	0.22	0.37	0.45	0.45	0.44	0.50	0.44	0.49
BASE EXCISION REPAIR	35	1	2.86%	0.56	0.35	0.44	0.56	0.43	0.52	0.57	0.53	0.53	0.51	0.52	0.50
UBIQUITIN MEDIATED PROTEOLYSIS	138	21	15.22%	0.55	0.41	0.42	0.30	0.23	0.23	0.30	0.30	0.32	0.53	0.40	0.47
PATHWAYS IN CANCER	328	32	9.76%	0.54	0.23	0.36	0.48	0.35	0.40	0.25	0.31	0.22	0.49	0.39	0.44
DNA REPLICATION	36	7	19.44%	0.54	0.31	0.38	0.52	0.35	0.45	0.53	0.53	0.52	0.49	0.54	0.52
HOMOLOGOUS RECOMBINATION	28	0	0.00%	0.52	0.25	0.37	0.45	0.30	0.38	0.41	0.37	0.38	0.53	0.51	0.49
PROSTATE CANCER	89	15	16.85%	0.52	0.20	0.33	0.45	0.24	0.30	0.25	0.29	0.22	0.25	0.27	0.21
CYSTEINE AND METHIONINE METABOLISM	34	0	0.00%	0.51	0.12	0.34	0.46	0.15	0.32	0.44	0.37	0.39	0.54	0.49	0.52
MISMATCH REPAIR	23	1	4.35%	0.51	0.27	0.40	0.43	0.30	0.45	0.48	0.50	0.50	0.48	0.53	0.52
BLADDER CANCER	42	11	26.19%	0.51	0.16	0.31	0.47	0.23	0.34	0.31	0.33	0.32	0.32	0.23	0.30
PROPANOATE METABOLISM	33	0	0.00%	0.50	0.13	0.29	0.28	0.04	0.13	0.44	0.38	0.42	0.27	0.18	0.21
FATTY ACID METABOLISM	42	0	0.00%	0.49	0.32	0.38	0.20	0.35	0.27	0.22	0.27	0.18	0.18	0.22	0.16
PEROXISOME	78	0	0.00%	0.49	0.15	0.39	-0.05	0.21	0.07	0.10	0.10	0.07	0.15	0.16	0.16
PURINE METABOLISM	159	0	0.00%	0.49	0.20	0.37	0.47	0.23	0.41	0.42	0.39	0.41	0.55	0.47	0.48
ONE CARBON POOL BY FOLATE	17	0	0.00%	0.49	0.14	0.33	0.47	0.18	0.36	0.52	0.49	0.51	0.41	0.39	0.39
TYROSINE METABOLISM	42	0	0.00%	0.48	0.14	0.30	0.36	0.12	0.24	0.41	0.36	0.33	0.42	0.36	0.37
STEROID BIOSYNTHESIS	17	0	0.00%	0.48	0.19	0.30	0.47	0.26	0.35	0.46	0.40	0.41	0.53	0.43	0.45
GLUTATHIONE METABOLISM	50	0	0.00%	0.48	0.11	0.30	0.30	0.00	0.18	0.47	0.45	0.45	0.36	0.31	0.29
GLYCINE SERINE AND THREONINE METABOLISM	31	0	0.00%	0.47	0.09	0.30	0.44	0.17	0.32	0.54	0.46	0.50	0.47	0.40	0.40
LYSINE DEGRADATION	44	0	0.00%	0.47	0.15	0.27	0.36	0.18	0.24	0.47	0.41	0.43	0.53	0.50	0.51
VALINE LEUCINE AND ISOLEUCINE DEGRADATION	44	0	0.00%	0.47	0.07	0.25	0.35	0.08	0.20	0.47	0.41	0.48	0.36	0.21	0.26
AMINOACYL TRNA BIOSYNTHESIS	41	0	0.00%	0.47	0.15	0.31	0.47	0.26	0.34	0.52	0.47	0.50	0.42	0.44	0.50
REGULATION OF ACTIN CYTOSKELETON	216	0	0.00%	0.47	0.11	0.26	0.31	0.05	0.16	0.18	0.24	0.17	0.21	0.27	0.19
PANCREATIC CANCER	70	15	21.43%	0.46	0.30	0.35	0.40	0.43	0.40	0.18	0.23	0.16	0.07	0.14	0.06
NEUROTROPHIN SIGNALING PATHWAY	126	9	7.14%	0.46	0.09	0.25	0.32	0.07	0.17	0.38	0.38	0.39	0.20	0.10	0.20
PPAR SIGNALING PATHWAY	69	0	0.00%	0.45	0.28	0.36	0.50	0.22	0.39	0.13	0.17	0.11	0.34	0.25	0.31
COLORECTAL CANCER	62	10	16.13%	0.45	0.16	0.27	0.41	0.23	0.31	0.38	0.39	0.37	0.57	0.52	0.52
HISTIDINE METABOLISM	29	0	0.00%	0.45	0.08	0.25	0.38	0.14	0.24	0.39	0.32	0.31	0.33	0.22	0.20
TRYPTOPHAN METABOLISM	40	0	0.00%	0.45	0.03	0.23	0.37	-0.01	0.17	0.41	0.32	0.32	0.38	0.19	0.28
PYRUVATE METABOLISM	40	0	0.00%	0.44	0.13	0.31	0.33	0.13	0.27	0.40	0.39	0.38	0.06	-0.02	0.04
NON HOMOLOGOUS END JOINING	14	2	14.29%	0.44	0.29	0.35	0.45	0.31	0.37	0.36	0.32	0.36	0.46	0.48	0.49
NUCLEOTIDE EXCISION REPAIR	44	4	9.09%	0.44	0.30	0.42	0.34	0.25	0.36	0.38	0.38	0.38	0.45	0.54	0.49
SELENOAMINO ACID METABOLISM	26	0	0.00%	0.44	0.25	0.34	0.41	0.29	0.35	0.21	0.25	0.24	0.48	0.44	0.46
PARKINSONS DISEASE	133	0	0.00%	0.42	0.17	0.22	0.17	0.15	0.24	0.28	0.25	0.24	0.43	0.36	0.39
CHRONIC MYELOID LEUKEMIA	73	21	28.77%	0.42	0.16	0.23	0.28	0.23	0.22	0.20	0.21	0.17	0.51	0.49	0.49
PROTEASOME	48	0	0.00%	0.41	0.02	0.24	0.20	0.22	0.15	0.47	0.35	0.43	0.28	0.19	0.25
RNA POLYMERASE	29	0	0.00%	0.41	0.24	0.39	0.45	0.36	0.51	0.31	0.32	0.33	0.40	0.42	0.42
TERPENOID BACKBONE BIOSYNTHESIS	15	0	0.00%	0.41	0.15	0.30	0.42	0.28	0.37	0.07	0.04	0.06	0.08	0.14	0.18
GLIOMA	65	11	16.92%	0.40	0.14	0.21	0.46	0.29	0.35	0.05	0.13	0.02	-0.04	0.01	-0.09
MELANOMA	71	11	15.49%	0.39	0.18	0.21	0.41	0.27	0.31	0.24	0.31	0.22	0.12	0.18	0.10
CIRCADIAN RHYTHM MAMMAL	13	0	0.00%	0.39	0.17	0.35	0.19	0.07	0.12	0.32	0.35	0.33	0.13	0.16	0.20
LYSOSOME	121	0	0.00%	0.39	-0.05	0.17	0.21	-0.03	0.03	0.13	0.12	0.15	-0.10	-0.04	-0.07
GLYOXYLATE AND DICARBOXYLATE METABOLISM	16	0	0.00%	0.39	0.13	0.27	0.44	0.23	0.35	0.51	0.47	0.51	0.45	0.38	0.44
SPLICEOSOME	128	0	0.00%	0.39	0.12	0.33	0.17	0.02	0.19	0.43	0.39	0.42	0.56	0.58	0.58
ARGININE AND PROLINE METABOLISM	54	0	0.00%	0.39	0.11	0.21	0.28	0.19	0.21	0.37	0.32	0.30	-0.27	-0.19	-0.19
FOLATE BIOSYNTHESIS	11	0	0.00%	0.39	0.15	0.30	0.33	0.09	0.28	0.46	0.43	0.48	0.37	0.35	0.42
GLYCOLYSIS GLUCONEOGENESIS	62	0	0.00%	0.39	0.03	0.27	0.29	0.23	0.26	0.45	0.45	0.46	0.43	0.38	0.39
ARACHIDONIC ACID METABOLISM	58	0	0.00%	0.38	0.32	0.34	0.16	0.01	0.14	0.24	0.27	0.20	-0.04	-0.02	-0.08
APOPTOSIS	88	3	3.41%	0.38	0.01	0.23	0.14	-0.13	-0.03	0.23	0.25	0.16	0.02	0.04	-0.02
AMYOTROPHIC LATERAL SCLEROSIS ALS	53	1	1.89%	0.37	-0.02	0.18	0.35	0.34	0.32	0.46	0.43	0.45	0.39	0.42	0.35
PENTOSE PHOSPHATE PATHWAY	27	0	0.00%	0.37	0.07	0.23	0.27	0.05	0.21	0.42	0.42	0.44	0.29	0.24	0.30
VIBRIO CHOLERAE INFECTION	56	0	0.00%	0.37	0.09	0.22	0.05	0.04	0.07	0.17	0.21	0.15	-0.11	-0.16	-0.18

PHENYLALANINE METABOLISM	18	0	0.00%	0.36	0.06	0.20	0.35	0.09	0.23	0.33	0.25	0.24	0.30	0.20	0.19
FRUCTOSE AND MANNOSE METABOLISM	34	0	0.00%	0.35	0.11	0.25	0.34	0.14	0.23	0.05	0.02	0.02	0.19	0.19	0.19
TYPE II DIABETES MELLITUS	47	0	0.00%	0.35	0.00	0.15	0.25	0.03	0.09	0.38	0.36	0.39	0.33	0.22	0.29
ALDOSTERONE REGULATED SODIUM REABSORPTION	42	1	2.38%	0.34	0.14	0.24	0.32	0.12	0.24	0.33	0.37	0.34	0.11	0.19	0.10
PATHOGENIC ESCHERICHIA COLI INFECTION	59	3	5.08%	0.33	-0.09	0.17	0.23	-0.06	0.12	0.23	0.22	0.18	-0.21	-0.17	-0.24
JAK STAT SIGNALING PATHWAY	155	6	3.87%	0.33	0.07	0.14	0.24	-0.03	0.06	0.23	0.29	0.20	0.19	0.21	0.13
CITRATE CYCLE TCA CYCLE	32	0	0.00%	0.33	0.10	0.20	0.14	0.04	0.01	0.33	0.37	0.37	0.37	0.31	0.34
RENIN ANGIOTENSIN SYSTEM	17	0	0.00%	0.30	0.16	0.20	0.33	0.24	0.25	0.25	0.29	0.23	0.41	0.34	0.40
AMINO SUGAR AND NUCLEOTIDE SUGAR METABOLISM	44	0	0.00%	0.30	0.02	0.18	0.26	0.09	0.15	0.26	0.28	0.33	0.30	0.30	0.32
N GLYCAN BIOSYNTHESIS	46	0	0.00%	0.30	0.28	0.32	0.05	0.05	0.11	0.34	0.34	0.37	0.25	0.24	0.23
LIMONENE AND PINENE DEGRADATION	10	0	0.00%	0.30	0.01	0.11	0.06	-0.05	-0.03	0.01	-0.02	-0.04	0.11	0.02	0.08
NON SMALL CELL LUNG CANCER	54	9	16.67%	0.30	0.10	0.11	0.29	0.20	0.19	0.00	0.06	-0.03	0.06	-0.01	-0.04
NOTCH SIGNALING PATHWAY	47	4	8.51%	0.29	0.07	0.22	0.34	0.15	0.33	0.34	0.35	0.33	0.38	0.37	0.32
GALACTOSE METABOLISM	26	0	0.00%	0.28	-0.03	0.18	0.24	0.02	0.12	0.12	0.06	0.08	0.16	0.12	0.19
GAP JUNCTION	90	1	1.11%	0.28	0.00	0.15	0.43	0.29	0.35	0.25	0.32	0.25	-0.07	0.02	-0.04
RIBOFLAVIN METABOLISM	16	0	0.00%	0.27	0.04	0.21	0.27	0.14	0.21	0.18	0.20	0.22	-0.07	0.04	0.05
ALZHEIMERS DISEASE	169	1	0.59%	0.27	0.01	0.13	0.23	0.19	0.28	0.23	0.21	0.18	0.51	0.48	0.50
TOLL LIKE RECEPTOR SIGNALING PATHWAY	102	0	0.00%	0.27	-0.12	0.04	0.22	-0.15	0.03	0.22	0.15	0.20	0.25	0.12	0.22
ALPHA LINOLENIC ACID METABOLISM	19	0	0.00%	0.26	0.14	0.23	0.21	0.06	0.20	-0.16	-0.10	-0.17	-0.14	-0.13	-0.15
HEDGEHOG SIGNALING PATHWAY	56	1	1.79%	0.26	-0.03	0.13	0.38	0.16	0.26	0.08	0.12	0.03	-0.13	-0.05	-0.15
CARDIAC MUSCLE CONTRACTION	80	0	0.00%	0.25	0.34	0.28	0.35	0.14	0.31	-0.06	-0.03	-0.10	-0.18	-0.13	-0.21
NITROGEN METABOLISM	23	0	0.00%	0.25	0.22	0.28	0.35	0.07	0.27	0.41	0.39	0.43	0.33	0.41	0.34
FOCAL ADHESION	201	4	1.99%	0.25	0.35	0.23	0.28	0.34	0.29	0.26	0.34	0.26	0.00	-0.09	-0.05
RETINOL METABOLISM	64	0	0.00%	0.25	0.35	0.28	0.21	0.26	0.21	0.15	0.26	0.21	0.38	0.40	0.39
CYTOKINE CYTOKINE RECEPTOR INTERACTION	267	3	1.12%	0.25	-0.15	0.01	0.19	-0.16	0.02	0.17	0.23	0.13	0.18	0.23	0.12
CHEMOKINE SIGNALING PATHWAY	190	1	0.53%	0.25	-0.18	0.02	0.20	-0.16	0.01	0.13	0.21	0.11	0.18	0.06	0.14
SNARE INTERACTIONS IN VESICULAR TRANSPORT	38	0	0.00%	0.24	0.29	0.21	0.16	0.22	0.19	0.42	0.36	0.38	0.33	0.28	0.28
SYSTEMIC LUPUS ERYTHEMATOSUS	140	0	0.00%	0.22	0.10	0.20	0.14	0.06	0.11	0.38	0.32	0.31	0.14	0.12	0.13
LINOLEIC ACID METABOLISM	29	0	0.00%	0.22	-0.02	0.16	0.12	-0.02	0.11	0.04	0.08	0.03	-0.12	-0.14	-0.17
LONG TERM DEPRESSION	70	0	0.00%	0.20	0.07	0.07	-0.06	0.17	0.02	0.02	0.10	0.03	0.01	0.03	-0.03
OXIDATIVE PHOSPHORYLATION	135	0	0.00%	0.20	0.23	0.25	0.18	0.16	0.24	0.20	0.18	0.16	0.03	0.05	-0.02
DRUG METABOLISM OTHER ENZYMES	51	0	0.00%	0.20	0.19	0.24	0.37	0.21	0.28	0.48	0.43	0.42	0.48	0.43	0.44
B CELL RECEPTOR SIGNALING PATHWAY	75	1	1.33%	0.19	-0.13	-0.04	0.14	-0.14	-0.04	0.06	0.12	0.03	-0.10	-0.14	-0.13
TIGHT JUNCTION	134	1	0.75%	0.19	0.40	0.26	0.28	0.36	0.30	0.24	0.29	0.23	0.18	0.10	0.08
LEUKOCYTE TRANSENDOTHELIAL MIGRATION	118	0	0.00%	0.19	0.23	0.13	0.23	0.02	0.08	0.16	0.25	0.16	0.36	0.45	0.34
T CELL RECEPTOR SIGNALING PATHWAY	108	2	1.85%	0.19	-0.18	-0.06	0.13	-0.19	-0.06	0.02	0.08	0.00	0.04	-0.07	0.02
TGF BETA SIGNALING PATHWAY	86	19	22.09%	0.18	0.29	0.16	0.21	0.31	0.21	0.26	0.29	0.27	-0.04	-0.11	-0.11
GLYCOSAMINOGLYCAN DEGRADATION	21	0	0.00%	0.17	-0.13	0.11	0.11	-0.11	0.05	0.14	0.03	0.07	0.28	0.12	0.19
FC GAMMA R MEDIATED PHAGOCYTOSIS	97	0	0.00%	0.17	-0.22	-0.01	0.18	0.10	0.08	0.05	0.12	0.01	-0.12	-0.06	-0.16
ASCORBATE AND ALDARATE METABOLISM	25	0	0.00%	0.16	0.12	0.12	0.20	0.12	0.15	0.22	0.20	0.22	-0.13	-0.10	-0.12
MATURITY ONSET DIABETES OF THE YOUNG	25	0	0.00%	0.15	0.07	0.11	0.20	0.09	0.12	0.09	0.02	0.04	0.27	0.25	0.28
NICOTINATE AND NICOTINAMIDE METABOLISM	24	0	0.00%	0.14	-0.04	-0.03	0.15	-0.06	0.05	0.40	0.33	0.39	0.13	0.14	0.11
ADIPOCYTOKINE SIGNALING PATHWAY	67	0	0.00%	0.14	0.35	0.26	0.37	0.32	0.31	0.19	0.22	0.16	0.05	0.15	0.05
ERBB SIGNALING PATHWAY	87	5	5.75%	0.14	0.20	0.10	0.11	0.28	0.16	-0.04	0.00	-0.06	0.09	0.04	-0.01
MTOR SIGNALING PATHWAY	52	0	0.00%	0.14	0.27	0.12	0.16	0.29	0.15	0.16	0.23	0.18	0.44	0.48	0.44
RIG I LIKE RECEPTOR SIGNALING PATHWAY	71	0	0.00%	0.14	0.05	0.05	0.17	0.07	0.05	0.01	-0.01	0.04	-0.07	-0.11	-0.04
RIBOSOME	88	0	0.00%	0.13	0.10	0.18	-0.04	-0.07	0.01	0.08	0.13	0.09	0.18	0.23	0.20
NATURAL KILLER CELL MEDIATED CYTOTOXICITY	137	0	0.00%	0.12	-0.27	-0.10	0.07	-0.26	-0.10	0.01	0.10	-0.02	0.47	0.34	0.36
PORPHYRIN AND CHLOROPHYLL METABOLISM	41	0	0.00%	0.12	0.09	0.18	0.23	0.19	0.26	0.18	0.18	0.23	-0.02	0.04	0.03
MAPK SIGNALING PATHWAY	267	9	3.37%	0.11	0.27	0.08	0.38	0.17	0.24	0.27	0.33	0.25	0.50	0.52	0.48
ACUTE MYELOID LEUKEMIA	60	3	5.00%	0.11	0.29	0.12	0.06	0.21	0.09	0.09	0.06	-0.01	0.24	0.23	0.15
PRIMARY IMMUNODEFICIENCY	35	0	0.00%	0.11	-0.27	-0.11	0.02	-0.31	-0.15	0.00	-0.06	0.06	0.04	-0.06	0.08
PROTEIN EXPORT	24	0	0.00%	0.10	0.07	0.09	0.19	0.03	0.16	0.33	0.24	0.27	0.39	0.32	0.35
EPITHELIAL CELL SIGNALING IN HELICOBACTER PYLORI INFECTION	68	0	0.00%	0.10	0.38	0.23	0.17	0.17	0.12	0.00	0.06	-0.02	-0.16	-0.10	-0.18
BIOSYNTHESIS OF UNSATURATED FATTY ACIDS	22	0	0.00%	0.10	0.14	0.07	0.03	0.05	-0.02	-0.22	-0.17	-0.25	0.08	0.00	-0.01
PENTOSE AND GLUCURONATE INTERCONVERSIONS	28	0	0.00%	0.10	0.23	0.19	0.28	0.32	0.29	0.31	0.30	0.30	0.27	0.27	0.27
GLYCOSPHINGOLIPID BIOSYNTHESIS GANGLIO SERIES	15	0	0.00%	0.09	0.04	0.11	0.09	0.04	0.12	0.35	0.33	0.33	-0.07	-0.07	-0.09
ANTIGEN PROCESSING AND PRESENTATION	89	0	0.00%	0.09	-0.26	-0.09	0.01	-0.30	-0.15	0.28	0.21	0.29	-0.06	-0.13	-0.03
CYTOSOLIC DNA SENSING PATHWAY	56	0	0.00%	0.09	-0.17	-0.03	0.09	-0.06	0.00	0.38	0.35	0.40	0.22	0.18	0.22
CELL ADHESION MOLECULES CAMS	134	0	0.00%	0.08	-0.26	-0.10	0.05	-0.26	-0.10	0.19	0.24	0.14	-0.01	-0.07	-0.02
ALANINE ASPARTATE AND GLUTAMATE METABOLISM	32	0	0.00%	0.08	-0.03	0.06	0.23	0.06	0.13	0.49	0.43	0.47	0.26	0.24	0.30
DORSO VENTRAL AXIS FORMATION	25	0	0.00%	0.08	0.36	0.16	0.09	0.31	0.19	0.03	0.08	0.01	-0.06	0.00	-0.08
GLYCOSPHINGOLIPID BIOSYNTHESIS LACTO AND NEOLACTO SERIES	26	0	0.00%	0.08	0.01	0.10	0.14	0.03	0.12	-0.08	-0.04	-0.14	-0.07	-0.03	-0.11
AUTOIMMUNE THYROID DISEASE	53	0	0.00%	0.08	-0.16	-0.07	0.03	-0.23	-0.12	0.01	-0.08	-0.01	0.12	0.24	0.13

AXON GUIDANCE	129	2	1.55%	0.08	0.37	0.15	0.11	0.32	0.20	0.21	0.27	0.19	0.13	0.19	0.11
INOSITOL PHOSPHATE METABOLISM	54	0	0.00%	0.08	0.37	0.21	0.06	0.32	0.19	0.04	0.08	0.01	0.00	0.07	-0.04
GLYCOSAMINOGLYCAN BIOSYNTHESIS CHONDROITIN SULFATE	22	0	0.00%	0.07	0.21	0.08	0.07	0.17	0.06	-0.14	-0.15	-0.12	0.01	0.04	-0.04
HYPERTROPHIC CARDIOMYOPATHY HCM	85	3	3.53%	0.07	0.36	0.14	0.30	0.30	0.29	0.30	0.34	0.30	-0.03	0.01	-0.05
GLYCEROLIPID METABOLISM	49	0	0.00%	0.07	0.35	0.14	0.15	0.31	0.18	0.09	0.14	0.07	0.01	0.07	0.00
BUTANOATE METABOLISM	34	0	0.00%	0.06	-0.04	0.04	-0.10	0.05	-0.05	0.42	0.34	0.35	0.46	0.36	0.40
ABC TRANSPORTERS	44	0	0.00%	0.06	0.23	0.16	0.19	0.18	0.11	0.47	0.48	0.49	0.19	0.20	0.17
METABOLISM OF XENOBIOTICS BY CYTOCHROME P450	70	0	0.00%	0.06	0.28	0.17	-0.14	0.09	-0.05	0.20	0.26	0.20	-0.10	-0.07	-0.15
GRAFT VERSUS HOST DISEASE	42	0	0.00%	0.05	-0.28	-0.12	0.00	-0.32	-0.16	0.10	0.14	0.11	0.30	0.29	0.24
SULFUR METABOLISM	13	0	0.00%	0.05	0.19	0.24	0.08	0.07	0.17	0.25	0.18	0.23	0.21	0.20	0.29
HEMATOPOIETIC CELL LINEAGE	88	0	0.00%	0.05	-0.31	-0.15	0.03	-0.29	-0.14	0.19	0.23	0.12	0.20	0.22	0.13
ALLOGRAFT REJECTION	38	0	0.00%	0.04	-0.28	-0.13	-0.02	-0.33	-0.17	0.12	0.17	0.15	0.03	0.11	-0.02
ETHER LIPID METABOLISM	33	0	0.00%	0.04	0.28	0.10	0.13	0.28	0.20	0.03	0.10	0.02	-0.06	-0.03	-0.08
VIRAL MYOCARDITIS	73	2	2.74%	0.04	-0.30	-0.13	0.00	-0.30	-0.14	0.23	0.26	0.16	0.13	0.05	0.14
GLYCOSAMINOGLYCAN BIOSYNTHESIS KERATAN SULFATE	15	0	0.00%	0.03	0.02	0.04	0.15	0.07	0.14	0.02	0.02	0.01	-0.29	-0.21	-0.26
ADHERENS JUNCTION	75	5	6.67%	0.03	0.38	0.16	0.14	0.34	0.20	0.33	0.38	0.36	0.07	-0.01	-0.04
INTESTINAL IMMUNE NETWORK FOR IGA PRODUCTION	48	1	2.08%	0.03	-0.29	-0.13	-0.03	-0.34	-0.18	0.41	0.38	0.37	0.13	0.22	0.08
GLYCOSAMINOGLYCAN BIOSYNTHESIS HEPARAN SULFATE	26	0	0.00%	0.03	0.12	0.03	0.19	-0.08	0.09	0.02	-0.01	-0.04	0.15	0.02	0.05
TYPE I DIABETES MELLITUS	44	0	0.00%	0.02	-0.27	-0.13	0.01	-0.32	-0.15	-0.02	-0.07	0.04	0.11	0.09	0.18
ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY ARVC	76	0	0.00%	0.01	0.17	0.01	0.10	0.21	0.11	0.20	0.24	0.28	-0.06	-0.01	-0.08
ENDOMETRIAL CANCER	52	4	7.69%	0.01	0.14	-0.01	0.02	0.15	0.04	0.00	0.00	-0.08	-0.03	0.00	-0.07
OTHER GLYCAN DEGRADATION	16	0	0.00%	0.01	0.00	0.04	0.04	0.16	0.13	-0.15	-0.15	-0.14	0.00	0.05	0.08
TASTE TRANSDUCTION	52	0	0.00%	0.00	0.21	0.10	0.12	0.19	0.17	0.09	0.12	0.08	-0.20	-0.13	-0.16
VEGF SIGNALING PATHWAY	76	0	0.00%	0.00	0.24	0.07	0.05	0.31	0.17	-0.12	-0.04	-0.13	-0.03	0.02	-0.08
DRUG METABOLISM CYTOCHROME P450	72	0	0.00%	0.00	0.28	0.14	0.08	0.27	0.15	0.34	0.35	0.29	0.06	0.08	0.01
LEISHMANIA INFECTION	72	3	4.17%	0.00	-0.30	-0.13	-0.03	-0.29	-0.15	0.18	0.19	0.20	0.25	0.24	0.29
VASCULAR SMOOTH MUSCLE CONTRACTION	115	0	0.00%	0.00	0.29	0.09	0.11	0.31	0.18	0.25	0.31	0.24	-0.13	-0.05	-0.15
THYROID CANCER	29	3	10.34%	-0.02	0.23	0.02	-0.02	0.16	0.01	0.05	0.01	-0.04	0.10	0.06	-0.02
REGULATION OF AUTOPHAGY	35	0	0.00%	-0.03	0.05	-0.04	0.03	0.10	0.02	0.06	0.06	0.06	-0.06	-0.06	-0.06
NEUROACTIVE LIGAND RECEPTOR INTERACTION	272	0	0.00%	-0.03	0.35	0.13	0.18	0.37	0.26	0.56	0.55	0.54	0.02	0.09	-0.01
BASAL CELL CARCINOMA	55	2	3.64%	-0.03	0.29	0.09	0.03	0.20	0.06	0.04	0.05	-0.02	-0.02	0.00	-0.05
OLFACTORY TRANSDUCTION	389	0	0.00%	-0.03	-0.01	0.04	-0.09	-0.08	-0.08	0.31	0.27	0.25	0.43	0.35	0.38
STARCH AND SUCROSE METABOLISM	52	0	0.00%	-0.03	0.04	0.02	-0.01	0.10	0.07	-0.07	-0.13	-0.13	-0.01	-0.09	-0.08
LONG TERM POTENTIATION	70	2	2.86%	-0.04	0.28	0.08	0.06	0.27	0.15	0.06	0.14	0.06	0.35	0.40	0.39
PHOSPHATIDYLINOSITOL SIGNALING SYSTEM	76	0	0.00%	-0.04	0.31	0.11	0.08	0.33	0.19	0.09	0.14	0.07	0.01	0.08	-0.05
INSULIN SIGNALING PATHWAY	137	1	0.73%	-0.04	0.18	0.00	0.07	0.24	0.12	0.04	0.11	0.07	0.13	0.23	0.15
GLYCEROPHOSPHOLIPID METABOLISM	77	0	0.00%	-0.04	0.23	0.12	0.04	0.21	0.17	-0.05	0.01	-0.06	-0.14	-0.12	-0.18
GLYCOSPHINGOLIPID BIOSYNTHESIS GLOBO SERIES	14	0	0.00%	-0.05	0.10	0.03	0.03	0.10	0.07	0.12	0.07	0.07	0.10	0.04	0.02
ECM RECEPTOR INTERACTION	84	0	0.00%	-0.05	-0.04	0.04	0.05	0.02	0.06	0.30	0.30	0.25	-0.06	-0.15	-0.09
FC EPSILON RI SIGNALING PATHWAY	79	0	0.00%	-0.05	0.34	0.14	0.34	0.23	0.36	0.12	0.11	0.16	-0.03	-0.03	-0.11
PRION DISEASES	35	0	0.00%	-0.05	0.29	0.08	0.08	0.29	0.15	0.12	0.21	0.11	0.07	0.11	0.05
RENAL CELL CARCINOMA	70	6	8.57%	-0.06	0.28	0.03	0.05	0.29	0.14	0.11	0.16	0.11	-0.02	0.07	-0.02
STEROID HORMONE BIOSYNTHESIS	55	0	0.00%	-0.06	0.07	0.08	0.02	0.09	0.08	-0.10	0.00	-0.09	-0.01	0.01	0.03
ASTHMA	30	0	0.00%	-0.06	-0.33	-0.18	-0.12	-0.38	-0.24	-0.16	-0.20	-0.08	0.08	0.17	0.03
TAURINE AND HYPOTAURINE METABOLISM	10	0	0.00%	-0.07	-0.07	-0.01	0.04	-0.02	0.01	0.09	0.13	0.15	0.19	0.18	0.13
PANTOTHENATE AND COA BIOSYNTHESIS	16	0	0.00%	-0.08	0.23	0.04	-0.04	0.22	0.03	0.12	0.15	0.05	-0.20	-0.10	-0.13
PROXIMAL TUBULE BICARBONATE RECLAMATION	23	0	0.00%	-0.08	0.17	0.09	0.34	0.09	0.23	0.43	0.41	0.44	0.20	0.28	0.22
SPHINGOLIPID METABOLISM	40	0	0.00%	-0.08	0.26	0.05	-0.05	0.20	0.05	0.29	0.30	0.27	0.04	0.18	0.19
ENDOCYTOSIS	183	1	0.55%	-0.09	0.32	0.09	0.03	0.27	0.13	-0.03	0.04	-0.03	-0.13	-0.08	-0.16
GNRH SIGNALING PATHWAY	101	0	0.00%	-0.09	0.30	0.06	-0.03	0.18	0.08	-0.04	0.01	-0.08	-0.10	-0.07	-0.13
NOD LIKE RECEPTOR SIGNALING PATHWAY	62	0	0.00%	-0.12	-0.14	-0.07	-0.07	-0.16	-0.07	0.04	0.11	0.02	0.12	0.18	0.05
PRIMARY BILE ACID BIOSYNTHESIS	16	0	0.00%	-0.13	0.08	-0.01	0.34	0.26	0.30	-0.18	-0.16	-0.20	-0.03	-0.03	-0.06
BASAL TRANSCRIPTION FACTORS	36	0	0.00%	-0.13	0.08	-0.08	-0.06	0.09	-0.01	0.31	0.28	0.32	0.12	0.16	0.12
GLYCOSYLPHOSPHATIDYLINOSITOL GPI ANCHOR BIOSYNTHESIS	25	0	0.00%	-0.13	0.20	0.07	-0.10	-0.01	0.00	-0.12	-0.03	-0.09	-0.21	-0.03	-0.13
CALCIUM SIGNALING PATHWAY	178	0	0.00%	-0.13	0.30	0.04	0.01	0.27	0.13	0.19	0.25	0.16	-0.14	-0.02	-0.13
COMPLEMENT AND COAGULATION CASCADES	69	0	0.00%	-0.14	0.24	0.06	0.05	0.30	0.19	0.30	0.37	0.28	0.19	0.28	0.20
HUNTINGTONS DISEASE	185	5	2.70%	-0.14	0.17	-0.04	0.28	0.15	0.30	0.27	0.25	0.24	-0.15	-0.15	-0.18
DILATED CARDIOMYOPATHY	92	3	3.26%	-0.15	0.20	0.01	0.22	0.00	0.11	0.29	0.33	0.28	-0.05	0.01	-0.05
VASOPRESSIN REGULATED WATER REABSORPTION	44	0	0.00%	-0.15	0.00	0.00	-0.13	0.15	-0.02	-0.27	-0.13	-0.18	-0.20	-0.13	-0.11
WNT SIGNALING PATHWAY	151	15	9.93%	-0.16	0.03	0.00	0.11	0.31	0.17	-0.06	0.00	-0.08	0.05	0.04	-0.01
BETA ALANINE METABOLISM	22	0	0.00%	-0.18	0.00	-0.04	0.09	0.03	0.03	0.42	0.39	0.36	0.14	0.18	0.17
MELANOGENESIS	102	3	2.94%	-0.18	0.18	-0.01	-0.04	0.22	0.06	-0.03	0.02	-0.08	-0.15	-0.08	-0.11
VALINE LEUCINE AND ISOLEUCINE BIOSYNTHESIS	11	0	0.00%	-0.19	0.14	-0.02	0.00	0.17	0.05	0.21	0.24	0.22	-0.15	0.00	0.00
RNA DEGRADATION	59	0	0.00%	-0.19	0.10	-0.07	0.51	0.37	0.47	0.33	0.33	0.33	0.44	0.38	0.35

O GLYCAN BIOSYNTHESIS	30	0	0.00%	-0.32	-0.04	-0.18	-0.22	-0.05	-0.11	0.22	0.23	0.17	-0.13	-0.15	-0.13	

Correlations between the Pathifier score of each Reactome pathway and three CIN measurements in the four breast cancer cohorts

Note:

1. Overlap = length of the overlap with the CELL CYCLE pathway in Reactome

2. Percentage = percentage of the overlap with the CELL CYCLE pathway in Reactome

Pathway Name	Length	Overlap	Percentage	METABRIC Discovery Cohort			METABRIC Validation Cohort			TCGA RNA-seq Cohort			TCGA Microarray Cohort		
				No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes	No. of breaks	GII	No. of amplified/deleted genes
CELL CYCLE	421	421	100.00%	0.65	0.32	0.45	0.59	0.36	0.50	0.63	0.57	0.59	0.57	0.52	0.52
CELL CYCLE MITOTIC	325	325	100.00%	0.64	0.32	0.45	0.62	0.36	0.51	0.65	0.59	0.61	0.57	0.52	0.52
MITOTIC G2 G2 M PHASES	81	81	100.00%	0.64	0.33	0.44	0.56	0.36	0.48	0.59	0.50	0.53	0.57	0.52	0.53
LOSS OF NLP FROM MITOTIC CENTROSOMES	59	59	100.00%	0.64	0.33	0.46	0.33	0.28	0.26	0.64	0.57	0.59	0.55	0.48	0.54
DNA REPLICATION	192	192	100.00%	0.64	0.31	0.44	0.62	0.36	0.51	0.65	0.59	0.61	0.57	0.52	0.52
MITOTIC M M G1 PHASES	172	172	100.00%	0.64	0.31	0.44	0.62	0.35	0.50	0.65	0.58	0.60	0.57	0.51	0.51
MITOTIC PROMETAPHASE	87	87	100.00%	0.64	0.33	0.44	0.60	0.36	0.50	0.63	0.58	0.59	0.55	0.50	0.50
RECRUITMENT OF MITOTIC CENTROSOME PROTEINS AND COMPLEXES	66	66	100.00%	0.63	0.32	0.47	0.27	0.10	0.27	0.43	0.38	0.41	0.54	0.51	0.53
CELL CYCLE CHECKPOINTS	124	124	100.00%	0.63	0.29	0.44	0.49	0.24	0.41	0.52	0.45	0.50	0.58	0.53	0.53
MHC CLASS II ANTIGEN PRESENTATION	91	14	15.38%	0.63	0.26	0.43	0.41	0.13	0.30	0.39	0.35	0.40	0.55	0.49	0.49
SIGNALING BY SCF KIT	78	5	6.41%	0.62	0.35	0.48	0.31	0.08	0.16	0.09	0.12	0.06	0.46	0.38	0.41
FACTORS INVOLVED IN MEGAKARYOCYTE DEVELOPMENT AND PLATELET PRODUCTION	132	13	9.85%	0.62	0.32	0.44	0.62	0.38	0.51	0.32	0.34	0.34	0.56	0.51	0.50
INHIBITION OF THE PROTEOLYTIC ACTIVITY OF APC C REQUIRED FOR THE ONSET OF ANAPHASE BY MITOTIC SPINDLE CHECKPOINT COMPONENTS	24	24	100.00%	0.62	0.31	0.46	0.53	0.27	0.45	0.46	0.42	0.40	0.57	0.49	0.50
REGULATION OF MITOTIC CELL CYCLE	85	85	100.00%	0.62	0.25	0.44	0.48	0.20	0.38	0.51	0.41	0.47	0.59	0.50	0.52
APC CDC20 MEDIATED DEGRADATION OF NEK2A	28	28	100.00%	0.62	0.35	0.48	0.56	0.34	0.49	0.37	0.31	0.32	0.56	0.49	0.51
MITOTIC G1 G1 S PHASES	137	137	100.00%	0.62	0.29	0.43	0.61	0.33	0.49	0.59	0.54	0.57	0.56	0.52	0.53
KINESINS	24	6	25.00%	0.62	0.34	0.43	0.60	0.39	0.51	0.56	0.53	0.51	0.54	0.49	0.47
CYCLIN A B1 ASSOCIATED EVENTS DURING G2 M TRANSITION	15	15	100.00%	0.61	0.33	0.42	0.60	0.38	0.50	0.59	0.54	0.57	0.56	0.50	0.50
G0 AND EARLY G1	25	25	100.00%	0.61	0.30	0.42	0.60	0.34	0.49	0.60	0.55	0.56	0.56	0.51	0.53
METABOLISM OF NUCLEOTIDES	72	3	4.17%	0.61	0.29	0.44	0.46	0.23	0.38	0.41	0.34	0.36	0.53	0.47	0.47
HIV LIFE CYCLE	125	17	13.60%	0.61	0.32	0.44	-0.08	0.03	0.03	0.36	0.33	0.34	0.57	0.54	0.54
G2 M CHECKPOINTS	45	45	100.00%	0.60	0.32	0.41	0.57	0.38	0.49	0.58	0.56	0.56	0.56	0.53	0.52
SYNTHESIS OF DNA	92	92	100.00%	0.60	0.28	0.43	0.57	0.30	0.46	0.60	0.53	0.56	0.57	0.55	0.55
E2F MEDIATED REGULATION OF DNA REPLICATION	35	35	100.00%	0.60	0.28	0.41	0.55	0.33	0.45	0.59	0.56	0.56	0.52	0.49	0.47
APC C CDH1 MEDIATED DEGRADATION OF CDC20 AND OTHER APC C CDH1 TARGETED PROTEINS IN LATE MITOSIS EARLY G1	72	72	100.00%	0.60	0.22	0.42	0.44	0.16	0.35	0.48	0.38	0.44	0.60	0.49	0.53
G1 S SPECIFIC TRANSCRIPTION	19	19	100.00%	0.59	0.25	0.39	0.58	0.30	0.44	0.60	0.55	0.55	0.52	0.47	0.46
ACTIVATION OF ATR IN RESPONSE TO REPLICATION STRESS	38	38	100.00%	0.59	0.31	0.39	0.55	0.37	0.47	0.58	0.56	0.56	0.55	0.53	0.52
APC C CDC20 MEDIATED DEGRADATION OF CYCLIN B	26	26	100.00%	0.59	0.33	0.44	0.46	0.32	0.42	0.39	0.34	0.35	0.56	0.49	0.51
M G1 TRANSITION	81	81	100.00%	0.59	0.25	0.40	0.56	0.27	0.43	0.44	0.37	0.43	0.56	0.52	0.52
DNA REPAIR	112	29	25.89%	0.58	0.39	0.51	0.01	0.15	0.04	0.37	0.34	0.35	0.52	0.53	0.52
SLC MEDIATED TRANSMEMBRANE TRANSPORT	241	7	2.90%	0.58	0.20	0.36	0.23	0.30	0.23	-0.23	-0.17	-0.26	-0.01	-0.03	-0.10
ASSEMBLY OF THE PRE REPLICATIVE COMPLEX	65	65	100.00%	0.58	0.22	0.38	0.52	0.21	0.39	0.58	0.44	0.50	0.57	0.51	0.52
G2 M DNA DAMAGE CHECKPOINT	12	12	100.00%	0.57	0.38	0.47	0.57	0.43	0.54	0.54	0.50	0.52	0.51	0.50	0.49
G1 PHASE	38	38	100.00%	0.57	0.27	0.36	0.48	0.31	0.37	0.54	0.50	0.50	0.51	0.44	0.46
ASSOCIATION OF LICENSING FACTORS WITH THE PRE REPLICATIVE COMPLEX	14	14	100.00%	0.57	0.25	0.37	0.54	0.30	0.40	0.58	0.54	0.55	0.53	0.50	0.49
FANCONI ANEMIA PATHWAY	25	9	36.00%	0.56	0.46	0.48	0.53	0.42	0.50	0.43	0.47	0.45	0.48	0.50	0.49
RNA POL II TRANSCRIPTION	105	3	2.86%	0.56	0.37	0.49	0.47	0.31	0.43	0.40	0.36	0.40	0.56	0.54	0.56
APC C CDC20 MEDIATED DEGRADATION OF MITOTIC PROTEINS	73	73	100.00%	0.56	0.19	0.38	0.20	0.17	0.13	0.53	0.41	0.47	0.57	0.48	0.51
APOPTOSIS	148	53	35.81%	0.56	0.19	0.41	0.20	0.13	0.09	0.48	0.41	0.46	0.52	0.39	0.44
ACTIVATION OF THE PRE REPLICATIVE COMPLEX	31	31	100.00%	0.56	0.30	0.37	0.55	0.36	0.45	0.56	0.54	0.54	0.56	0.53	0.53
PHOSPHORYLATION OF THE APC C	23	23	100.00%	0.56	0.35	0.44	0.53	0.34	0.47	0.47	0.43	0.43	0.56	0.51	0.51
DEADENYLATION DEPENDENT MRNA DECAY	48	0	0.00%	0.56	0.33	0.49	0.53	0.40	0.49	0.38	0.36	0.37	0.42	0.33	0.33
LATE PHASE OF HIV LIFE CYCLE	104	15	14.42%	0.56	0.23	0.39	0.50	0.31	0.40	0.35	0.32	0.34	0.55	0.56	0.56
GLUCOSE TRANSPORT	38	7	18.42%	0.55	0.26	0.38	0.48	0.25	0.35	0.50	0.46	0.51	0.48	0.50	0.52
SIGNALLING BY NGF	217	19	8.76%	0.55	0.18	0.36	0.35	0.26	0.28	0.42	0.41	0.43	0.40	0.40	0.36
DNA STRAND ELONGATION	30	30	100.00%	0.55	0.32	0.39	0.52	0.36	0.45	0.56	0.56	0.55	0.52	0.56	0.54
EXTENSION OF TELOMERES	27	27	100.00%	0.55	0.36	0.45	0.47	0.35	0.48	0.52	0.55	0.54	0.45	0.52	0.49
CYCLIN E ASSOCIATED EVENTS DURING G1 S TRANSITION	65	65	100.00%	0.55	0.19	0.39	0.46	0.19	0.37	0.51	0.43	0.49	0.57	0.47	0.50
G1 S TRANSITION	112	112	100.00%	0.55	0.27	0.36	0.52	0.26	0.42	0.62	0.55	0.58	0.57	0.52	0.52
HEMOSTASIS	466	23	4.94%	0.54	0.22	0.33	0.39	0.10	0.22	0.26	0.34	0.26	0.57	0.50	0.53
E2F ENABLED INHIBITION OF PRE REPLICATION COMPLEX FORMATION	10	10	100.00%	0.54	0.32	0.39	0.51	0.36	0.45	0.57	0.55	0.55	0.49	0.49	0.49
PROTEIN FOLDING	53	4	7.55%	0.53	0.37	0.50	0.43	0.27	0.42	0.50	0.43	0.48	0.60	0.50	0.55
INTERACTIONS OF VPR WITH HOST CELLULAR PROTEINS	33	7	21.21%	0.53	0.17	0.36	0.46	0.21	0.34	0.49	0.44	0.47	0.48	0.49	0.51
LAGGING STRAND SYNTHESIS	19	19	100.00%	0.53	0.33	0.42	0.51	0.36	0.49	0.51	0.54	0.53	0.44	0.51	0.49
ANTIGEN PROCESSING UBIQUITINATION PROTEASOME DEGRADATION	212	71	33.49%	0.53	0.19	0.38	0.48	0.23	0.32	0.42	0.37	0.42	0.11	0.13	0.08
TRANSPORT OF RIBONUCLEOPROTEINS INTO THE HOST NUCLEUS	27	7	25.93%	0.52	0.21	0.37	0.48	0.23	0.38	0.38	0.28	0.32	0.47	0.50	0.51
GLOBAL GENOMIC NER GG NER	35	18	51.43%	0.52	0.38	0.48	0.40	0.29	0.42	0.42	0.43	0.44	0.44	0.54	0.49
APOPTOTIC CLEAVAGE OF CELLULAR PROTEINS	40	2	5.00%	0.52	0.16	0.33	0.46	0.20	0.36	0.00	0.04	-0.03	0.35	0.30	0.31
CHROMOSOME MAINTENANCE	122	122	100.00%	0.52	0.34	0.42	0.41	0.31	0.37	0.25	0.20	0.21	0.42	0.37	0.37
RECYCLING PATHWAY OF L1	27	0	0.00%	0.52	0.32	0.38	0.42	0.31	0.32	0.24	0.28	0.22	0.52	0.44	0.41
NUCLEOTIDE EXCISION REPAIR	51	18	35.29%	0.52	0.33	0.48	0.44	0.29	0.44	0.42	0.42	0.42	0.48	0.54	0.51
CDC6 ASSOCIATION WITH THE ORC ORIGIN COMPLEX	11	11	100.00%	0.52	0.18	0.31	0.25	0.14	0.24	0.58	0.56	0.57	0.53	0.50	0.49
MICRORNA MIRNA BIOGENESIS	23	0	0.00%	0.52	0.19	0.38	0.42	0.24	0.35	0.34	0.34	0.34	0.54	0.54	0.56
PREFOLDIN MEDIATED TRANSFER OF SUBSTRATE TO CCT TRIC	28	4	14.29%	0.52	0.29	0.43	0.47	0.22	0.40	0.63	0.53	0.57	0.55	0.48	0.51
TRANSPORT OF MATURE MRNA DERIVED FROM AN INTRONLESS TRANSCRIPT	33	7	21.21%	0.52	0.20	0.38	0.44	0.22	0.39	0.48	0.46	0.47	0.50	0.50	0.51
TRANSCRIPTIONAL REGULATION OF WHITE ADIPOCYTE DIFFERENTIATION	72	2	2.78%	0.52	0.24	0.36	0.03	0.20	0.06	0.29	0.28	0.31	0.22	0.19	0.17
REGULATION OF GLUCOKINASE BY GLUCOKINASE REGULATORY PROTEIN	27	7	25.93%	0.51	0.20	0.36	0.45	0.20	0.36	0.45	0.45	0.46	0.48	0.51	0.51
UNWINDING OF DNA	11	11	100.00%	0.51	0.27	0.32	0.52	0.34	0.41	0.55	0.53	0.52	0.52	0.53	0.52
MRNA SPLICING	111	1	0.90%	0.51	0.30	0.47	0.32	0.11	0.30	0.47	0.41	0.44	0.58	0.53	0.54
METABOLISM OF CARBOHYDRATES	247	14	5.67%	0.51	0.26	0.34	0.44	0.30	0.35	0.21	0.26	0.20	0.55	0.49	0.51
POL SWITCHING	13	13	100.00%	0.51	0.34	0.43	0.48	0.35	0.48	0.53	0.54	0.53	0.42	0.50	0.48
GLUCOSE METABOLISM	69	7	10.14%	0.51	0.24	0.36	-0.05	0.13	0.01	0.44	0.44	0.45	0.41	0.39	0.40
SYNTHESIS AND INTERCONVERSION OF NUCLEOTIDE DI AND TRIPHOSPHATES	19	1	5.26%	0.51	0.25	0.42	0.38	0.19	0.32	0.37	0.32	0.34	0.50	0.41	0.41
ORC1 REMOVAL FROM CHROMATIN	67	67	100.00%	0.51	0.13	0.34	0.17	0.16	0.10	0.51	0.41	0.47	0.56	0.45	0.48
REGULATION OF MRNA STABILITY BY PROTEINS THAT BIND AU RICH ELEMENTS	84	47	55.95%	0.51	0.17	0.35	0.32	0.26	0.24	0.46	0.37	0.42	0.45	0.36	0.39

SIGNALING BY FGFR MUTANTS	44	2	4.55%	0.51	0.11	0.29	0.40	0.13	0.24	0.37	0.35	0.32	0.32	0.28	0.22
SCFSKP2 MEDIATED DEGRADATION OF P27 P21	56	56	100.00%	0.51	0.15	0.37	0.00	0.10	-0.03	0.50	0.41	0.47	0.58	0.49	0.51
PYRUVATE METABOLISM AND CITRIC ACID TCA CYCLE	48	0	0.00%	0.50	0.15	0.33	0.15	0.11	0.07	0.31	0.31	0.34	0.38	0.31	0.35
INFLUENZA LIFE CYCLE	203	13	6.40%	0.50	0.15	0.35	0.06	0.00	0.11	0.13	0.16	0.14	0.34	0.36	0.32
TRANSPORT OF MATURE TRANSCRIPT TO CYTOPLASM	54	7	12.96%	0.50	0.23	0.38	0.41	0.20	0.36	0.55	0.51	0.54	0.50	0.52	0.52
TRANSCRIPTION COUPLED NER TC NER	45	18	40.00%	0.50	0.34	0.47	0.42	0.28	0.43	0.40	0.41	0.41	0.49	0.54	0.51
PROCESSIVE SYNTHESIS ON THE LAGGING STRAND	15	15	100.00%	0.50	0.33	0.40	0.47	0.34	0.43	0.47	0.49	0.48	0.40	0.48	0.47
CHOLESTEROL BIOSYNTHESIS	24	0	0.00%	0.50	0.21	0.35	0.44	0.28	0.35	0.31	0.30	0.32	0.48	0.39	0.39
CYTOSOLIC TRNA AMINOACYLATION	24	0	0.00%	0.50	0.13	0.31	0.47	0.16	0.32	0.54	0.44	0.49	0.42	0.33	0.38
REMOVAL OF THE FLAP INTERMEDIATE FROM THE C STRAND	10	10	100.00%	0.49	0.29	0.36	0.46	0.31	0.44	0.31	0.34	0.33	0.42	0.50	0.50
CLASS B 2 SECRETIN FAMILY RECEPTORS	88	0	0.00%	0.49	0.15	0.31	0.40	0.25	0.31	-0.08	-0.09	-0.09	0.06	0.04	0.02
IRON UPTAKE AND TRANSPORT	36	0	0.00%	0.49	0.29	0.41	0.34	0.23	0.27	0.35	0.35	0.29	0.48	0.47	0.45
TRANSMEMBRANE TRANSPORT OF SMALL MOLECULES	413	10	2.42%	0.49	0.35	0.39	0.42	0.19	0.30	0.29	0.32	0.27	0.48	0.43	0.42
HYALURONAN UPTAKE AND DEGRADATION	10	0	0.00%	0.49	0.33	0.41	0.43	0.31	0.40	0.32	0.33	0.29	0.43	0.39	0.39
PLATELET SENSITIZATION BY LDL	16	9	56.25%	0.49	0.17	0.25	0.42	0.16	0.26	-0.18	-0.11	-0.18	0.42	0.28	0.33
APOPTOTIC EXECUTION PHASE	54	2	3.70%	0.49	0.15	0.34	0.50	0.22	0.39	0.01	0.06	-0.01	-0.03	-0.05	-0.05
TRNA AMINOACYLATION	42	0	0.00%	0.49	0.15	0.32	0.49	0.23	0.37	0.52	0.46	0.49	0.40	0.40	0.45
FORMATION OF TUBULIN FOLDING INTERMEDIATES BY CCT TRIC	22	4	18.18%	0.49	0.26	0.37	0.49	0.27	0.42	0.62	0.52	0.56	0.54	0.47	0.51
METABOLISM OF AMINO ACIDS AND DERIVATIVES	200	43	21.50%	0.48	0.16	0.32	-0.01	0.16	0.06	0.51	0.42	0.48	0.57	0.42	0.49
MAP KINASE ACTIVATION IN TLR CASCADE	50	6	12.00%	0.48	0.20	0.32	0.37	0.16	0.22	0.33	0.33	0.33	0.41	0.31	0.35
PYRIMIDINE METABOLISM	24	2	8.33%	0.48	0.37	0.36	0.42	0.36	0.37	0.30	0.33	0.24	0.43	0.42	0.41
P53 DEPENDENT G1 DNA DAMAGE RESPONSE	57	57	100.00%	0.48	0.12	0.34	0.17	0.21	0.17	0.49	0.39	0.46	0.54	0.44	0.47
ANTIVIRAL MECHANISM BY IFN STIMULATED GENES	66	11	16.67%	0.48	0.10	0.28	0.48	0.19	0.32	0.06	0.05	0.10	0.54	0.47	0.51
NRAGE SIGNALS DEATH THROUGH JNK	43	0	0.00%	0.48	0.41	0.49	0.42	0.41	0.44	0.12	0.13	0.10	0.50	0.50	0.45
PROCESSING OF CAPPED INTRON CONTAINING PRE MRNA	140	8	5.71%	0.48	0.18	0.39	0.38	0.18	0.33	0.53	0.46	0.50	0.61	0.55	0.56
BASIGIN INTERACTIONS	30	0	0.00%	0.48	0.13	0.32	0.46	0.19	0.36	0.48	0.42	0.48	0.34	0.23	0.31
ELONGATION ARREST AND RECOVERY	32	0	0.00%	0.47	0.27	0.39	0.48	0.34	0.46	0.29	0.27	0.28	0.52	0.51	0.52
REGULATORY RNA PATHWAYS	26	0	0.00%	0.47	0.12	0.31	0.55	0.30	0.49	0.35	0.35	0.36	0.55	0.55	0.57
PLATELET HOMEOSTASIS	78	9	11.54%	0.47	0.23	0.28	0.43	0.24	0.30	0.31	0.36	0.29	0.46	0.42	0.43
REPAIR SYNTHESIS FOR GAP FILLING BY DNA POL IN TC NER	14	14	100.00%	0.47	0.30	0.40	0.44	0.32	0.46	0.50	0.52	0.51	0.42	0.49	0.46
HOST INTERACTIONS OF HIV FACTORS	132	59	44.70%	0.47	0.12	0.31	0.30	0.28	0.28	0.42	0.35	0.40	0.50	0.40	0.43
L1CAM INTERACTIONS	86	0	0.00%	0.47	0.42	0.39	0.40	0.30	0.32	0.26	0.31	0.25	0.25	0.30	0.21
BASE EXCISION REPAIR	19	7	36.84%	0.47	0.30	0.33	0.43	0.40	0.43	0.28	0.29	0.29	0.38	0.38	0.34
ABORTIVE ELONGATION OF HIV1 TRANSCRIPT IN THE ABSENCE OF TAT	23	0	0.00%	0.47	0.28	0.37	0.44	0.30	0.43	0.35	0.33	0.33	0.49	0.48	0.47
SCF BETA TRCP MEDIATED DEGRADATION OF EMI1	51	51	100.00%	0.46	0.08	0.30	0.22	0.14	0.12	0.53	0.38	0.45	0.51	0.37	0.44
NEP NS2 INTERACTS WITH THE CELLULAR EXPORT MACHINERY	27	8	29.63%	0.46	0.17	0.34	0.46	0.18	0.30	0.38	0.28	0.33	0.49	0.50	0.50
METABOLISM OF RNA	330	58	17.58%	0.46	0.16	0.37	0.19	0.06	0.21	0.40	0.34	0.38	0.50	0.47	0.46
HYALURONAN METABOLISM	14	0	0.00%	0.46	0.35	0.42	0.43	0.30	0.40	0.30	0.30	0.27	0.44	0.40	0.41
SIGNALING BY RHO GTPASES	113	0	0.00%	0.46	0.12	0.26	0.54	0.40	0.50	0.30	0.35	0.26	0.50	0.46	0.46
P53 INDEPENDENT G1 S DNA DAMAGE CHECKPOINT	51	51	100.00%	0.46	0.11	0.30	0.24	0.17	0.15	0.48	0.37	0.44	0.49	0.39	0.42
MRNA PROCESSING	161	11	6.83%	0.46	0.16	0.37	0.33	0.13	0.29	0.46	0.43	0.44	0.55	0.54	0.55
SIGNALING BY FGFR1 MUTANTS	30	2	6.67%	0.46	0.24	0.34	0.46	0.22	0.31	0.40	0.31	0.24	0.23	0.22	0.17
FORMATION OF RNA POL II ELONGATION COMPLEX	45	3	6.67%	0.46	0.25	0.38	0.41	0.32	0.44	0.34	0.34	0.34	0.49	0.52	0.51
EARLY PHASE OF HIV LIFE CYCLE	21	2	9.52%	0.46	0.16	0.26	0.49	0.23	0.38	0.41	0.37	0.40	0.34	0.40	0.37
ASSOCIATION OF TRIC CCT WITH TARGET PROTEINS DURING BIOSYNTHESIS	27	0	0.00%	0.46	0.29	0.40	0.31	0.17	0.31	0.62	0.54	0.58	0.52	0.51	0.53
MITOCHONDRIAL PROTEIN IMPORT	58	0	0.00%	0.46	0.25	0.32	0.23	0.25	0.30	0.41	0.37	0.39	0.43	0.40	0.39
METABOLISM OF POLYAMINES	15	0	0.00%	0.45	0.07	0.27	0.39	0.08	0.24	0.44	0.31	0.32	0.19	0.14	0.13
DOWNSTREAM SIGNALING EVENTS OF B CELL RECEPTOR BCR	97	52	53.61%	0.45	0.04	0.28	0.31	0.14	0.17	0.43	0.35	0.41	0.46	0.31	0.38
TRANSPORT OF GLUCOSE AND OTHER SUGARS BILE SALTS AND ORGANIC ACIDS METAL IONS AND AMINE COMPOUNDS	89	0	0.00%	0.45	0.16	0.29	0.39	0.19	0.30	-0.18	-0.15	-0.21	-0.16	-0.17	-0.17
S PHASE	109	109	100.00%	0.45	0.24	0.31	0.60	0.32	0.48	0.62	0.56	0.59	0.58	0.55	0.54
METABOLISM OF NON CODING RNA	49	7	14.29%	0.45	0.26	0.37	0.48	0.29	0.45	0.47	0.42	0.45	0.51	0.53	0.53
TRAF6 MEDIATED INDUCTION OF NFKB AND MAP KINASES UPON TLR7 8 OR 9 ACTIVATION	77	9	11.69%	0.45	0.14	0.27	0.34	0.15	0.21	0.39	0.37	0.37	0.08	0.12	0.06
SIGNALING BY GPCR	920	9	0.98%	0.45	0.10	0.23	0.29	-0.01	0.11	0.25	0.34	0.25	0.23	0.25	0.19
CDT1 ASSOCIATION WITH THE CDC6 ORC ORIGIN COMPLEX	56	56	100.00%	0.45	0.07	0.29	0.23	0.14	0.14	0.50	0.36	0.42	0.51	0.41	0.43
FORMATION OF THE HIV1 EARLY ELONGATION COMPLEX	34	3	8.82%	0.44	0.25	0.35	0.12	0.14	0.08	0.36	0.35	0.35	0.51	0.53	0.53
PURINE METABOLISM	33	0	0.00%	0.44	0.17	0.30	0.39	0.15	0.30	0.52	0.46	0.49	0.48	0.44	0.46
CLASS I MHC MEDIATED ANTIGEN PROCESSING PRESENTATION	251	72	28.69%	0.44	0.06	0.27	0.30	0.01	0.19	0.40	0.35	0.40	0.53	0.40	0.45
SULFUR AMINO ACID METABOLISM	24	0	0.00%	0.44	0.13	0.32	0.40	0.17	0.30	0.30	0.22	0.20	0.37	0.27	0.27
G ALPHA S SIGNALLING EVENTS	121	0	0.00%	0.44	0.40	0.40	0.46	0.30	0.36	0.48	0.52	0.48	0.12	0.17	0.10
DOUBLE STRAND BREAK REPAIR	24	8	33.33%	0.44	0.36	0.39	0.34	0.31	0.40	0.19	0.24	0.22	0.50	0.48	0.47
AUTODEGRADATION OF CDH1 BY CDH1 APC C	64	64	100.00%	0.44	0.08	0.29	0.24	0.17	0.15	0.45	0.35	0.41	0.52	0.40	0.44
HIV INFECTION	207	64	30.92%	0.43	0.03	0.24	0.29	0.05	0.22	0.42	0.35	0.40	0.59	0.49	0.53
DESTABILIZATION OF MRNA BY KSRP	17	0	0.00%	0.43	0.36	0.36	0.49	0.38	0.46	0.32	0.31	0.33	0.37	0.44	0.42
CASPASE MEDIATED CLEAVAGE OF CYTOSKELETAL PROTEINS	13	0	0.00%	0.43	0.05	0.25	0.44	0.17	0.33	0.33	0.26	0.32	0.23	0.12	0.16
CDK MEDIATED PHOSPHORYLATION AND REMOVAL OF CDC6	48	48	100.00%	0.42	0.06	0.27	0.21	0.15	0.12	0.49	0.36	0.42	0.50	0.40	0.41
RNA POL II PRE TRANSCRIPTION EVENTS	61	3	4.92%	0.42	0.25	0.35	0.41	0.33	0.39	0.34	0.34	0.35	0.52	0.52	0.53
TRANSPORT OF VITAMINS NUCLEOSIDES AND RELATED MOLECULES	31	0	0.00%	0.42	0.17	0.32	0.41	0.19	0.36	0.30	0.34	0.33	0.25	0.23	0.23
NFKB AND MAP KINASES ACTIVATION MEDIATED BY TLR4 SIGNALING REPERTOIRE	72	9	12.50%	0.42	0.16	0.23	0.32	0.12	0.19	0.36	0.34	0.35	0.13	0.16	0.11
DIABETES PATHWAYS	133	3	2.26%	0.42	0.06	0.29	0.42	0.25	0.32	0.39	0.34	0.38	0.39	0.28	0.35
REGULATION OF APOPTOSIS	58	46	79.31%	0.42	0.04	0.26	0.16	0.23	0.13	0.48	0.35	0.42	0.34	0.27	0.31
VIF MEDIATED DEGRADATION OF APOBEC3G	52	46	88.46%	0.42	0.05	0.26	0.24	0.23	0.20	0.44	0.34	0.40	0.35	0.27	0.31
INHIBITION OF REPLICATION INITIATION OF DAMAGED DNA BY RB1 E2F1	13	13	100.00%	0.42	0.27	0.30	0.28	0.20	0.19	0.49	0.49	0.49	0.44	0.38	0.40
TOLL RECEPTOR CASCADES	118	9	7.63%	0.42	0.08	0.21	0.22	-0.02	0.09	0.16	0.18	0.13	0.39	0.32	0.37
ALPHA LINOLENIC ACID ALA METABOLISM	12	0	0.00%	0.42	0.14	0.28	0.36	0.15	0.25	0.31	0.33	0.37	0.39	0.38	0.44
REGULATION OF ORNITHINE DECARBOXYLASE ODC	49	43	87.76%	0.42	0.05	0.26	0.36	0.08	0.25	0.49	0.35	0.42	0.31	0.22	0.27
AMINO ACID SYNTHESIS AND INTERCONVERSION TRANSAMINATION	17	0	0.00%	0.42	0.07	0.24	0.43	0.16	0.28	-0.34	-0.28	-0.36	0.40	0.44	0.43
PI3K EVENTS IN ERBB4 SIGNALING	38	3	7.89%	0.41	0.29	0.33	0.11	0.17	0.10	0.25	0.25	0.24	0.11	0.10	0.08
AUTODEGRADATION OF THE E3 UBIQUITIN LIGASE COP1	51	51	100.00%	0.41	0.05	0.26	0.20	0.19	0.15	0.50	0.36	0.43	0.30	0.21	0.26
SIGNALING BY FGFR1 FUSION MUTANTS	19	2	10.53%	0.41	0.21	0.30	0.49	0.34	0.39	0.44	0.30	0.26	0.09	0.09	0.05
JNK C JUN KINASES PHOSPHORYLATION AND ACTIVATION MEDIATED BY ACTIVATED HUMAN TAK1	16	0	0.00%	0.41	0.06	0.26	0.30	0.04	0.20	0.28	0.25	0.27	0.43	0.30	0.37
CROSS PRESENTATION OF SOLUBLE EXOGENOUS ANTIGENS ENDOSOMES	48	43	89.58%	0.41	0.03	0.26	0.20	0.15	0.13	0.49	0.35	0.41	0.29	0.20	0.25
IRAK1 RECRUITS IKK COMPLEX	10	0	0.00%	0.41	0.14	0.32	0.23	0.09	0.15	0.29	0.32	0.28	-0.04	0.05	-0.01

DESTABILIZATION OF MRNA BY TRISTETRAPROLIN TTP	17	0	0.00%	0.41	0.37	0.42	0.42	0.34	0.40	0.22	0.22	0.25	0.29	0.35	0.38
ACTIVATION OF NF KAPPAB IN B CELLS	64	49	76.56%	0.41	0.03	0.25	0.35	0.08	0.26	0.44	0.35	0.41	0.32	0.20	0.28
HOMOLOGOUS RECOMBINATION REPAIR OF REPLICATION INDEPENDENT DOUBLE STRAND BREAKS	17	8	47.06%	0.41	0.36	0.40	0.30	0.25	0.35	0.28	0.27	0.28	0.50	0.47	0.45
PKB MEDIATED EVENTS	29	0	0.00%	0.41	0.22	0.36	0.50	0.32	0.44	0.31	0.32	0.34	0.45	0.27	0.28
P75 NTR RECEPTOR MEDIATED SIGNALLING	81	7	8.64%	0.41	0.28	0.36	0.44	0.16	0.35	0.44	0.39	0.42	0.21	0.31	0.25
FORMATION OF TRANSCRIPTION COUPLED NER TC NER REPAIR COMPLEX	30	3	10.00%	0.41	0.22	0.39	0.24	0.20	0.31	0.32	0.33	0.33	0.44	0.50	0.49
DESTABILIZATION OF MRNA BY AUF1 HNRNP D0	53	46	86.79%	0.41	0.04	0.26	0.35	0.07	0.24	0.49	0.35	0.42	0.31	0.21	0.26
MRNA CAPPING	30	3	10.00%	0.41	0.16	0.30	0.14	0.19	0.25	0.29	0.29	0.29	0.49	0.51	0.51
PI3K CASCADE	71	0	0.00%	0.41	0.22	0.26	0.33	0.26	0.25	0.43	0.39	0.41	0.52	0.39	0.40
SIGNALING BY INSULIN RECEPTOR	108	1	0.93%	0.41	0.42	0.33	0.28	0.27	0.24	0.37	0.36	0.36	0.35	0.26	0.24
GPCR LIGAND BINDING	408	0	0.00%	0.40	0.13	0.21	0.31	-0.03	0.12	0.17	0.24	0.14	0.51	0.44	0.47
PIP3 ACTIVATES AKT SIGNALING	29	3	10.34%	0.40	0.11	0.24	0.08	0.14	0.07	0.18	0.19	0.17	0.27	0.26	0.25
GASTRIN CREB SIGNALLING PATHWAY VIA PKC AND MAPK	205	1	0.49%	0.40	0.11	0.24	0.41	0.37	0.40	0.20	0.27	0.18	-0.26	-0.17	-0.27
REGULATION OF HYPOXIA INDUCIBLE FACTOR HIF BY OXYGEN	25	4	16.00%	0.40	0.19	0.36	0.36	0.14	0.33	0.36	0.33	0.37	0.38	0.32	0.37
PERK REGULATED GENE EXPRESSION	29	0	0.00%	0.40	0.39	0.43	0.45	0.40	0.45	0.32	0.31	0.33	0.24	0.32	0.31
ACTIVATION OF GENES BY ATF4	26	0	0.00%	0.40	0.34	0.34	0.45	0.41	0.45	0.24	0.28	0.30	0.25	0.35	0.33
SIGNALING BY WNT	65	58	89.23%	0.40	0.02	0.25	0.34	0.07	0.25	0.47	0.37	0.44	0.09	0.03	0.07
IL1 SIGNALING	39	3	7.69%	0.40	-0.04	0.22	0.36	0.04	0.22	0.24	0.26	0.21	-0.07	-0.02	-0.09
ADAPTIVE IMMUNE SYSTEM	539	99	18.37%	0.39	0.00	0.19	0.24	-0.04	0.08	0.31	0.24	0.30	0.49	0.39	0.45
IMMUNE SYSTEM	933	107	11.47%	0.39	-0.01	0.18	0.24	-0.04	0.08	0.42	0.39	0.38	0.50	0.36	0.42
GLYCOLYSIS	29	5	17.24%	0.39	0.17	0.25	0.39	0.20	0.30	0.47	0.41	0.44	0.44	0.34	0.38
TAK1 ACTIVATES NFKB BY PHOSPHORYLATION AND ACTIVATION OF IKKS COMPLEX	23	0	0.00%	0.39	0.05	0.24	0.34	0.07	0.23	-0.10	-0.03	-0.09	-0.07	-0.01	-0.11
G ALPHA Q SIGNALLING EVENTS	184	0	0.00%	0.39	0.10	0.24	0.43	0.37	0.40	0.31	0.38	0.29	0.50	0.50	0.48
MRNA 3 END PROCESSING	35	0	0.00%	0.38	0.19	0.29	0.46	0.26	0.42	0.41	0.39	0.41	0.43	0.41	0.40
PROCESSING OF CAPPED INTRONLESS PRE MRNA	23	0	0.00%	0.38	0.25	0.36	0.35	0.21	0.36	0.45	0.41	0.43	0.48	0.47	0.49
PYRUVATE METABOLISM	19	0	0.00%	0.38	0.17	0.26	0.41	0.17	0.34	-0.18	-0.16	-0.23	0.33	0.26	0.30
SHC MEDIATED CASCADE	28	0	0.00%	0.38	0.11	0.21	0.16	0.06	0.06	0.32	0.33	0.30	0.22	0.20	0.14
DESTABILIZATION OF MRNA BY BRF1	17	0	0.00%	0.38	0.33	0.35	0.40	0.31	0.38	0.28	0.27	0.29	0.39	0.44	0.45
SIGNALING BY CONSTITUTIVELY ACTIVE EGFR	18	4	22.22%	0.37	0.27	0.31	0.36	0.27	0.27	-0.02	-0.01	-0.04	-0.01	-0.03	-0.07
DEPOSITION OF NEW CENPA CONTAINING NUCLEOSOMES AT THE CENTROMERE	64	64	100.00%	0.37	0.27	0.33	0.38	0.30	0.34	0.36	0.32	0.31	0.48	0.44	0.42
CLEAVAGE OF GROWING TRANSCRIPT IN THE TERMINATION REGION	44	0	0.00%	0.37	0.23	0.37	0.38	0.20	0.37	0.44	0.41	0.43	0.50	0.48	0.50
APOPTOSIS INDUCED DNA FRAGMENTATION	13	0	0.00%	0.37	0.23	0.30	0.39	0.23	0.34	0.41	0.35	0.37	0.37	0.28	0.34
DEADENYLATION OF MRNA	22	0	0.00%	0.37	0.20	0.26	0.08	0.09	0.02	0.37	0.35	0.35	0.33	0.25	0.31
SIGNALING BY THE B CELL RECEPTOR BCR	126	52	41.27%	0.37	-0.06	0.18	0.22	0.13	0.13	0.38	0.31	0.37	0.28	0.17	0.23
ER PHAGOSOME PATHWAY	61	46	75.41%	0.37	-0.03	0.17	0.28	-0.04	0.14	0.41	0.30	0.39	0.22	0.14	0.20
MITOCHONDRIAL TRNA AMINOACYLATION	21	0	0.00%	0.37	0.32	0.36	0.43	0.37	0.45	0.45	0.44	0.46	0.05	0.20	0.20
MYD88 MAL CASCADE INITIATED ON PLASMA MEMBRANE	83	9	10.84%	0.36	0.20	0.21	0.32	0.15	0.21	0.20	0.22	0.17	0.02	0.06	-0.02
VIRAL MESSENGER RNA SYNTHESIS	14	0	0.00%	0.36	0.19	0.33	0.36	0.16	0.35	0.38	0.34	0.36	0.36	0.29	0.29
INNATE IMMUNE SYSTEM	279	10	3.58%	0.36	-0.02	0.15	0.19	-0.06	0.05	0.20	0.25	0.15	0.18	0.22	0.11
MRNA SPLICING MINOR PATHWAY	45	0	0.00%	0.36	0.22	0.33	0.29	0.10	0.27	0.42	0.37	0.41	0.50	0.50	0.50
SLBP DEPENDENT PROCESSING OF REPLICATION DEPENDENT HISTONE PRE MRNAS	11	0	0.00%	0.36	0.26	0.33	0.32	0.20	0.32	0.47	0.43	0.46	0.46	0.44	0.44
RNA POL III TRANSCRIPTION INITIATION FROM TYPE 2 PROMOTER	23	0	0.00%	0.35	0.33	0.40	0.40	0.38	0.42	0.24	0.28	0.29	0.38	0.44	0.41
PURINE RIBONUCLEOSIDE MONOPHOSPHATE BIOSYNTHESIS	11	0	0.00%	0.35	0.15	0.24	0.38	0.21	0.30	0.50	0.46	0.47	0.39	0.38	0.42
ACTIVATION OF BH3 ONLY PROTEINS	17	5	29.41%	0.35	-0.04	0.20	0.16	0.05	0.19	0.39	0.37	0.40	0.49	0.41	0.48
INTRINSIC PATHWAY FOR APOPTOSIS	30	5	16.67%	0.35	-0.10	0.17	0.28	-0.05	0.17	0.47	0.42	0.48	0.50	0.43	0.48
PURINE SALVAGE	13	0	0.00%	0.35	0.14	0.26	0.13	-0.01	0.10	0.39	0.32	0.37	0.38	0.28	0.29
ERK MAPK TARGETS	21	5	23.81%	0.35	0.26	0.23	0.36	0.27	0.30	0.27	0.31	0.29	0.28	0.27	0.25
LATENT INFECTION OF HOMO SAPIENS WITH MYCOBACTERIUM TUBERCULOSIS	33	0	0.00%	0.35	0.19	0.27	0.24	0.03	0.14	0.21	0.18	0.18	0.23	0.15	0.19
PROCESSING OF INTRONLESS PRE MRNAS	14	0	0.00%	0.35	0.24	0.32	0.37	0.25	0.35	0.41	0.38	0.37	0.41	0.40	0.40
MYOGENESIS	28	0	0.00%	0.35	0.11	0.24	0.37	0.20	0.28	0.25	0.28	0.25	0.16	0.24	0.16
DEVELOPMENTAL BIOLOGY	396	5	1.26%	0.35	0.39	0.32	0.17	0.31	0.20	0.41	0.39	0.40	-0.20	-0.21	-0.24
P75NTR SIGNALS VIA NFKB	14	3	21.43%	0.35	0.02	0.22	0.35	0.06	0.25	0.45	0.39	0.43	0.14	0.19	0.14
CTLA4 INHIBITORY SIGNALING	21	9	42.86%	0.35	0.01	0.10	0.28	0.07	0.11	0.01	0.01	-0.09	0.20	0.09	0.21
INTEGRATION OF PROVIRUS	16	0	0.00%	0.35	0.11	0.18	0.37	0.15	0.29	0.02	-0.05	-0.01	0.07	-0.02	0.03
CELL DEATH SIGNALLING VIA NRAGE NRIF AND NADE	60	6	10.00%	0.34	0.39	0.38	0.23	0.31	0.28	0.42	0.42	0.43	0.44	0.35	0.40
P75NTR RECRUITS SIGNALLING COMPLEXES	12	3	25.00%	0.34	0.01	0.22	0.35	0.07	0.26	0.31	0.30	0.32	0.14	0.19	0.13
DCC MEDIATED ATTRACTIVE SIGNALING	13	0	0.00%	0.34	0.23	0.32	0.48	0.26	0.39	0.38	0.39	0.41	0.19	0.24	0.24
NEGATIVE REGULATION OF FGFR SIGNALING	37	6	16.22%	0.34	0.15	0.17	0.30	0.19	0.18	0.34	0.35	0.33	0.26	0.23	0.19
SOS MEDIATED SIGNALLING	14	1	7.14%	0.34	0.04	0.14	0.26	0.12	0.15	0.35	0.30	0.32	0.34	0.29	0.31
TELOMERE MAINTENANCE	75	75	100.00%	0.34	0.29	0.34	0.35	0.31	0.35	0.34	0.32	0.31	0.08	0.07	0.08
GPCR DOWNSTREAM SIGNALING	805	0	0.00%	0.34	-0.07	0.13	0.28	-0.07	0.08	0.27	0.36	0.27	0.50	0.49	0.47
UNFOLDED PROTEIN RESPONSE	80	3	3.75%	0.34	0.04	0.29	0.31	0.09	0.27	0.32	0.28	0.31	0.18	0.17	0.21
RNA POL II TRANSCRIPTION PRE INITIATION AND PROMOTER OPENING	41	3	7.32%	0.33	0.11	0.29	0.36	0.30	0.39	0.36	0.34	0.36	0.49	0.48	0.49
SIGNALLING TO ERKS	36	1	2.78%	0.33	0.18	0.20	0.27	0.21	0.21	-0.22	-0.14	-0.14	0.25	0.23	0.28
MRNA DECAY BY 3 TO 5 EXORIBONUCLEASE	11	0	0.00%	0.33	0.28	0.32	0.40	0.33	0.41	-0.19	-0.08	-0.10	0.16	0.16	0.21
AMINO ACID TRANSPORT ACROSS THE PLASMA MEMBRANE	31	0	0.00%	0.33	0.01	0.17	0.38	0.11	0.25	0.30	0.25	0.32	0.40	0.35	0.42
TRANSCRIPTION	210	44	20.95%	0.33	0.28	0.36	0.32	0.29	0.34	0.40	0.35	0.36	0.11	0.10	0.11
RNA POL III CHAIN ELONGATION	17	0	0.00%	0.33	0.27	0.34	0.40	0.39	0.43	0.27	0.30	0.32	0.09	0.17	0.16
GAP JUNCTION DEGRADATION	10	0	0.00%	0.33	0.13	0.20	0.21	-0.01	0.04	0.36	0.21	0.23	0.23	0.08	0.10
ACTIVATED TAK1 MEDIATES P38 MAPK ACTIVATION	18	0	0.00%	0.33	0.07	0.21	0.32	0.09	0.21	0.03	0.05	0.05	0.15	0.21	0.18
INTERACTION BETWEEN L1 AND ANKYRINS	23	0	0.00%	0.33	0.20	0.23	0.20	0.19	0.14	0.30	0.36	0.29	0.32	0.33	0.33
MEIOSIS	116	80	68.97%	0.33	0.26	0.33	0.37	0.32	0.33	0.33	0.29	0.29	0.21	0.16	0.17
MRNA DECAY BY 5 TO 3 EXORIBONUCLEASE	15	0	0.00%	0.33	0.21	0.34	0.07	0.09	0.15	0.32	0.29	0.27	0.34	0.24	0.19
REGULATION OF PYRUVATE DEHYDROGENASE PDH COMPLEX	13	0	0.00%	0.33	0.09	0.27	0.31	0.17	0.29	0.04	0.05	0.00	0.39	0.37	0.38
ACTIVATION OF CHAPERONE GENES BY XBP1S	46	3	6.52%	0.32	0.01	0.25	0.34	0.22	0.27	0.46	0.41	0.43	0.22	0.24	0.22
INSULIN SYNTHESIS AND PROCESSING	21	0	0.00%	0.32	0.19	0.23	0.24	0.17	0.17	0.35	0.31	0.35	0.21	0.16	0.17
PEPTIDE LIGAND BINDING RECEPTORS	188	0	0.00%	0.32	-0.09	0.12	0.31	-0.01	0.15	0.21	0.26	0.19	0.37	0.32	0.36
PASSIVE TRANSPORT BY AQUAPORINS	11	0	0.00%	0.32	0.09	0.25	0.33	0.17	0.28	0.26	0.29	0.27	0.01	-0.01	-0.07
ACTIVATED TLR4 SIGNALLING	93	9	9.68%	0.32	0.16	0.17	0.28	0.10	0.15	0.26	0.26	0.23	0.44	0.35	0.43
NUCLEAR EVENTS KINASE AND TRANSCRIPTION FACTOR ACTIVATION	24	5	20.83%	0.32	0.23	0.20	0.31	0.29	0.28	0.23	0.27	0.25	0.31	0.26	0.27
SEMA4D INDUCED CELL MIGRATION AND GROWTH CONE COLLAPSE	27	0	0.00%	0.31	-0.04	0.14	0.37	0.37	0.39	0.13	0.04	0.08	0.08	-0.11	0.01
THE ROLE OF NEF IN HIV1 REPLICATION AND DISEASE PATHOGENESIS	28	0	0.00%	0.31	0.25	0.31	0.07	0.34	0.22	0.12	0.13	0.18	0.12	0.14	0.12

PI 3K CASCADE	56	3	5.36%	0.31	0.22	0.22	0.19	0.17	0.13	0.33	0.33	0.31	0.27	0.26	0.19
SIGNALLING TO RAS	27	1	3.70%	0.31	0.19	0.18	0.27	0.20	0.20	0.13	0.06	0.06	0.32	0.24	0.30
PROLONGED ERK ACTIVATION EVENTS	19	1	5.26%	0.31	0.10	0.15	0.25	0.17	0.19	0.02	0.08	0.07	0.24	0.29	0.25
INTEGRIN CELL SURFACE INTERACTIONS	79	0	0.00%	0.31	0.10	0.14	0.21	0.03	0.09	0.23	0.28	0.22	-0.09	-0.23	-0.12
FACILITATIVE NA INDEPENDENT GLUCOSE TRANSPORTERS	12	0	0.00%	0.31	-0.01	0.16	0.25	-0.02	0.11	-0.01	-0.01	-0.07	-0.01	-0.04	-0.15
SIGNALING BY ERBB4	90	10	11.11%	0.31	-0.08	0.18	-0.03	0.24	0.08	0.22	0.24	0.21	-0.16	-0.05	-0.11
TRYPTOPHAN CATABOLISM	11	0	0.00%	0.31	-0.02	0.14	0.18	-0.12	0.02	-0.36	-0.27	-0.36	0.29	0.13	0.21
RESOLUTION OF AP SITES VIA THE MULTIPLE NUCLEOTIDE PATCH REPLACEMENT PATHWAY	17	7	41.18%	0.31	0.26	0.30	0.44	0.39	0.42	0.25	0.27	0.26	0.37	0.36	0.32
CLASS A1 RHODOPSIN LIKE RECEPTORS	305	0	0.00%	0.31	-0.08	0.09	0.26	-0.08	0.07	0.29	0.35	0.25	0.37	0.32	0.37
GROWTH HORMONE RECEPTOR SIGNALING	24	0	0.00%	0.30	0.11	0.19	0.20	-0.01	0.06	0.34	0.31	0.31	0.29	0.24	0.30
ANTIGEN PROCESSING CROSS PRESENTATION	76	46	60.53%	0.30	-0.08	0.12	0.30	0.28	0.27	0.39	0.30	0.38	0.19	0.10	0.18
CELL SURFACE INTERACTIONS AT THE VASCULAR WALL	91	0	0.00%	0.30	-0.11	0.11	0.27	-0.03	0.14	0.22	0.28	0.19	0.30	0.21	0.29
CIRCADIAN REPRESSION OF EXPRESSION BY REV ERBA	23	0	0.00%	0.30	0.17	0.20	0.28	0.14	0.19	-0.01	0.00	0.00	0.12	0.03	0.04
POST CHAPERONIN TUBULIN FOLDING PATHWAY	19	4	21.05%	0.30	0.28	0.34	0.38	0.24	0.39	0.44	0.42	0.46	0.34	0.34	0.37
SHC RELATED EVENTS	17	1	5.88%	0.30	0.07	0.13	0.28	0.11	0.17	0.27	0.13	0.14	0.33	0.25	0.28
MEIOTIC RECOMBINATION	86	50	58.14%	0.30	0.24	0.31	0.31	0.28	0.31	0.29	0.26	0.25	0.11	0.11	0.11
FRS2 MEDIATED CASCADE	36	1	2.78%	0.30	0.15	0.17	0.15	0.13	0.09	0.22	0.27	0.25	0.20	0.19	0.14
POTASSIUM CHANNELS	98	0	0.00%	0.30	0.03	0.23	0.24	0.06	0.20	0.30	0.33	0.25	-0.15	-0.05	-0.12
TIE2 SIGNALING	17	0	0.00%	0.29	0.13	0.23	0.46	0.30	0.36	0.00	-0.04	-0.06	0.21	0.11	0.09
FORMATION OF INCISION COMPLEX IN GG NER	23	6	26.09%	0.29	0.25	0.34	0.09	0.12	0.20	0.27	0.25	0.27	0.47	0.39	0.45
SIGNALING BY PDGF	122	7	5.74%	0.29	0.32	0.25	0.33	0.31	0.28	0.31	0.35	0.29	-0.02	0.04	-0.05
GLUCAGON TYPE LIGAND RECEPTORS	33	0	0.00%	0.29	0.08	0.23	0.31	0.13	0.26	0.14	0.11	0.17	0.48	0.38	0.42
EGFR DOWNREGULATION	25	3	12.00%	0.29	0.27	0.25	0.24	0.28	0.23	0.15	0.20	0.14	-0.04	0.00	-0.05
ARMS MEDIATED ACTIVATION	17	1	5.88%	0.29	0.12	0.17	0.26	0.19	0.21	-0.01	0.07	0.06	0.23	0.28	0.24
SPRY REGULATION OF FGF SIGNALING	14	6	42.86%	0.29	0.24	0.17	0.30	0.19	0.17	0.21	0.21	0.17	0.28	0.20	0.23
PROSTACYCLIN SIGNALLING THROUGH PROSTACYCLIN RECEPTOR	19	0	0.00%	0.29	0.15	0.25	0.35	0.22	0.27	0.38	0.36	0.33	0.36	0.35	0.35
GABA B RECEPTOR ACTIVATION	38	0	0.00%	0.29	0.02	0.21	0.28	0.08	0.22	0.27	0.28	0.20	0.32	0.34	0.33
RAF MAP KINASE CASCADE	10	1	10.00%	0.29	-0.02	0.16	0.30	0.15	0.21	0.39	0.36	0.35	0.26	0.14	0.17
INFLAMMASOMES	17	0	0.00%	0.28	-0.09	0.11	0.22	-0.10	0.07	0.52	0.49	0.51	-0.20	-0.03	-0.09
PLATELET AGGREGATION PLUG FORMATION	36	0	0.00%	0.28	0.07	0.20	0.34	0.11	0.22	0.46	0.48	0.42	-0.01	-0.13	-0.04
GABA RECEPTOR ACTIVATION	52	0	0.00%	0.28	0.03	0.21	0.29	0.08	0.23	0.30	0.31	0.23	0.43	0.44	0.43
REGULATION OF INSULIN LIKE GROWTH FACTOR IGF ACTIVITY BY INSULIN LIKE GROWTH FACTOR BINDING PROTEINS IGFBPS	16	0	0.00%	0.28	0.21	0.25	0.37	0.21	0.28	0.38	0.39	0.35	0.31	0.21	0.29
G ALPHA Z SIGNALLING EVENTS	44	0	0.00%	0.28	-0.02	0.17	0.41	0.30	0.34	0.51	0.50	0.50	0.46	0.37	0.43
TRANS GOLGI NETWORK VESICLE BUDDING	60	0	0.00%	0.28	-0.08	0.13	0.40	0.11	0.30	0.20	0.22	0.26	0.21	0.19	0.16
ERKS ARE INACTIVATED	12	5	41.67%	0.28	0.17	0.15	0.31	0.19	0.21	0.28	0.29	0.28	0.29	0.19	0.24
SHC MEDIATED SIGNALLING	15	1	6.67%	0.28	0.07	0.13	0.28	0.12	0.17	0.24	0.12	0.11	0.26	0.15	0.19
PECAM1 INTERACTIONS	10	0	0.00%	0.28	-0.01	0.04	0.16	-0.08	-0.02	0.07	0.07	0.09	-0.10	-0.17	-0.13
RORA ACTIVATES CIRCADIAN EXPRESSION	24	0	0.00%	0.28	0.17	0.20	0.27	0.16	0.18	-0.07	-0.05	-0.05	0.11	0.03	0.04
IL 7 SIGNALING	11	0	0.00%	0.27	-0.05	0.05	0.11	-0.18	-0.07	0.18	0.24	0.13	0.16	0.18	0.06
ADENYLATE CYCLASE INHIBITORY PATHWAY	13	0	0.00%	0.27	-0.01	0.18	0.30	0.04	0.20	0.39	0.40	0.40	0.04	0.10	0.10
SIGNALING BY HIPPO	22	2	9.09%	0.27	-0.01	0.12	0.20	-0.01	0.06	0.11	0.11	0.06	0.04	0.04	-0.01
G ALPHA1213 SIGNALLING EVENTS	74	0	0.00%	0.27	-0.02	0.15	0.31	0.19	0.32	0.05	0.10	0.06	0.51	0.48	0.48
INTEGRIN ALPHAIIB BETA3 SIGNALING	27	0	0.00%	0.27	0.05	0.19	0.27	0.09	0.16	0.45	0.45	0.42	0.02	-0.13	-0.02
TRIF MEDIATED TLR3 SIGNALING	74	9	12.16%	0.27	0.16	0.16	0.31	0.11	0.17	0.36	0.34	0.35	0.17	0.20	0.15
NFKB ACTIVATION THROUGH FADD RIP1 PATHWAY MEDIATED BY CASPASE 8 AND10	12	0	0.00%	0.27	0.16	0.16	0.27	0.07	0.17	0.07	0.02	0.09	-0.21	-0.10	-0.14
EXTRINSIC PATHWAY FOR APOPTOSIS	13	0	0.00%	0.27	0.32	0.23	0.32	0.29	0.31	0.20	0.24	0.13	0.11	0.17	0.04
CRMPS IN SEMA3A SIGNALING	14	0	0.00%	0.27	0.31	0.25	0.33	0.39	0.33	0.19	0.26	0.18	0.19	0.29	0.18
RNA POL I TRANSCRIPTION	89	44	49.44%	0.27	0.23	0.29	0.24	0.26	0.26	0.29	0.26	0.25	0.13	0.11	0.12
AMYLOIDS	83	41	49.40%	0.27	0.23	0.28	0.27	0.29	0.29	0.28	0.26	0.24	0.13	0.11	0.12
INITIAL TRIGGERING OF COMPLEMENT	16	0	0.00%	0.27	0.34	0.29	0.27	0.37	0.34	0.31	0.32	0.23	-0.35	-0.23	-0.30
RNA POL I RNA POL III AND MITOCHONDRIAL TRANSCRIPTION	122	44	36.07%	0.27	0.26	0.30	0.24	0.26	0.28	0.28	0.26	0.24	0.12	0.10	0.11
IL 2 SIGNALING	41	1	2.44%	0.26	-0.11	0.03	0.16	-0.13	-0.03	0.13	0.17	0.09	0.04	-0.05	0.07
FGFR LIGAND BINDING AND ACTIVATION	22	0	0.00%	0.26	-0.06	0.11	0.17	-0.01	0.06	0.34	0.36	0.32	0.22	0.22	0.14
NFKB IS ACTIVATED AND SIGNALS SURVIVAL	11	3	27.27%	0.26	-0.04	0.14	0.23	0.11	0.18	0.28	0.28	0.26	0.14	0.20	0.14
NGF SIGNALLING VIA TRKA FROM THE PLASMA MEMBRANE	137	12	8.76%	0.26	0.25	0.16	0.27	0.25	0.23	0.38	0.39	0.38	0.38	0.36	0.38
ASPARAGINE N LINKED GLYCOSYLATION	81	1	1.23%	0.26	0.20	0.28	0.07	0.08	0.13	0.29	0.29	0.31	0.03	0.06	0.04
TRAF6 MEDIATED IRF7 ACTIVATION IN TLR7 8 OR 9 SIGNALING	10	0	0.00%	0.26	-0.11	0.09	0.15	-0.15	-0.01	0.04	-0.04	0.04	-0.08	-0.14	-0.02
A TETRASACCHARIDE LINKER SEQUENCE IS REQUIRED FOR GAG SYNTHESIS	25	0	0.00%	0.26	0.29	0.18	0.25	0.28	0.23	0.22	0.23	0.19	-0.01	-0.06	0.02
ADENYLATE CYCLASE ACTIVATING PATHWAY	10	0	0.00%	0.26	-0.03	0.18	0.31	0.06	0.21	0.38	0.40	0.41	-0.03	0.07	0.09
DIGESTION OF DIETARY CARBOHYDRATE	12	0	0.00%	0.26	0.09	0.26	0.25	0.10	0.25	0.06	0.04	0.04	0.08	0.05	0.07
LIGAND GATED ION CHANNEL TRANSPORT	21	0	0.00%	0.26	-0.07	0.10	0.22	-0.02	0.08	0.25	0.26	0.26	0.13	0.17	0.23
MEIOTIC SYNAPSIS	73	73	100.00%	0.25	0.23	0.28	0.25	0.28	0.27	0.33	0.29	0.28	0.08	0.07	0.08
SYNTHESIS OF SUBSTRATES IN N GLYCAN BIOSYTHESIS	14	0	0.00%	0.25	0.14	0.23	0.24	0.16	0.23	0.07	0.05	0.04	0.06	0.08	0.06
INTEGRATION OF ENERGY METABOLISM	120	8	6.67%	0.25	0.04	0.19	0.26	0.27	0.24	0.41	0.41	0.42	0.46	0.43	0.46
RNA POL I PROMOTER OPENING	62	41	66.13%	0.25	0.20	0.26	0.20	0.22	0.22	0.27	0.24	0.23	0.12	0.11	0.12
KERATAN SULFATE DEGRADATION	11	0	0.00%	0.25	0.14	0.16	0.29	0.27	0.22	0.38	0.43	0.37	0.37	0.40	0.33
PROTEOLYTIC CLEAVAGE OF SNARE COMPLEX PROTEINS	17	0	0.00%	0.25	0.14	0.23	0.20	0.15	0.19	0.49	0.39	0.41	0.35	0.29	0.30
CYTOKINE SIGNALING IN IMMUNE SYSTEM	270	16	5.93%	0.25	-0.10	0.07	0.28	0.38	0.33	0.17	0.15	0.19	0.45	0.29	0.37
REGULATION OF KIT SIGNALING	17	0	0.00%	0.25	-0.03	0.03	0.17	-0.03	0.01	-0.01	0.01	-0.10	-0.14	-0.04	-0.14
VEGF LIGAND RECEPTOR INTERACTIONS	10	0	0.00%	0.25	0.19	0.18	0.24	0.24	0.18	0.26	0.36	0.31	0.25	0.33	0.26
G ALPHA I SIGNALLING EVENTS	195	0	0.00%	0.25	-0.15	0.06	0.44	0.44	0.45	0.53	0.48	0.54	0.40	0.42	0.40
CS DS DEGRADATION	12	0	0.00%	0.25	0.34	0.20	0.28	0.33	0.26	0.21	0.20	0.15	0.06	-0.02	0.06
GAB1 SIGNALOSOME	38	3	7.89%	0.24	0.18	0.15	0.11	0.15	0.08	0.14	0.16	0.13	-0.12	-0.05	-0.11
PRE NOTCH TRANSCRIPTION AND TRANSLATION	29	6	20.69%	0.24	-0.12	0.16	0.33	0.07	0.15	0.28	0.30	0.30	0.53	0.48	0.49
AXON GUIDANCE	251	3	1.20%	0.24	0.41	0.22	0.19	0.32	0.24	0.25	0.30	0.23	0.35	0.45	0.34
RESPONSE TO ELEVATED PLATELET CYTOSOLIC CA2	89	1	1.12%	0.24	0.37	0.25	0.26	0.38	0.31	0.28	0.36	0.27	0.15	0.07	0.11
SYNTHESIS OF PC	18	0	0.00%	0.24	0.04	0.16	0.14	0.20	0.20	0.11	0.13	0.09	-0.17	-0.17	-0.17
SIGNALING BY FGFR IN DISEASE	127	15	11.81%	0.24	0.22	0.15	0.21	0.24	0.19	0.34	0.35	0.33	0.27	0.25	0.18
SHC1 EVENTS IN ERBB4 SIGNALING	20	1	5.00%	0.24	0.18	0.12	0.30	0.09	0.16	0.08	0.05	0.03	0.20	0.18	0.20
BILE SALT AND ORGANIC ANION SLC TRANSPORTERS	11	0	0.00%	0.24	0.05	0.15	0.29	0.12	0.22	0.00	0.04	-0.02	-0.09	-0.06	-0.03
REGULATION OF IFNG SIGNALING	14	0	0.00%	0.24	0.26	0.18	0.23	0.27	0.23	0.23	0.24	0.23	-0.04	-0.10	0.00
MAPK TARGETS NUCLEAR EVENTS MEDIATED BY MAP KINASES	30	5	16.67%	0.24	0.26	0.14	0.30	0.25	0.24	0.26	0.29	0.26	0.21	0.20	0.24

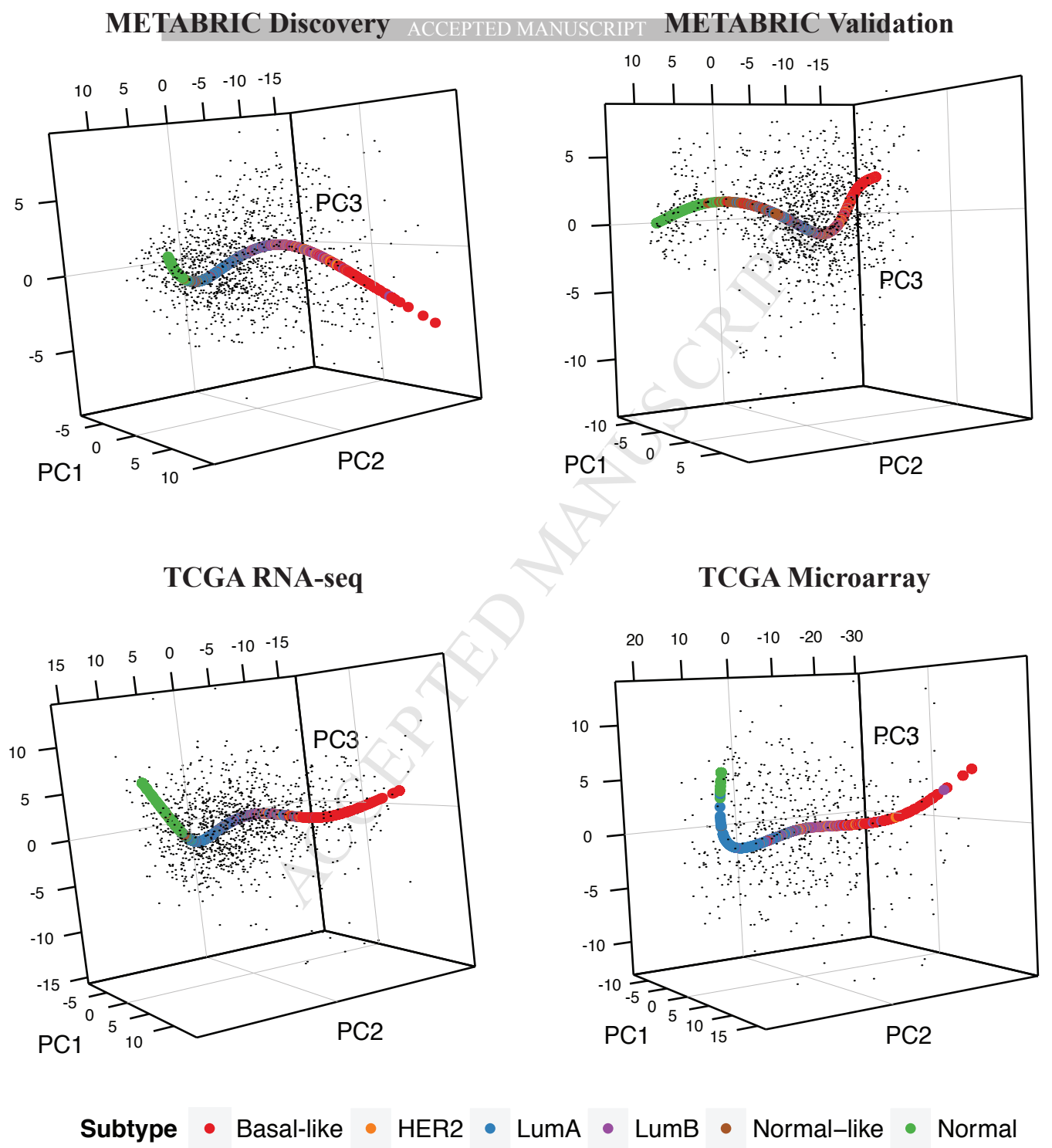
INWARDLY RECTIFYING K CHANNELS	31	0	0.00%	0.24	0.03	0.18	0.21	0.04	0.17	0.04	0.07	-0.04	0.40	0.39	0.39
G BETA GAMMA SIGNALLING THROUGH PI3KGAMMA	25	0	0.00%	0.24	0.16	0.11	0.28	0.17	0.20	0.23	0.27	0.17	0.35	0.36	0.33
ADP SIGNALLING THROUGH P2RY1	25	0	0.00%	0.23	0.07	0.19	0.22	0.06	0.17	0.18	0.23	0.17	0.26	0.26	0.24
YAP1 AND WWTR1 TAZ STIMULATED GENE EXPRESSION	24	0	0.00%	0.23	0.17	0.17	0.27	0.19	0.20	-0.03	-0.03	-0.08	0.39	0.30	0.34
MTORC1 MEDIATED SIGNALLING	11	0	0.00%	0.23	0.08	0.26	0.34	0.24	0.36	0.38	0.23	0.23	0.45	0.26	0.26
SIGNAL ATTENUATION	14	0	0.00%	0.23	0.13	0.10	0.17	0.08	0.17	0.31	0.23	0.28	0.32	0.26	0.28
DEGRADATION OF THE EXTRACELLULAR MATRIX	29	0	0.00%	0.23	0.06	0.17	0.14	0.24	0.16	0.01	-0.05	0.02	0.23	0.09	0.18
SEMA3A PAK DEPENDENT AXON REPULSION	15	1	6.67%	0.23	0.19	0.14	0.30	0.23	0.22	0.32	0.32	0.26	0.14	0.17	0.09
RETROGRADE NEUROTROPHIN SIGNALLING	13	0	0.00%	0.23	0.04	0.11	0.11	0.04	0.06	0.33	0.20	0.23	0.17	0.04	0.10
NEF MEDIATES DOWN MODULATION OF CELL SURFACE RECEPTORS BY RECRUITING THEM TO CLATHRIN ADAPTERS	21	0	0.00%	0.23	-0.06	0.08	0.09	0.28	0.18	0.14	0.21	0.15	0.16	0.18	0.13
IL RECEPTOR SHC SIGNALING	27	0	0.00%	0.23	-0.09	0.00	0.11	-0.17	-0.07	0.10	0.15	0.03	0.16	0.06	0.09
TRAF6 MEDIATED NFKB ACTIVATION	21	0	0.00%	0.23	0.10	0.12	0.24	0.11	0.11	0.13	0.13	0.13	-0.01	0.04	-0.02
INHIBITION OF VOLTAGE GATED CA2 CHANNELS VIA GBETA GAMMA SUBUNITS	25	0	0.00%	0.23	0.03	0.18	0.19	0.05	0.17	0.13	0.16	0.06	0.40	0.39	0.38
ACTIVATED AMPK STIMULATES FATTY ACID OXIDATION IN MUSCLE	19	0	0.00%	0.23	0.27	0.20	0.20	0.24	0.17	0.18	0.19	0.21	-0.08	-0.06	-0.11
GOLGI ASSOCIATED VESICLE BIOGENESIS	53	0	0.00%	0.22	0.02	0.25	0.04	0.23	0.08	0.19	0.21	0.24	0.09	0.10	0.03
NEUROTRANSMITTER RECEPTOR BINDING AND DOWNSTREAM TRANSMISSION IN THE POSTSYNAPTIC CELL	137	2	1.46%	0.22	-0.03	0.15	0.19	-0.01	0.14	0.31	0.33	0.29	-0.02	0.09	-0.02
ADHERENS JUNCTIONS INTERACTIONS	27	0	0.00%	0.22	0.04	0.14	0.32	0.19	0.22	0.39	0.39	0.39	-0.20	-0.14	-0.22
HS GAG BIOSYNTHESIS	31	0	0.00%	0.22	-0.03	0.17	0.30	0.06	0.19	0.38	0.32	0.38	0.11	-0.02	0.06
G PROTEIN ACTIVATION	27	0	0.00%	0.22	0.07	0.19	0.11	0.01	0.10	0.14	0.18	0.13	0.34	0.34	0.32
THROMBIN SIGNALLING THROUGH PROTEINASE ACTIVATED RECEPTORS PARS	32	0	0.00%	0.22	0.01	0.15	0.07	-0.08	0.03	0.25	0.32	0.33	0.41	0.28	0.33
PACKAGING OF TELOMERE ENDS	48	48	100.00%	0.22	0.20	0.25	0.17	0.22	0.20	0.29	0.24	0.23	0.10	0.09	0.10
MUSCLE CONTRACTION	48	0	0.00%	0.22	0.36	0.24	0.27	0.34	0.28	0.24	0.29	0.22	0.11	0.08	-0.01
CTNNB1 PHOSPHORYLATION CASCADE	16	9	56.25%	0.22	0.15	0.13	0.25	0.22	0.20	0.14	0.09	0.08	0.28	0.18	0.24
KERATAN SULFATE KERATIN METABOLISM	30	0	0.00%	0.22	0.21	0.10	0.25	0.25	0.21	0.36	0.41	0.36	0.34	0.40	0.36
LYSOSOME VESICLE BIOGENESIS	23	0	0.00%	0.22	0.02	0.20	0.09	-0.07	0.07	0.14	0.18	0.21	0.34	0.25	0.27
ADP SIGNALLING THROUGH P2RY12	21	0	0.00%	0.22	0.08	0.19	0.13	0.04	0.11	0.23	0.29	0.23	0.37	0.36	0.35
REGULATION OF RHEB GTPASE ACTIVITY BY AMPK	10	0	0.00%	0.22	0.06	0.20	0.21	0.00	0.19	-0.03	0.01	-0.09	-0.15	-0.06	-0.06
ACTIVATION OF KAINATE RECEPTORS UPON GLUTAMATE BINDING	31	0	0.00%	0.22	0.11	0.22	0.27	0.16	0.26	0.11	0.18	0.10	0.39	0.37	0.37
G BETA GAMMA SIGNALLING THROUGH PLC BETA	20	0	0.00%	0.22	0.09	0.20	0.12	0.04	0.11	0.08	0.15	0.07	0.40	0.38	0.39
TGF BETA RECEPTOR SIGNALING ACTIVATES SMADS	26	5	19.23%	0.22	0.14	0.27	0.24	0.32	0.24	-0.01	0.03	0.02	0.41	0.43	0.40
NITRIC OXIDE STIMULATES GUANYLATE CYCLASE	25	0	0.00%	0.22	0.29	0.26	0.29	0.31	0.33	0.24	0.31	0.26	-0.19	-0.10	-0.16
BIOSYNTHESIS OF THE N GLYCAN PRECURSOR DOLICHOL LIPID LINKED OLIGOSACCHARIDE LLO AND TRANSFER TO A NASCENT PROTEIN	29	0	0.00%	0.22	0.27	0.28	0.25	0.10	0.13	0.16	0.17	0.18	0.14	0.16	0.12
INHIBITION OF INSULIN SECRETION BY ADRENALINE NORADRENALINE	25	0	0.00%	0.21	0.04	0.17	0.23	0.06	0.18	0.37	0.42	0.41	0.41	0.36	0.38
G PROTEIN BETA GAMMA SIGNALLING	28	0	0.00%	0.21	0.14	0.09	0.28	0.16	0.19	0.16	0.20	0.11	0.35	0.37	0.34
INSULIN RECEPTOR RECYCLING	23	0	0.00%	0.21	0.24	0.23	0.31	0.24	0.28	0.01	0.03	0.01	-0.05	-0.06	-0.09
GLYCOSAMINOGLYCAN METABOLISM	111	0	0.00%	0.21	0.34	0.15	0.16	0.26	0.15	0.21	0.27	0.18	0.38	0.45	0.41
CELL JUNCTION ORGANIZATION	78	0	0.00%	0.21	0.35	0.25	0.36	0.24	0.31	0.23	0.30	0.23	0.22	0.19	0.21
RNA POL I TRANSCRIPTION TERMINATION	22	3	13.64%	0.21	0.34	0.29	0.19	0.26	0.27	0.34	0.34	0.35	0.37	0.43	0.44
THROMBOXANE SIGNALLING THROUGH TP RECEPTOR	23	0	0.00%	0.21	0.05	0.16	0.12	-0.02	0.10	0.31	0.34	0.33	0.43	0.38	0.39
GRB2 SOS PROVIDES LINKAGE TO MAPK SIGNALING FOR INTERGRINS	15	0	0.00%	0.21	0.06	0.20	0.41	0.26	0.34	0.36	0.35	0.34	0.00	-0.14	-0.03
SYNTHESIS OF PE	11	0	0.00%	0.21	0.29	0.29	0.10	0.23	0.27	-0.06	-0.06	-0.08	0.04	0.02	0.04
ABACAVIR TRANSPORT AND METABOLISM	10	0	0.00%	0.21	0.14	0.24	0.34	0.17	0.29	0.47	0.50	0.47	0.28	0.31	0.27
SIGNAL AMPLIFICATION	31	0	0.00%	0.21	0.06	0.16	0.19	0.03	0.16	0.16	0.21	0.15	0.26	0.29	0.27
ENDOSOMAL SORTING COMPLEX REQUIRED FOR TRANSPORT ESCRT	27	3	11.11%	0.21	0.25	0.21	-0.09	0.03	0.03	0.01	0.04	0.04	-0.05	0.00	-0.04
CREATION OF C4 AND C2 ACTIVATORS	10	0	0.00%	0.21	0.19	0.14	0.04	0.32	0.17	0.16	0.24	0.13	-0.05	0.02	-0.02
AMINE DERIVED HORMONES	15	0	0.00%	0.21	0.19	0.16	0.15	0.09	0.08	0.13	0.15	0.14	0.18	0.17	0.15
DOWNREGULATION OF TGF BETA RECEPTOR SIGNALING	23	5	21.74%	0.20	0.10	0.26	0.26	0.18	0.31	-0.01	0.06	0.02	0.33	0.39	0.40
SMOOTH MUSCLE CONTRACTION	25	0	0.00%	0.20	0.28	0.18	0.28	0.28	0.28	0.25	0.30	0.22	0.07	0.11	0.06
ANDROGEN BIOSYNTHESIS	10	0	0.00%	0.20	0.18	0.16	0.18	0.13	0.17	0.05	0.01	0.03	0.05	0.00	-0.02
INTERFERON SIGNALING	159	12	7.55%	0.20	-0.10	0.04	0.25	0.36	0.31	0.05	0.09	0.04	0.25	0.15	0.22
RAS ACTIVATION UOPN CA2 INFUX THROUGH NMDA RECEPTOR	17	1	5.88%	0.20	0.13	0.13	0.18	0.18	0.16	0.14	0.10	0.15	0.31	0.20	0.20
ETHANOL OXIDATION	10	0	0.00%	0.20	0.37	0.25	0.26	0.32	0.25	0.26	0.31	0.24	0.23	0.29	0.23
CHONDROITIN SULFATE DERMATAN SULFATE METABOLISM	49	0	0.00%	0.20	0.29	0.15	0.22	0.29	0.21	0.09	0.13	0.06	-0.10	-0.16	-0.09
P130CAS LINKAGE TO MAPK SIGNALING FOR INTEGRINS	15	0	0.00%	0.20	0.04	0.20	0.30	0.14	0.22	0.39	0.42	0.40	0.00	-0.14	-0.03
ACTIVATION OF THE AP1 FAMILY OF TRANSCRIPTION FACTORS	10	0	0.00%	0.20	0.27	0.16	0.18	0.25	0.19	-0.03	0.06	0.04	0.17	0.18	0.19
TRANSPORT TO THE GOLGI AND SUBSEQUENT MODIFICATION	33	1	3.03%	0.20	-0.10	0.07	-0.08	0.09	0.03	0.18	0.20	0.20	0.01	-0.03	0.04
P38MAPK EVENTS	13	0	0.00%	0.20	0.25	0.19	0.14	0.21	0.12	-0.18	-0.12	-0.08	0.19	0.08	0.10
KERATAN SULFATE BIOSYNTHESIS	26	0	0.00%	0.20	0.18	0.09	0.28	0.25	0.23	0.26	0.29	0.22	0.25	0.23	0.31
CHEMOKINE RECEPTORS BIND CHEMOKINES	57	0	0.00%	0.20	-0.20	-0.03	0.16	-0.18	-0.01	0.06	-0.04	0.08	0.31	0.20	0.28
SIGNALLING TO P38 VIA RIT AND RIN	15	1	6.67%	0.20	-0.06	0.16	0.25	0.07	0.20	0.30	0.25	0.26	0.26	0.13	0.10
RECYCLING OF BILE ACIDS AND SALTS	11	0	0.00%	0.20	0.14	0.18	0.19	0.10	0.19	0.06	0.14	0.12	0.25	0.25	0.30
AQUAPORIN MEDIATED TRANSPORT	51	3	5.88%	0.19	0.01	0.15	0.35	0.11	0.25	0.46	0.48	0.47	0.43	0.44	0.43
ACTIVATION OF CHAPERONE GENES BY ATF6 ALPHA	11	0	0.00%	0.19	0.01	0.07	0.20	0.19	0.27	0.11	0.11	0.11	0.16	0.23	0.26
ELEVATION OF CYTOSOLIC CA2 LEVELS	10	0	0.00%	0.19	-0.05	0.06	0.09	-0.10	-0.01	0.24	0.26	0.22	0.25	0.25	0.18
SIGNALING BY TGF BETA RECEPTOR COMPLEX	63	14	22.22%	0.19	0.04	0.22	0.42	0.31	0.43	0.14	0.16	0.18	0.33	0.38	0.43
TRANSCRIPTIONAL ACTIVITY OF SMAD2 SMAD3 SMAD4 HETEROTRIMER	38	12	31.58%	0.19	0.02	0.21	0.16	0.01	0.19	0.16	0.17	0.19	0.42	0.41	0.48
CHONDROITIN SULFATE BIOSYNTHESIS	21	0	0.00%	0.19	0.34	0.20	0.28	0.30	0.25	0.01	0.06	-0.02	-0.03	-0.10	0.03
NOREPINEPHRINE NEUROTRANSMITTER RELEASE CYCLE	10	0	0.00%	0.19	0.22	0.24	0.29	0.12	0.19	0.48	0.41	0.45	0.12	0.10	0.13
SHC1 EVENTS IN EGFR SIGNALING	15	1	6.67%	0.18	0.11	0.10	-0.11	0.09	-0.06	-0.01	-0.02	-0.05	-0.09	-0.07	-0.12
SIGNAL REGULATORY PROTEIN SIRP FAMILY INTERACTIONS	12	0	0.00%	0.18	0.35	0.26	0.15	0.02	0.02	0.13	0.14	0.07	-0.05	0.04	-0.09
THE NLRP3 INFLAMMASOME	12	0	0.00%	0.18	0.37	0.26	0.24	0.36	0.31	0.29	0.30	0.20	-0.16	-0.01	-0.13
REGULATION OF IFNA SIGNALING	24	0	0.00%	0.18	0.08	0.08	0.00	-0.16	-0.15	0.13	0.19	0.13	0.10	0.00	0.12
REGULATION OF WATER BALANCE BY RENAL AQUAPORINS	44	3	6.82%	0.18	0.02	0.14	0.29	0.28	0.29	0.45	0.48	0.47	0.37	0.42	0.41
TGF BETA RECEPTOR SIGNALING IN EMT EPITHELIAL TO MESENCHYMAL TRANSITION	16	3	18.75%	0.18	0.36	0.26	0.28	0.37	0.35	-0.03	0.02	-0.05	0.33	0.36	0.37
PLATELET ACTIVATION SIGNALING AND AGGREGATION	208	1	0.48%	0.18	0.42	0.28	0.25	0.40	0.33	0.20	0.29	0.20	0.13	0.13	0.09
CONVERSION FROM APC C CDC20 TO APC C CDH1 IN LATE ANAPHASE	22	22	100.00%	0.18	0.15	0.09	0.56	0.32	0.46	0.19	0.21	0.21	0.57	0.48	0.51
TRAFFICKING AND PROCESSING OF ENDOSOMAL TLR	14	0	0.00%	0.18	-0.12	-0.01	0.10	-0.14	-0.08	0.17	0.14	0.17	-0.09	-0.19	-0.04
REGULATION OF INSULIN SECRETION	93	3	3.23%	0.18	0.02	0.15	0.12	-0.07	0.06	0.33	0.34	0.33	0.49	0.47	0.48
NEGATIVE REGULATORS OF RIG I MDA5 SIGNALING	31	4	12.90%	0.18	0.03	0.14	0.18	-0.01	0.04	-0.17	-0.08	-0.11	0.04	-0.02	0.06
SMAD2 SMAD3 SMAD4 HETEROTRIMER REGULATES TRANSCRIPTION	27	11	40.74%	0.17	-0.01	0.19	0.15	0.02	0.18	-0.18	-0.12	-0.16	0.42	0.41	0.46
FGFR1 LIGAND BINDING AND ACTIVATION	14	0	0.00%	0.17	0.03	0.11	0.16	0.05	0.12	0.12	0.16	0.08	0.21	0.22	0.20
NUCLEOTIDE BINDING DOMAIN LEUCINE RICH REPEAT CONTAINING RECEPTOR NLR SIGNALING PATHWAYS	46	0	0.00%	0.17	-0.25	0.00	0.14	-0.08	0.01	0.40	0.39	0.42	-0.19	-0.06	-0.14

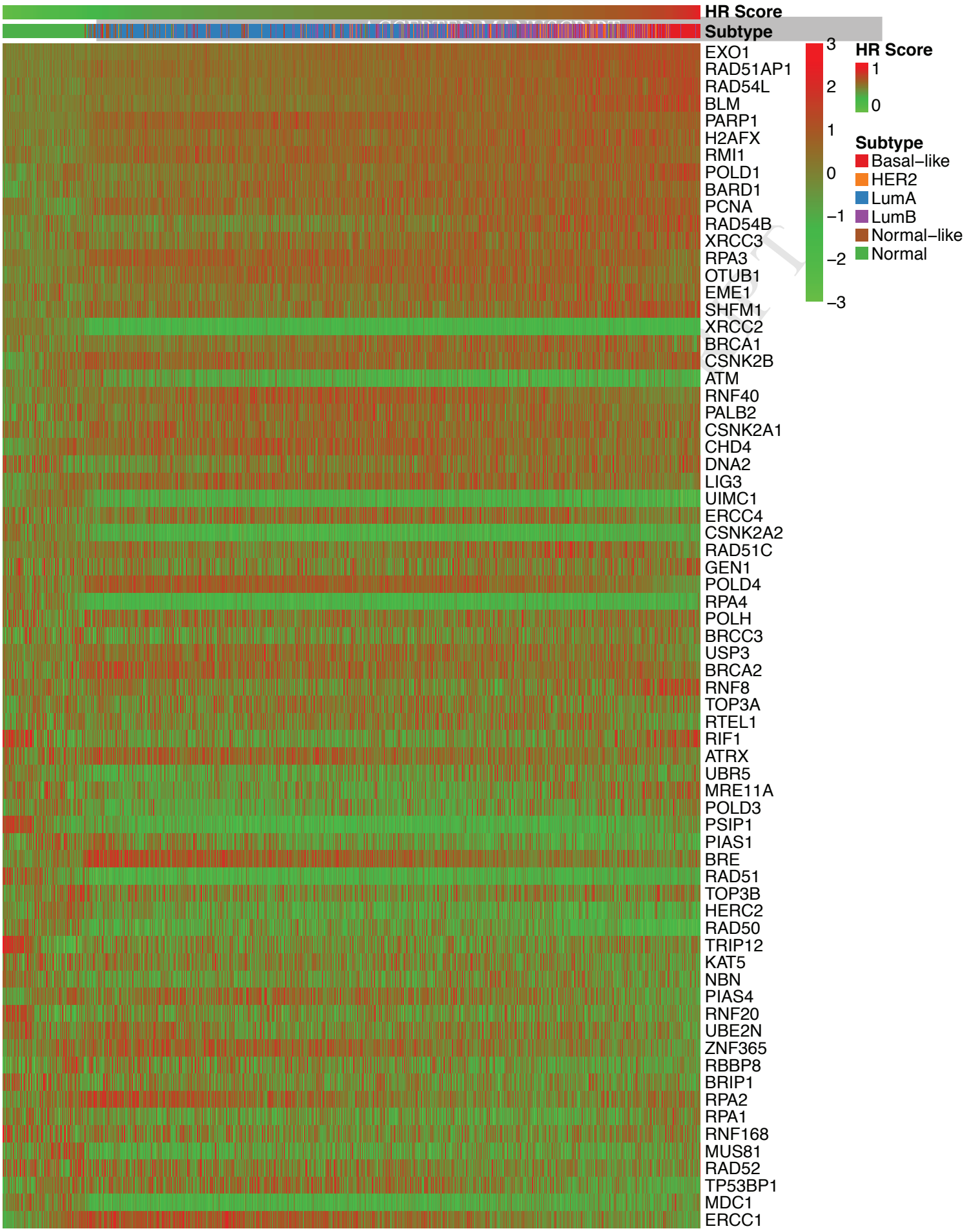
RESPIRATORY ELECTRON TRANSPORT ATP SYNTHESIS BY CHEMIOSMOTIC COUPLING AND HEAT PRODUCTION BY UNCOUPLING PROTEINS	98	0	0.00%	0.17	0.20	0.23	0.17	0.14	0.23	0.20	0.19	0.17	0.02	0.02	-0.05
PI METABOLISM	48	0	0.00%	0.17	0.05	0.10	0.23	0.25	0.21	0.20	0.21	0.21	0.11	0.12	0.04
OPIOID SIGNALLING	78	8	10.26%	0.17	0.07	0.17	0.31	0.31	0.29	0.36	0.41	0.38	-0.19	-0.08	-0.18
GRB2 EVENTS IN ERBB2 SIGNALING	22	1	4.55%	0.17	0.24	0.12	0.28	0.10	0.16	-0.06	-0.02	-0.07	0.05	-0.05	-0.06
CALNEXIN CALRETICULIN CYCLE	11	0	0.00%	0.17	0.00	0.11	0.18	0.07	0.13	0.29	0.26	0.28	-0.05	0.01	0.02
SIGNALING BY NODAL	18	0	0.00%	0.17	0.21	0.13	0.13	0.15	0.08	0.23	0.26	0.29	-0.04	-0.08	-0.01
INSULIN RECEPTOR SIGNALLING CASCADE	87	1	1.15%	0.17	0.33	0.18	0.29	0.23	0.21	0.37	0.36	0.37	0.45	0.35	0.35
METABOLISM OF MRNA	284	51	17.96%	0.17	0.10	0.12	0.07	-0.02	0.10	0.09	0.04	0.08	0.43	0.38	0.36
SEMA4D IN SEMAPHORIN SIGNALING	32	0	0.00%	0.17	-0.19	0.00	0.13	-0.14	0.00	0.04	0.06	0.01	-0.05	-0.14	-0.04
INTERFERON GAMMA SIGNALING	63	0	0.00%	0.17	-0.17	-0.01	0.12	-0.20	-0.04	0.22	0.24	0.20	0.00	-0.11	0.03
STRIATED MUSCLE CONTRACTION	27	0	0.00%	0.17	0.36	0.25	0.19	0.31	0.24	0.11	0.17	0.10	0.04	0.07	-0.02
ADVANCED GLYCOSYLATION ENDPRODUCT RECEPTOR SIGNALING	13	0	0.00%	0.17	-0.06	0.06	0.19	0.01	0.13	0.11	0.15	0.08	0.07	0.12	0.04
FGFR4 LIGAND BINDING AND ACTIVATION	12	0	0.00%	0.17	-0.02	0.06	0.14	0.00	0.04	0.33	0.35	0.31	0.21	0.22	0.18
HIGHLY CALCIUM PERMEABLE POSTSYNAPTIC NICOTINIC ACETYLCHOLINE RECEPTORS	13	0	0.00%	0.16	0.05	0.16	0.10	0.02	0.10	-0.28	-0.20	-0.25	-0.37	-0.29	-0.30
INTERFERON ALPHA BETA SIGNALING	64	1	1.56%	0.16	-0.05	0.04	0.15	-0.08	0.01	0.08	0.05	0.12	-0.02	-0.07	0.01
SIGNALING BY NOTCH2	12	0	0.00%	0.16	0.15	0.19	0.18	0.14	0.24	0.30	0.37	0.38	-0.03	0.12	0.09
COMMON PATHWAY	14	0	0.00%	0.16	0.26	0.18	0.23	0.22	0.22	0.16	0.20	0.14	0.28	0.32	0.27
HEPARAN SULFATE HEPARIN HS GAG METABOLISM	52	0	0.00%	0.16	0.30	0.10	0.12	0.24	0.12	0.11	0.17	0.10	-0.03	-0.15	-0.05
CELL EXTRACELLULAR MATRIX INTERACTIONS	14	0	0.00%	0.16	0.24	0.17	0.34	0.24	0.30	-0.01	0.08	0.00	0.01	0.06	-0.03
TCA CYCLE AND RESPIRATORY ELECTRON TRANSPORT	141	0	0.00%	0.16	0.18	0.23	0.17	0.13	0.23	0.20	0.18	0.17	-0.06	-0.07	-0.11
GLUCAGON SIGNALING IN METABOLIC REGULATION	34	3	8.82%	0.16	0.05	0.14	0.17	0.06	0.15	0.29	0.34	0.31	0.33	0.27	0.29
RNA POL III TRANSCRIPTION INITIATION FROM TYPE 3 PROMOTER	26	0	0.00%	0.16	0.35	0.20	0.21	0.34	0.28	0.20	0.21	0.20	-0.01	0.03	-0.02
PRESYNAPTIC NICOTINIC ACETYLCHOLINE RECEPTORS	12	0	0.00%	0.16	0.02	0.13	0.06	-0.03	0.05	0.08	0.04	0.08	-0.39	-0.34	-0.31
TRAF6 MEDIATED IRF7 ACTIVATION	30	0	0.00%	0.16	0.00	0.05	0.17	0.02	0.04	0.00	-0.03	0.01	-0.10	-0.12	-0.05
TRAF3 DEPENDENT IRF ACTIVATION PATHWAY	14	0	0.00%	0.15	0.04	0.07	0.14	0.00	0.03	0.08	0.05	0.10	-0.04	-0.07	0.01
RIG I MDA5 MEDIATED INDUCTION OF IFN ALPHA BETA PATHWAYS	73	4	5.48%	0.15	0.01	0.03	0.13	-0.01	0.01	-0.03	-0.05	0.00	-0.01	-0.05	0.00
CD28 DEPENDENT VAV1 PATHWAY	11	0	0.00%	0.15	0.01	0.01	0.12	-0.02	0.04	0.10	0.04	0.06	0.05	-0.03	0.06
N GLYCAN TRIMMING IN THE ER AND CALNEXIN CALRETICULIN CYCLE	13	0	0.00%	0.15	0.02	0.07	0.18	0.10	0.12	0.13	0.12	0.11	-0.05	0.01	0.02
ACETYLCHOLINE BINDING AND DOWNSTREAM EVENTS	16	0	0.00%	0.15	0.04	0.15	0.09	0.02	0.09	-0.26	-0.17	-0.22	-0.37	-0.29	-0.30
AMINE LIGAND BINDING RECEPTORS	38	0	0.00%	0.15	0.10	0.15	0.24	0.16	0.20	0.42	0.43	0.36	0.41	0.40	0.38
BINDING AND ENTRY OF HIV VIRION	10	0	0.00%	0.15	0.20	0.23	0.08	-0.04	0.07	0.29	0.22	0.25	0.26	0.21	0.24
REGULATION OF GENE EXPRESSION IN BETA CELLS	20	0	0.00%	0.15	0.10	0.09	0.20	0.11	0.08	0.06	0.08	0.02	0.30	0.26	0.22
N GLYCAN ANTENNAE ELONGATION IN THE MEDIAL TRANS GOLGI	18	0	0.00%	0.14	-0.14	0.03	-0.10	0.12	0.02	-0.19	-0.17	-0.24	-0.31	-0.22	-0.31
NOD1 2 SIGNALING PATHWAY	30	0	0.00%	0.14	-0.16	0.04	0.13	-0.15	0.03	0.11	0.15	0.05	0.13	0.17	0.05
PI3K AKT ACTIVATION	38	3	7.89%	0.14	0.20	0.09	0.13	0.15	0.10	0.29	0.28	0.28	0.41	0.36	0.35
ANTIGEN PRESENTATION FOLDING ASSEMBLY AND PEPTIDE LOADING OF CLASS I MHC	21	1	4.76%	0.14	-0.16	-0.03	0.11	-0.19	-0.04	0.13	0.08	0.16	0.00	-0.04	0.04
CHYLOMICRON MEDIATED LIPID TRANSPORT	16	0	0.00%	0.14	-0.06	0.05	0.08	-0.03	0.03	-0.01	-0.02	-0.02	0.06	0.00	0.07
HORMONE LIGAND BINDING RECEPTORS	10	0	0.00%	0.14	0.16	0.15	0.06	0.07	0.07	0.12	0.08	0.02	0.04	-0.09	-0.10
REGULATION OF COMPLEMENT CASCADE	14	0	0.00%	0.14	0.35	0.21	0.40	0.31	0.34	0.25	0.32	0.21	0.28	0.34	0.23
RESPIRATORY ELECTRON TRANSPORT	79	0	0.00%	0.14	0.18	0.21	0.17	0.17	0.23	0.18	0.17	0.15	0.30	0.26	0.30
COSTIMULATION BY THE CD28 FAMILY	63	9	14.29%	0.14	-0.24	-0.10	0.06	-0.28	-0.12	-0.01	-0.04	-0.04	0.16	0.01	0.13
SIGNALING BY NOTCH4	12	0	0.00%	0.14	0.10	0.16	0.18	0.15	0.25	0.39	0.42	0.44	0.15	0.14	0.13
SIGNALING BY FGFR	112	13	11.61%	0.14	0.17	0.09	0.17	0.22	0.16	0.34	0.35	0.33	0.27	0.23	0.18
REGULATION OF BETA CELL DEVELOPMENT	30	0	0.00%	0.14	0.18	0.13	0.19	0.15	0.10	0.10	0.13	0.07	0.33	0.28	0.31
SEMAPHORIN INTERACTIONS	68	1	1.47%	0.14	-0.11	0.03	0.30	0.02	0.17	0.23	0.28	0.21	0.29	0.30	0.27
IL 3 5 AND GM CSF SIGNALING	43	0	0.00%	0.14	-0.10	-0.04	0.11	-0.22	-0.08	0.13	0.21	0.10	0.03	-0.06	-0.03
CD28 CO STIMULATION	32	0	0.00%	0.14	-0.01	-0.04	0.07	0.32	0.17	0.04	0.09	-0.02	0.12	0.01	0.07
APOBEC3G MEDIATED RESISTANCE TO HIV1 INFECTION	12	0	0.00%	0.14	-0.15	-0.04	-0.10	-0.26	-0.22	0.39	0.35	0.36	0.08	0.03	0.04
ACTIVATION OF CHAPERONES BY ATF6 ALPHA	13	0	0.00%	0.14	0.14	0.27	0.21	0.19	0.29	0.15	0.14	0.13	0.11	0.15	0.18
ACETYLCHOLINE NEUROTRANSMITTER RELEASE CYCLE	10	0	0.00%	0.14	0.16	0.22	-0.19	-0.01	-0.06	0.27	0.19	0.17	0.08	0.10	0.11
APOPTOTIC CLEAVAGE OF CELL ADHESION PROTEINS	12	0	0.00%	0.13	-0.09	-0.02	0.24	-0.02	0.14	0.04	0.06	0.06	0.02	0.00	-0.05
INTRINSIC PATHWAY	17	0	0.00%	0.13	0.35	0.28	0.35	0.41	0.37	0.26	0.33	0.24	0.07	0.10	0.07
RNA POL I TRANSCRIPTION INITIATION	25	3	12.00%	0.13	0.25	0.23	0.22	0.29	0.33	0.28	0.29	0.30	0.45	0.45	0.45
REGULATION OF SIGNALING BY CBL	18	0	0.00%	0.13	0.24	0.13	-0.04	-0.33	-0.22	0.02	0.05	-0.05	-0.03	-0.01	-0.10
REGULATION OF INSULIN SECRETION BY GLUCAGON LIKE PEPTIDE1	43	3	6.98%	0.13	-0.01	0.10	0.30	0.08	0.20	0.22	0.26	0.27	0.37	0.39	0.40
GLYCOPROTEIN HORMONES	12	0	0.00%	0.13	0.20	0.16	0.12	0.12	0.13	0.20	0.23	0.18	-0.01	-0.15	-0.10
TANDEM PORE DOMAIN POTASSIUM CHANNELS	12	0	0.00%	0.13	-0.02	0.15	0.07	0.01	0.02	0.21	0.14	0.20	0.13	0.06	0.10
PI3K EVENTS IN ERBB2 SIGNALING	44	3	6.82%	0.12	0.33	0.19	0.07	0.15	0.06	0.17	0.21	0.16	0.07	0.00	0.00
METABOLISM OF PROTEINS	518	9	1.74%	0.12	0.18	0.20	0.20	0.12	0.24	0.44	0.38	0.41	0.27	0.33	0.25
PHOSPHOLIPASE C MEDIATED CASCADE	54	3	5.56%	0.12	-0.10	0.03	0.10	0.06	0.08	0.43	0.45	0.43	0.16	0.22	0.13
RECRUITMENT OF NUMA TO MITOTIC CENTROSOMES	10	10	100.00%	0.12	0.14	0.19	0.39	0.28	0.40	0.31	0.22	0.25	0.45	0.44	0.42
OTHER SEMAPHORIN INTERACTIONS	15	0	0.00%	0.12	0.00	0.09	0.04	-0.05	0.05	0.14	0.16	0.19	0.33	0.32	0.31
DOPAMINE NEUROTRANSMITTER RELEASE CYCLE	11	0	0.00%	0.12	0.17	0.18	0.13	0.13	0.16	0.41	0.38	0.39	0.07	0.09	0.08
PPARA ACTIVATES GENE EXPRESSION	104	0	0.00%	0.12	0.22	0.09	0.46	0.24	0.33	-0.11	-0.06	-0.09	0.49	0.37	0.41
PEPTIDE CHAIN ELONGATION	153	4	2.61%	0.12	0.09	0.15	0.39	0.22	0.36	0.09	0.13	0.10	0.20	0.25	0.21
CGMP EFFECTS	19	0	0.00%	0.12	0.26	0.20	0.23	0.30	0.28	0.25	0.32	0.26	0.10	0.16	0.12
CELL CELL COMMUNICATION	120	0	0.00%	0.12	0.37	0.20	0.08	0.31	0.18	0.10	0.16	0.07	0.38	0.27	0.37
HORMONE SENSITIVE LIPASE HSL MEDIATED TRIACYLGLYCEROL HYDROLYSIS	13	3	23.08%	0.11	0.08	0.08	0.09	-0.03	-0.01	0.17	0.27	0.22	0.12	0.17	0.15
HS GAG DEGRADATION	20	0	0.00%	0.11	0.09	0.17	0.27	0.05	0.21	-0.09	-0.01	-0.05	-0.04	-0.07	-0.02
TIGHT JUNCTION INTERACTIONS	29	0	0.00%	0.11	0.39	0.24	0.23	0.39	0.35	0.52	0.49	0.49	0.21	0.16	0.25
SIGNAL TRANSDUCTION BY L1	34	0	0.00%	0.11	0.24	0.10	0.03	0.23	0.09	0.07	0.14	0.09	-0.05	-0.01	-0.07
INFLUENZA VIRAL RNA TRANSCRIPTION AND REPLICATION	169	5	2.96%	0.11	0.07	0.11	0.34	0.20	0.34	0.08	0.12	0.08	0.23	0.27	0.24
FORMATION OF ATP BY CHEMIOSMOTIC COUPLING	16	0	0.00%	0.11	0.06	0.10	0.03	-0.05	0.05	0.28	0.21	0.23	0.04	0.07	0.07
TRANSLATION	222	4	1.80%	0.11	0.09	0.13	0.09	0.00	0.13	0.14	0.17	0.13	0.24	0.28	0.22
PEPTIDE HORMONE BIOSYNTHESIS	14	0	0.00%	0.11	0.21	0.13	0.08	0.08	0.10	0.11	0.15	0.14	-0.02	-0.11	-0.06
ANTIGEN ACTIVATES B CELL RECEPTOR LEADING TO GENERATION OF SECOND MESSENGERS	29	0	0.00%	0.10	-0.27	-0.10	0.03	-0.27	-0.12	0.00	0.05	-0.04	-0.06	-0.03	-0.09
HDL MEDIATED LIPID TRANSPORT	15	0	0.00%	0.10	-0.02	0.05	0.03	0.01	0.02	0.06	0.07	0.02	0.07	0.09	-0.02
COMPLEMENT CASCADE	32	0	0.00%	0.10	0.40	0.21	0.26	0.41	0.33	0.34	0.39	0.30	0.26	0.35	0.23
LIPOPROTEIN METABOLISM	28	0	0.00%	0.10	-0.01	0.05	0.03	0.00	0.01	0.09	0.10	0.05	0.11	0.07	0.09
GLUTAMATE NEUROTRANSMITTER RELEASE CYCLE	15	0	0.00%	0.10	0.17	0.17	-0.03	0.14	0.07	0.33	0.30	0.32	-0.34	-0.29	-0.31
NEF MEDIATED DOWNREGULATION OF MHC CLASS I COMPLEX CELL SURFACE EXPRESSION	10	0	0.00%	0.10	-0.09	0.01	0.02	0.24	0.13	-0.09	-0.04	-0.04	0.22	0.11	0.13
PLATELET ADHESION TO EXPOSED COLLAGEN	12	0	0.00%	0.10	0.03	0.04	0.17	0.10	0.12	0.00	0.05	-0.06	-0.17	-0.19	-0.16

COPI MEDIATED TRANSPORT	10	0	0.00%	0.10	0.07	0.15	0.24	0.19	0.25	0.19	0.20	0.19	-0.04	0.04	0.01
RIP MEDIATED NFKB ACTIVATION VIA DAI	18	0	0.00%	0.10	-0.06	-0.02	0.03	0.00	-0.04	0.03	0.03	-0.02	0.01	0.06	0.00
ENERGY DEPENDENT REGULATION OF MTOR BY LKB1 AMPK	18	0	0.00%	0.10	0.24	0.14	0.05	0.18	0.09	0.28	0.30	0.31	-0.24	-0.14	-0.15
P2Y RECEPTORS	12	0	0.00%	0.10	-0.16	-0.03	0.25	0.15	0.22	0.38	0.40	0.31	0.07	-0.05	0.08
SIGNALING BY NOTCH3	12	0	0.00%	0.09	0.12	0.14	0.13	0.10	0.19	0.36	0.40	0.41	0.16	0.13	0.14
VOLTAGE GATED POTASSIUM CHANNELS	43	0	0.00%	0.09	0.09	0.15	-0.13	0.11	0.01	0.44	0.46	0.42	0.06	0.16	0.11
NEGATIVE REGULATION OF THE PI3K AKT NETWORK	9	0	0.00%	0.09	0.05	0.00	0.00	0.02	-0.08	0.06	0.09	0.03	0.17	0.13	0.14
METABOLISM OF VITAMINS AND COFACTORS	51	2	3.92%	0.09	0.36	0.15	0.33	0.20	0.23	0.45	0.43	0.46	0.31	0.38	0.38
SYNTHESIS OF PIPS AT THE GOLGI MEMBRANE	17	0	0.00%	0.09	0.19	0.17	0.16	0.23	0.19	0.20	0.21	0.25	-0.02	0.02	-0.02
N GLYCAN ANTENNAE ELONGATION	14	0	0.00%	0.09	-0.10	0.01	-0.04	0.14	0.03	-0.16	-0.16	-0.22	0.15	0.15	0.18
REGULATION OF AMPK ACTIVITY VIA LKB1	15	0	0.00%	0.09	0.27	0.15	0.08	0.19	0.11	0.14	0.13	0.14	-0.06	0.00	-0.03
ENDOSOMAL VACUOLAR PATHWAY	9	0	0.00%	0.09	-0.18	-0.06	0.07	-0.20	-0.07	0.01	-0.03	0.06	-0.06	-0.09	0.00
OXYGEN DEPENDENT PROLINE HYDROXYLATION OF HYPOXIA INDUCIBLE FACTOR ALPHA	18	4	22.22%	0.09	0.13	0.13	0.06	0.25	0.19	0.19	0.20	0.20	0.06	0.20	0.14
PROSTANOID LIGAND RECEPTORS	10	0	0.00%	0.08	0.35	0.25	0.18	0.25	0.22	0.23	0.29	0.19	0.11	0.23	0.12
SYNTHESIS OF PIPS AT THE PLASMA MEMBRANE	31	0	0.00%	0.08	-0.11	-0.05	0.12	-0.01	-0.01	0.22	0.26	0.22	0.10	0.02	-0.02
TETRAHYDROBIOPTERIN BH4 SYNTHESIS RECYCLING SALVAGE AND REGULATION	13	3	23.08%	0.08	0.11	0.01	0.26	0.15	0.21	0.18	0.13	0.13	0.02	0.04	-0.03
TRANSPORT OF ORGANIC ANIONS	11	0	0.00%	0.08	0.32	0.21	0.33	0.32	0.44	0.34	0.39	0.35	-0.01	0.05	0.02
CA DEPENDENT EVENTS	30	3	10.00%	0.08	-0.11	0.03	0.01	0.02	0.05	0.21	0.30	0.24	-0.14	-0.07	-0.12
EXTRACELLULAR MATRIX ORGANIZATION	87	0	0.00%	0.08	-0.05	0.07	0.15	0.04	0.13	0.17	0.12	0.18	0.12	-0.01	0.08
DOWNREGULATION OF ERBB2 ERBB3 SIGNALING	12	3	25.00%	0.08	0.04	0.02	-0.04	-0.03	-0.12	0.17	0.18	0.13	0.05	-0.03	-0.05
CREB PHOSPHORYLATION THROUGH THE ACTIVATION OF CAMKII	15	1	6.67%	0.08	-0.05	0.05	-0.03	-0.05	0.01	0.12	0.11	0.14	0.31	0.19	0.21
IMMUNOREGULATORY INTERACTIONS BETWEEN A LYMPHOID AND A NON LYMPHOID CELL	70	0	0.00%	0.07	-0.28	-0.13	0.01	-0.31	-0.16	-0.28	-0.19	-0.28	0.16	0.16	0.20
TCR SIGNALING	54	0	0.00%	0.07	-0.29	-0.13	0.00	-0.34	-0.17	-0.08	-0.07	-0.01	-0.03	0.08	-0.05
DOWNSTREAM TCR SIGNALING	37	0	0.00%	0.07	-0.29	-0.12	-0.01	-0.34	-0.18	-0.05	-0.08	-0.01	-0.22	-0.14	-0.22
LIPID DIGESTION MOBILIZATION AND TRANSPORT	46	3	6.52%	0.07	0.02	0.03	0.09	0.04	0.03	0.18	0.22	0.17	0.22	0.19	0.20
GLUTATHIONE CONJUGATION	23	0	0.00%	0.07	0.25	0.13	0.10	0.18	0.10	-0.01	-0.01	-0.08	-0.06	-0.06	-0.10
GLYCOGEN BREAKDOWN GLYCOGENOLYSIS	18	0	0.00%	0.07	-0.08	0.04	0.23	0.25	0.27	-0.06	0.01	-0.01	0.01	-0.07	-0.06
ACTIVATION OF IRF3 IRF7 MEDIATED BY TBK1 IKK EPSILON	14	3	21.43%	0.07	-0.12	-0.04	0.09	0.00	-0.01	0.15	0.13	0.11	0.30	0.33	0.27
BOTULINUM NEUROTOXICITY	19	0	0.00%	0.06	0.18	0.16	0.13	0.18	0.19	0.46	0.37	0.39	0.32	0.26	0.26
NEPHRIN INTERACTIONS	20	0	0.00%	0.06	0.29	0.22	0.22	0.26	0.30	0.19	0.15	0.18	0.11	0.06	0.01
DAG AND IP3 SIGNALING	32	3	9.38%	0.06	-0.08	0.06	-0.01	0.00	0.04	-0.12	-0.10	-0.12	0.04	0.13	0.09
PLC BETA MEDIATED EVENTS	43	3	6.98%	0.06	-0.14	0.00	0.04	0.05	0.08	0.11	0.20	0.12	-0.18	-0.09	-0.14
PKA MEDIATED PHOSPHORYLATION OF CREB	18	3	16.67%	0.06	-0.11	0.04	0.04	-0.08	0.01	0.33	0.37	0.38	-0.14	-0.01	0.03
SIGNALING BY ILS	107	4	3.74%	0.06	0.07	0.17	0.28	-0.07	0.10	0.12	0.17	0.08	0.04	0.15	0.01
CREB PHOSPHORYLATION THROUGH THE ACTIVATION OF RAS	27	1	3.70%	0.06	0.34	0.11	0.24	0.31	0.24	0.16	0.18	0.13	0.34	0.32	0.27
OPSINS	10	0	0.00%	0.06	-0.04	0.13	0.05	-0.08	0.05	-0.06	-0.02	-0.02	0.01	0.07	0.15
SEMA3A PLEXIN REPULSION SIGNALING BY INHIBITING INTEGRIN ADHESION	13	0	0.00%	0.06	0.27	0.17	0.19	0.21	0.17	0.17	0.22	0.19	0.04	0.11	0.02
3 UTR MEDIATED TRANSLATIONAL REGULATION	176	4	2.27%	0.06	0.04	0.08	0.42	0.29	0.39	0.07	0.12	0.08	0.22	0.26	0.22
CELL CELL JUNCTION ORGANIZATION	56	0	0.00%	0.06	0.37	0.20	0.34	0.41	0.37	0.32	0.36	0.32	0.18	0.13	0.20
GLUCONEOGENESIS	34	2	5.88%	0.06	-0.09	0.05	0.49	0.32	0.45	0.43	0.43	0.44	0.48	0.45	0.48
CYTOSOLIC SULFONATION OF SMALL MOLECULES	14	0	0.00%	0.05	0.11	0.19	0.08	0.03	0.11	0.20	0.21	0.21	0.16	0.22	0.23
TRIGLYCERIDE BIOSYNTHESIS	38	0	0.00%	0.05	0.31	0.17	0.29	0.33	0.29	0.01	0.06	-0.06	0.10	0.13	0.00
MEMBRANE TRAFFICKING	129	4	3.10%	0.05	-0.05	0.13	0.33	0.10	0.23	0.26	0.25	0.27	0.03	0.00	-0.02
GPVI MEDIATED ACTIVATION CASCADE	31	0	0.00%	0.05	-0.25	-0.14	-0.07	-0.34	-0.23	-0.03	-0.07	-0.05	-0.12	-0.10	-0.14
SYNTHESIS SECRETION AND DEACYLATION OF GHRELIN	16	0	0.00%	0.05	0.01	0.05	-0.01	-0.09	-0.01	0.10	0.03	0.02	0.04	0.09	0.01
FGFR2C LIGAND BINDING AND ACTIVATION	12	0	0.00%	0.05	0.07	0.08	0.09	0.07	0.10	0.33	0.35	0.30	0.21	0.13	0.12
RECEPTOR LIGAND BINDING INITIATES THE SECOND PROTEOLYTIC CLEAVAGE OF NOTCH RECEPTOR	12	3	25.00%	0.05	0.10	0.12	0.07	0.06	0.14	0.16	0.22	0.21	0.14	0.19	0.14
PLATELET CALCIUM HOMEOSTASIS	18	0	0.00%	0.04	0.03	-0.04	0.05	-0.03	-0.05	0.10	0.01	0.03	-0.04	-0.03	-0.06
SIGNALING BY NOTCH1	70	7	10.00%	0.04	0.18	0.15	0.07	0.04	0.12	-0.13	-0.06	-0.14	-0.17	-0.15	-0.25
SIGNALING BY FGFR3 MUTANTS	11	0	0.00%	0.04	0.15	0.08	0.12	0.23	0.14	0.31	0.32	0.28	0.13	0.16	0.08
NUCLEOTIDE LIKE PURINERGIC RECEPTORS	16	0	0.00%	0.04	-0.16	-0.09	0.14	0.00	0.09	0.26	0.26	0.20	-0.07	-0.10	-0.06
GENERATION OF SECOND MESSENGER MOLECULES	27	0	0.00%	0.04	-0.31	-0.16	-0.03	-0.36	-0.20	-0.05	-0.08	-0.04	-0.31	-0.19	-0.25
BILE ACID AND BILE SALT METABOLISM	27	0	0.00%	0.04	0.11	0.10	-0.05	0.02	-0.02	-0.19	-0.16	-0.19	0.04	0.05	0.07
TERMINATION OF O GLYCAN BIOSYNTHESIS	24	0	0.00%	0.04	0.03	0.04	0.01	0.05	0.00	0.08	0.08	-0.01	-0.03	-0.05	-0.05
SIGNALING BY ACTIVATED POINT MUTANTS OF FGFR1	11	0	0.00%	0.04	0.04	0.03	0.02	0.03	0.04	0.15	0.18	0.17	0.18	0.20	0.17
IL 6 SIGNALING	11	0	0.00%	0.04	0.14	0.13	-0.05	0.08	0.10	0.24	0.19	0.13	0.03	0.00	0.02
PD1 SIGNALING	18	0	0.00%	0.04	-0.31	-0.16	-0.04	-0.36	-0.21	-0.07	-0.13	-0.01	-0.02	-0.12	0.03
REGULATION OF THE FANCONI ANEMIA PATHWAY	11	8	72.73%	0.04	-0.11	-0.11	0.26	0.07	0.15	0.21	0.22	0.19	0.38	0.35	0.36
SYNTHESIS SECRETION AND INACTIVATION OF GIP	14	0	0.00%	0.03	0.02	0.05	-0.04	-0.09	-0.01	0.01	-0.03	-0.05	-0.12	-0.12	-0.12
INCRETIN SYNTHESIS SECRETION AND INACTIVATION	22	0	0.00%	0.03	0.02	0.05	-0.03	-0.09	-0.01	0.04	0.00	-0.02	-0.10	-0.02	-0.05
SYNTHESIS SECRETION AND INACTIVATION OF GLP1	19	0	0.00%	0.03	0.01	0.05	-0.03	-0.09	-0.01	0.04	0.00	-0.02	-0.10	-0.02	-0.05
GLUCURONIDATION	18	0	0.00%	0.03	0.14	0.08	0.05	0.15	0.05	-0.14	-0.17	-0.18	-0.10	-0.11	-0.14
DARPP 32 EVENTS	25	8	32.00%	0.03	0.09	0.03	0.14	0.24	0.16	0.20	0.23	0.20	0.23	0.15	0.13
SEROTONIN RECEPTORS	12	0	0.00%	0.03	0.04	0.06	-0.01	-0.04	-0.02	0.29	0.31	0.27	0.12	0.09	0.03
SYNTHESIS OF PIPS AT THE EARLY ENDOSOME MEMBRANE	12	0	0.00%	0.02	0.09	0.05	0.01	0.00	-0.04	-0.22	-0.26	-0.29	-0.12	-0.14	-0.18
TRANSFERRIN ENDOCYTOSIS AND RECYCLING	25	0	0.00%	0.02	0.23	0.11	0.34	0.21	0.26	0.04	0.05	0.02	0.00	-0.02	-0.06
FORMATION OF FIBRIN CLOT CLOTTING CASCADE	32	0	0.00%	0.02	0.29	0.15	0.13	0.30	0.21	0.30	0.37	0.29	0.07	0.12	0.08
PHOSPHORYLATION OF CD3 AND TCR ZETA CHAINS	16	0	0.00%	0.02	-0.32	-0.16	-0.05	-0.37	-0.21	-0.08	-0.14	-0.02	-0.06	-0.16	-0.01
SYNTHESIS OF PA	27	0	0.00%	0.02	0.25	0.12	0.02	0.25	0.15	0.00	0.05	-0.04	-0.13	-0.11	-0.15
ACYL CHAIN REMODELLING OF PG	16	0	0.00%	0.02	0.12	0.03	0.06	0.13	0.06	-0.06	-0.03	-0.11	-0.12	-0.13	-0.16
CD28 DEPENDENT PI3K AKT SIGNALING	22	0	0.00%	0.02	0.10	-0.03	0.25	-0.02	0.11	0.08	0.12	0.04	0.19	0.14	0.13
TRANSLOCATION OF ZAP 70 TO IMMUNOLOGICAL SYNAPSE	14	0	0.00%	0.02	-0.32	-0.17	-0.05	-0.37	-0.22	-0.09	-0.15	-0.03	0.22	0.24	0.17
DOWNSTREAM SIGNAL TRANSDUCTION	95	7	7.37%	0.02	0.27	0.08	0.13	0.25	0.15	0.33	0.34	0.30	0.23	0.22	0.17
DOWNREGULATION OF SMAD2 3 SMAD4 TRANSCRIPTIONAL ACTIVITY	20	5	25.00%	0.02	-0.05	0.12	0.01	-0.05	0.06	0.09	0.14	0.16	0.11	0.13	0.18
IONOTROPIC ACTIVITY OF KAINATE RECEPTORS	11	0	0.00%	0.02	0.03	0.00	0.20	0.27	0.28	0.16	0.19	0.15	-0.06	-0.13	-0.16
RAP1 SIGNALLING	17	2	11.76%	0.01	-0.03	-0.04	0.02	-0.07	-0.03	0.37	0.43	0.39	0.00	0.09	0.02
OLFACTORY SIGNALING PATHWAY	328	0	0.00%	0.01	-0.01	0.06	-0.06	-0.04	-0.03	0.32	0.27	0.26	0.39	0.32	0.35
ACYL CHAIN REMODELLING OF PI	15	0	0.00%	0.01	0.13	0.03	0.02	0.10	0.03	-0.07	-0.05	-0.12	-0.12	-0.12	-0.15
PROLACTIN RECEPTOR SIGNALING	14	3	21.43%	0.01	0.08	0.09	0.12	0.08	0.15	0.50	0.39	0.40	-0.37	-0.23	-0.30
METABOLISM OF PORPHYRINS	14	0	0.00%	0.01	0.03	0.05	0.06	0.04	0.06	-0.10	-0.07	-0.05	-0.07	0.04	0.08
SRP DEPENDENT COTRANSLATIONAL PROTEIN TARGETING TO MEMBRANE	179	4	2.23%	0.01	0.02	0.02	0.02	-0.04	0.07	0.09	0.13	0.09	0.24	0.28	0.24
FORMATION OF THE TERNARY COMPLEX AND SUBSEQUENTLY THE 43S COMPLEX	74	3	4.05%	0.00	0.00	0.01	0.01	-0.06	0.05	0.05	0.08	0.05	0.20	0.22	0.18

SYNTHESIS OF BILE ACIDS AND BILE SALTS VIA 7ALPHA HYDROXYCHOLESTEROL	15	0	0.00%	0.00	0.17	0.12	0.24	0.13	0.25	0.30	0.28	0.30	-0.22	-0.21	-0.21
POST NMDA RECEPTOR ACTIVATION EVENTS	33	1	3.03%	0.00	-0.08	0.01	-0.03	-0.10	-0.04	0.17	0.23	0.17	0.15	0.14	0.08
NCAM SIGNALING FOR NEURITE OUT GROWTH	64	1	1.56%	0.00	0.34	0.13	0.29	0.37	0.31	-0.08	-0.04	-0.10	-0.23	-0.33	-0.26
ACTIVATION OF THE MRNA UPON BINDING OF THE CAP BINDING COMPLEX AND EIFS AND SUBSEQUENT BINDING TO 43S	84	3	3.57%	0.00	0.01	0.00	0.39	0.29	0.39	0.03	0.07	0.03	0.24	0.24	0.22
SIGNALING BY ROBO RECEPTOR	30	1	3.33%	-0.01	0.01	0.07	0.07	0.05	0.11	-0.20	-0.11	-0.19	-0.31	-0.26	-0.30
AMINE COMPOUND SLC TRANSPORTERS	27	0	0.00%	-0.01	-0.04	-0.04	-0.05	-0.05	-0.04	0.15	0.11	0.07	-0.34	-0.28	-0.32
PRE NOTCH EXPRESSION AND PROCESSING	44	6	13.64%	-0.01	0.00	0.02	0.23	0.05	0.22	0.51	0.48	0.49	0.37	0.35	0.32
NOTCH HLH TRANSCRIPTION PATHWAY	13	0	0.00%	-0.01	-0.10	-0.01	0.01	-0.07	0.05	0.07	0.12	0.07	0.06	0.08	0.07
PURINE CATABOLISM	10	0	0.00%	-0.01	0.23	0.07	0.25	0.21	0.20	-0.08	-0.06	-0.09	0.27	0.26	0.23
NONSENSE MEDIATED DECAY ENHANCED BY THE EXON JUNCTION COMPLEX	176	7	3.98%	-0.01	0.00	0.00	0.28	0.19	0.30	0.08	0.13	0.09	0.22	0.27	0.22
FATTY ACYL COA BIOSYNTHESIS	18	0	0.00%	-0.01	0.22	0.06	0.08	0.26	0.16	0.04	0.07	-0.05	0.04	0.05	-0.05
BMAL1 CLOCK NPAS2 ACTIVATES CIRCADIAN EXPRESSION	36	0	0.00%	-0.01	0.19	0.05	0.09	0.16	0.11	0.10	0.11	0.09	0.35	0.28	0.29
FATTY ACID TRIACYLGLYCEROL AND KETONE BODY METABOLISM	168	0	0.00%	-0.02	0.30	0.06	0.34	0.14	0.31	-0.07	-0.02	-0.07	0.18	0.17	0.11
DEFENSINS	51	0	0.00%	-0.02	-0.26	-0.15	-0.04	-0.27	-0.14	0.01	0.03	-0.05	0.11	0.19	0.06
CITRIC ACID CYCLE TCA CYCLE	26	0	0.00%	-0.02	0.09	0.15	0.23	0.11	0.16	0.29	0.32	0.34	0.28	0.19	0.23
TRAFFICKING OF AMPA RECEPTORS	28	1	3.57%	-0.02	0.24	0.09	0.00	0.25	0.10	0.01	0.10	0.01	-0.07	-0.01	-0.02
RNA POL III TRANSCRIPTION	33	0	0.00%	-0.02	0.28	0.09	0.09	0.27	0.15	-0.11	-0.10	-0.11	-0.08	-0.05	-0.12
SYNTHESIS OF BILE ACIDS AND BILE SALTS VIA 24 HYDROXYCHOLESTEROL	10	0	0.00%	-0.02	0.16	0.08	-0.06	0.08	0.02	-0.02	-0.05	-0.10	-0.08	-0.10	-0.18
ACYL CHAIN REMODELLING OF PS	15	0	0.00%	-0.02	0.12	0.01	0.00	0.09	0.02	-0.05	-0.03	-0.11	-0.12	-0.12	-0.15
NOTCH1 INTRACELLULAR DOMAIN REGULATES TRANSCRIPTION	46	7	15.22%	-0.02	0.16	0.06	-0.03	0.17	0.02	-0.15	-0.07	-0.17	-0.28	-0.22	-0.33
ACYL CHAIN REMODELLING OF PC	22	0	0.00%	-0.02	0.12	0.01	0.00	0.10	0.01	-0.05	-0.03	-0.09	-0.14	-0.14	-0.17
ACYL CHAIN REMODELLING OF PE	21	0	0.00%	-0.02	0.12	0.01	0.00	0.03	0.04	-0.08	-0.06	-0.12	-0.14	-0.13	-0.17
DSCAM INTERACTIONS	11	0	0.00%	-0.02	0.03	-0.01	-0.01	0.04	0.00	0.03	0.02	-0.03	0.13	0.12	0.09
CIRCADIAN CLOCK	53	8	15.09%	-0.03	0.18	0.07	0.07	0.19	0.10	0.03	0.05	0.01	0.25	0.19	0.15
SIGNALING BY EGFR IN CANCER	109	11	10.09%	-0.03	0.33	0.11	0.23	0.26	0.22	0.30	0.32	0.30	0.09	0.06	0.02
ENOS ACTIVATION AND REGULATION	20	3	15.00%	-0.03	0.17	-0.02	0.32	0.14	0.18	0.59	0.56	0.58	0.05	0.10	0.04
TRAFFICKING OF GLUR2 CONTAINING AMPA RECEPTORS	16	0	0.00%	-0.03	0.19	0.05	-0.09	0.19	0.05	-0.09	0.00	-0.07	-0.07	0.03	0.00
POST TRANSLATIONAL MODIFICATION SYNTHESIS OF GPI ANCHORED PROTEINS	26	0	0.00%	-0.03	0.24	0.17	0.00	0.07	0.11	0.08	0.16	0.14	-0.09	0.08	0.00
ACTIVATION OF RAC	14	0	0.00%	-0.04	0.23	0.03	0.01	0.20	0.06	-0.07	-0.02	-0.09	0.05	0.08	-0.01
NETRIN1 SIGNALING	41	0	0.00%	-0.04	0.29	0.15	-0.01	0.23	0.16	0.00	0.05	-0.01	-0.16	-0.05	-0.10
GAP JUNCTION ASSEMBLY	18	0	0.00%	-0.04	-0.01	0.07	0.16	0.09	0.18	0.19	0.13	0.19	-0.09	-0.11	-0.07
GAP JUNCTION TRAFFICKING	27	0	0.00%	-0.04	-0.01	0.07	0.17	0.10	0.18	0.35	0.31	0.31	-0.08	-0.10	-0.05
GABA A RECEPTOR ACTIVATION	12	0	0.00%	-0.04	-0.03	-0.02	-0.02	0.00	-0.04	0.00	0.02	-0.01	0.10	0.19	0.22
EFFECTS OF PIP2 HYDROLYSIS	25	0	0.00%	-0.04	0.00	-0.09	0.26	0.32	0.36	0.37	0.39	0.35	0.24	0.24	0.24
ROLE OF SECOND MESSENGERS IN NETRIN1 SIGNALING	11	0	0.00%	-0.04	-0.06	-0.04	-0.09	-0.12	-0.10	0.21	0.17	0.14	0.14	0.18	0.22
SIGNALING BY BMP	23	1	4.35%	-0.04	0.14	-0.01	0.04	0.18	0.06	0.20	0.27	0.23	-0.12	-0.04	-0.12
PHASE II CONJUGATION	70	0	0.00%	-0.04	0.23	0.11	-0.07	0.16	0.03	-0.06	-0.01	-0.10	-0.02	-0.03	-0.09
ABC FAMILY PROTEINS MEDIATED TRANSPORT	34	0	0.00%	-0.04	0.31	0.08	0.06	0.24	0.11	0.34	0.37	0.35	0.09	0.05	0.05
EICOSANOID LIGAND BINDING RECEPTORS	16	0	0.00%	-0.04	0.04	0.09	0.12	0.19	0.14	0.25	0.31	0.21	0.19	0.28	0.17
ACTIVATED NOTCH1 TRANSMITS SIGNAL TO THE NUCLEUS	27	3	11.11%	-0.05	-0.02	0.04	0.19	0.17	0.26	0.30	0.34	0.34	-0.04	-0.07	-0.12
AKT PHOSPHORYLATES TARGETS IN THE CYTOSOL	12	3	25.00%	-0.05	0.04	0.04	-0.04	0.02	-0.06	-0.07	-0.05	-0.09	0.06	0.12	0.05
RNA POL III TRANSCRIPTION TERMINATION	19	0	0.00%	-0.05	0.25	0.06	0.30	0.24	0.27	-0.05	-0.02	-0.08	-0.10	-0.05	-0.10
ACTIVATION OF NMDA RECEPTOR UPON GLUTAMATE BINDING AND POSTSYNAPTIC EVENTS	37	1	2.70%	-0.05	0.21	0.08	0.05	0.26	0.15	0.19	0.25	0.19	0.12	0.13	0.07
SIGNALING BY ERBB2	101	11	10.89%	-0.06	0.30	0.10	0.12	0.22	0.14	0.29	0.30	0.30	0.10	0.02	0.03
TRAF6 MEDIATED INDUCTION OF TAK1 COMPLEX	14	3	21.43%	-0.06	0.07	0.01	-0.09	-0.02	-0.05	0.09	0.10	0.06	-0.06	-0.08	-0.06
BASE FREE SUGAR PHOSPHATE REMOVAL VIA THE SINGLE NUCLEOTIDE REPLACEMENT PATHWAY	10	0	0.00%	-0.06	0.15	0.11	0.12	0.11	0.14	0.19	0.19	0.19	-0.14	-0.02	0.02
CLASS C 3 METABOTROPIC GLUTAMATE PHEROMONE RECEPTORS	15	0	0.00%	-0.06	0.00	0.00	0.30	0.09	0.23	-0.15	-0.12	-0.13	0.01	0.02	-0.02
ABCA TRANSPORTERS IN LIPID HOMEOSTASIS	18	0	0.00%	-0.06	0.28	0.05	-0.02	0.18	0.05	0.15	0.19	0.15	-0.11	-0.08	-0.09
GABA SYNTHESIS RELEASE REUPTAKE AND DEGRADATION	17	0	0.00%	-0.06	0.11	0.10	-0.02	0.15	0.07	0.54	0.43	0.48	-0.20	-0.14	-0.17
VITAMIN B5 PANTOTHENATE METABOLISM	11	0	0.00%	-0.06	0.19	0.01	0.14	0.14	0.20	-0.11	-0.12	-0.16	-0.20	-0.08	-0.11
AMINO ACID AND OLIGOPEPTIDE SLC TRANSPORTERS	49	0	0.00%	-0.07	-0.06	-0.02	0.26	0.23	0.23	0.44	0.41	0.41	-0.12	-0.10	-0.07
IRAK2 MEDIATED ACTIVATION OF TAK1 COMPLEX UPON TLR7 8 OR 9 STIMULATION	9	3	33.33%	-0.07	0.02	-0.01	-0.13	0.01	-0.09	0.00	-0.01	-0.03	0.07	0.03	0.01
SIGNALING BY NOTCH	103	13	12.62%	-0.07	0.12	0.10	0.11	-0.01	0.12	-0.13	-0.06	-0.13	-0.21	-0.14	-0.25
MEMBRANE BINDING AND TARGETTING OF GAG PROTEINS	10	3	30.00%	-0.07	0.22	0.07	0.00	0.16	0.12	-0.12	-0.05	-0.10	-0.13	-0.09	-0.14
DOWNSTREAM SIGNALING OF ACTIVATED FGFR	100	7	7.00%	-0.07	0.27	0.09	0.11	0.22	0.14	0.32	0.35	0.32	0.22	0.20	0.16
MITOCHONDRIAL FATTY ACID BETA OXIDATION	14	0	0.00%	-0.07	0.05	-0.02	0.24	0.16	0.27	0.30	0.28	0.30	0.20	0.12	0.13
ACTIVATED POINT MUTANTS OF FGFR2	16	0	0.00%	-0.07	0.05	0.00	0.20	0.07	0.16	0.13	0.21	0.12	0.16	0.19	0.13
O LINKED GLYCOSYLATION OF MUCINS	59	0	0.00%	-0.08	-0.11	-0.06	-0.14	-0.09	-0.11	-0.17	-0.12	-0.21	-0.27	-0.25	-0.29
GLYCEROPHOSPHOLIPID BIOSYNTHESIS	82	0	0.00%	-0.08	0.21	0.03	-0.07	0.16	0.10	-0.14	-0.06	-0.17	-0.14	-0.12	-0.15
GAMMA CARBOXYLATION TRANSPORT AND AMINO TERMINAL CLEAVAGE OF PROTEINS	11	0	0.00%	-0.08	0.16	0.04	0.03	0.20	0.10	0.09	0.15	0.11	0.11	0.17	0.09
TRANSPORT OF INORGANIC CATIONS ANIONS AND AMINO ACIDS OLIGOPEPTIDES	94	0	0.00%	-0.08	0.24	0.04	0.04	0.22	0.07	-0.14	-0.09	-0.19	-0.37	-0.31	-0.36
PRE NOTCH PROCESSING IN GOLGI	16	0	0.00%	-0.08	0.04	-0.09	-0.03	0.05	-0.04	0.26	0.20	0.19	-0.16	-0.15	-0.17
ZINC TRANSPORTERS	15	0	0.00%	-0.08	0.18	0.10	0.14	0.24	0.22	0.22	0.21	0.26	0.16	0.17	0.22
PHOSPHOLIPID METABOLISM	198	0	0.00%	-0.09	0.26	0.04	-0.02	0.26	0.11	0.23	0.26	0.22	-0.15	-0.07	-0.16
UNBLOCKING OF NMDA RECEPTOR GLUTAMATE BINDING AND ACTIVATION	15	1	6.67%	-0.09	-0.01	-0.06	-0.08	-0.05	-0.06	0.08	0.14	0.08	0.32	0.17	0.23
PYRIMIDINE CATABOLISM	12	0	0.00%	-0.09	0.28	0.06	0.00	0.29	0.08	0.02	0.08	0.00	-0.07	0.02	-0.04
METABOLISM OF LIPIDS AND LIPOPROTEINS	478	3	0.63%	-0.09	0.31	0.04	0.00	0.22	0.06	0.16	0.21	0.16	0.54	0.45	0.47
RESOLUTION OF AP SITES VIA THE SINGLE NUCLEOTIDE REPLACEMENT PATHWAY	12	0	0.00%	-0.09	0.14	0.09	0.03	0.19	0.12	-0.12	-0.04	-0.05	-0.13	-0.01	-0.02
NA CL DEPENDENT NEUROTRANSMITTER TRANSPORTERS	17	0	0.00%	-0.10	-0.05	-0.08	-0.02	-0.01	-0.07	0.11	0.09	0.13	-0.12	-0.17	-0.17
NRIF SIGNALS CELL DEATH FROM THE NUCLEUS	15	4	26.67%	-0.10	0.19	0.11	0.11	0.12	0.18	0.21	0.26	0.27	0.05	0.15	0.13
ROLE OF DCC IN REGULATING APOPTOSIS	10	0	0.00%	-0.10	-0.02	-0.07	-0.03	0.09	-0.05	0.26	0.21	0.24	-0.18	-0.21	-0.16
STEROID HORMONES	29	0	0.00%	-0.11	0.20	-0.01	-0.03	0.19	0.03	-0.12	-0.16	-0.15	0.10	0.11	0.09
SPHINGOLIPID DE NOVO BIOSYNTHESIS	31	0	0.00%	-0.11	0.24	0.03	-0.04	0.23	0.07	0.18	0.26	0.21	0.15	0.21	0.13
BETA DEFENSINS	42	0	0.00%	-0.11	-0.26	-0.17	-0.14	-0.31	-0.19	0.01	0.04	-0.03	0.15	0.20	0.09
METABOLISM OF STEROID HORMONES AND VITAMINS A AND D	35	0	0.00%	-0.11	0.19	-0.01	-0.03	0.18	0.01	0.32	0.33	0.29	0.15	0.13	0.12
COLLAGEN FORMATION	58	0	0.00%	-0.11	-0.10	-0.03	-0.01	-0.02	0.01	-0.09	-0.12	-0.06	-0.03	-0.11	-0.07
REGULATED PROTEOLYSIS OF P75NTR	10	0	0.00%	-0.11	0.16	0.10	-0.05	0.13	0.05	0.23	0.29	0.28	0.04	0.15	0.12
IKK COMPLEX RECRUITMENT MEDIATED BY RIP1	10	0	0.00%	-0.11	-0.07	-0.09	-0.02	0.25	0.06	0.01	0.08	0.00	0.13	0.19	0.10
BIOLOGICAL OXIDATIONS	139	0	0.00%	-0.12	0.27	0.06	-0.01	0.24	0.10	0.20	0.22	0.14	0.07	0.08	0.01
PHASE1 FUNCTIONALIZATION OF COMPOUNDS	70	0	0.00%	-0.13	0.20	0.00	0.05	0.26	0.12	0.31	0.32	0.25	0.28	0.28	0.23
XENOBIOTICS	16	0	0.00%	-0.13	0.04	-0.04	-0.04	-0.03	0.05	0.23	0.14	0.18	0.10	0.03	0.05
SYNTHESIS OF BILE ACIDS AND BILE SALTS	19	0	0.00%	-0.13	0.08	-0.01	-0.13	0.03	-0.03	0.31	0.28	0.27	-0.19	-0.17	-0.18

SYNTHESIS OF GLYCOSYLPHOSPHATIDYLINOSITOL GPI	17	0	0.00%	-0.14	0.13	-0.02	-0.05	0.05	0.06	-0.26	-0.12	-0.19	-0.16	0.03	-0.05
REGULATION OF INSULIN SECRETION BY ACETYLCHOLINE	11	0	0.00%	-0.14	0.20	0.02	-0.09	0.15	-0.01	-0.16	-0.08	-0.15	-0.24	-0.15	-0.24
SPHINGOLIPID METABOLISM	69	0	0.00%	-0.15	0.26	0.08	-0.09	0.22	0.04	0.26	0.28	0.25	0.04	0.14	0.05
REVERSIBLE HYDRATION OF CARBON DIOXIDE	12	0	0.00%	-0.15	0.17	0.01	0.18	0.14	0.18	0.11	0.17	0.15	-0.22	-0.18	-0.23
GENERIC TRANSCRIPTION PATHWAY	352	12	3.41%	-0.15	0.15	-0.05	-0.11	0.14	0.07	0.32	0.27	0.30	0.12	0.07	0.05
PTM GAMMA CARBOXYLATION HYPUSINE FORMATION AND ARYLSULFATASE ACTIVATION	27	0	0.00%	-0.16	0.20	0.01	-0.05	0.20	0.07	0.07	0.13	0.07	-0.12	-0.08	-0.17
ION TRANSPORT BY P TYPE ATPASES	34	0	0.00%	-0.17	0.09	-0.14	-0.06	0.09	-0.04	0.17	0.19	0.17	-0.24	-0.23	-0.24
ENDOGENOUS STEROLS	15	0	0.00%	-0.17	0.07	-0.08	-0.07	0.14	0.00	0.04	0.03	-0.03	-0.03	0.02	-0.08
NUCLEAR SIGNALING BY ERBB4	38	3	7.89%	-0.18	0.25	0.02	-0.05	0.25	0.10	0.54	0.48	0.51	-0.22	-0.11	-0.17
GLYCOSPHINGOLIPID METABOLISM	38	0	0.00%	-0.20	0.05	-0.03	0.18	0.06	0.07	0.37	0.34	0.38	0.17	0.22	0.25
NEUROTRANSMITTER RELEASE CYCLE	34	0	0.00%	-0.20	0.11	0.02	-0.13	0.12	0.01	0.35	0.31	0.33	-0.34	-0.28	-0.30
ORGANIC CATION ANION ZWITTERION TRANSPORT	13	0	0.00%	-0.22	0.18	-0.04	-0.17	0.16	-0.05	0.03	0.10	0.07	-0.19	-0.14	-0.22
CYTOCHROME P450 ARRANGED BY SUBSTRATE TYPE	51	0	0.00%	-0.22	0.09	-0.09	-0.07	0.17	0.01	0.06	0.08	-0.01	-0.03	-0.02	-0.07
METAL ION SLC TRANSPORTERS	22	0	0.00%	-0.22	0.11	-0.08	0.14	0.22	0.18	-0.16	-0.12	-0.21	0.11	0.16	0.09
SYNTHESIS OF VERY LONG CHAIN FATTY ACYL COAS	14	0	0.00%	-0.22	-0.09	-0.14	0.11	0.29	0.20	0.04	0.07	-0.05	0.02	0.05	-0.05
NCAM1 INTERACTIONS	39	0	0.00%	-0.23	-0.26	-0.20	0.23	0.27	0.26	0.01	0.03	-0.02	-0.19	-0.25	-0.21
SYNTHESIS OF PIPS AT THE LATE ENDOSOME MEMBRANE	10	0	0.00%	-0.24	-0.07	-0.16	-0.19	-0.01	-0.08	0.13	0.12	0.15	-0.16	-0.19	-0.22
TRANSMISSION ACROSS CHEMICAL SYNAPSES	186	2	1.08%	-0.24	0.16	-0.01	0.03	0.28	0.15	0.28	0.34	0.25	0.41	0.41	0.34
BRANCHED CHAIN AMINO ACID CATABOLISM	17	0	0.00%	-0.25	0.10	-0.06	0.13	0.23	0.12	0.42	0.37	0.44	0.34	0.25	0.27
PEROXISOMAL LIPID METABOLISM	21	0	0.00%	-0.26	-0.08	-0.10	0.08	-0.04	0.09	0.31	0.30	0.32	0.20	0.22	0.25
ION CHANNEL TRANSPORT	55	0	0.00%	-0.26	0.07	-0.17	0.04	0.10	-0.01	0.19	0.22	0.20	-0.25	-0.25	-0.27
POST TRANSLATIONAL PROTEIN MODIFICATION	188	1	0.53%	-0.27	0.19	-0.08	0.29	0.07	0.13	0.36	0.37	0.38	-0.03	0.01	-0.05
NEURONAL SYSTEM	279	2	0.72%	-0.27	0.17	-0.04	0.38	0.39	0.38	0.22	0.26	0.17	0.43	0.45	0.39
THE ACTIVATION OF ARYLSULFATASES	12	0	0.00%	-0.28	0.03	-0.11	-0.14	-0.02	-0.09	-0.24	-0.19	-0.28	-0.27	-0.21	-0.29
NUCLEAR RECEPTOR TRANSCRIPTION PATHWAY	49	0	0.00%	-0.31	0.10	-0.11	-0.01	0.24	0.10	0.41	0.40	0.42	0.26	0.23	0.21

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XRCC3
RPA3
OTUB1
EME1
SHFM1
XRCC2
BRCA1
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ATM
RNF40
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DNA2
LIG3
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ERCC4
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USP3
BRCA2
RNF8
TOP3A
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ATRX
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MRE11A
POLD3
PSIP1
PIAS1
BRE
RAD51
TOP3B
HERC2
RAD50
TRIP12
KAT5
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PIAS4
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BRIP1
RPA2
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ERCC1
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−3
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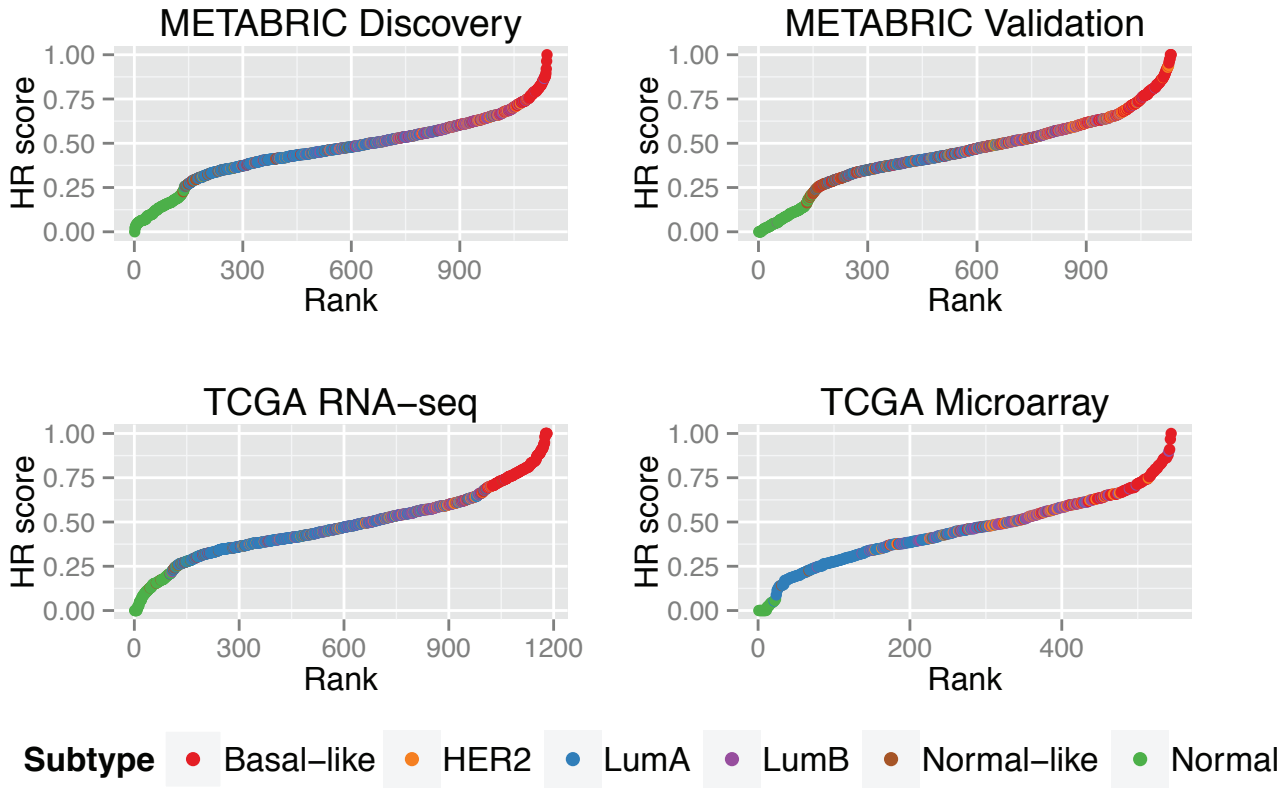
HER2
LumA
LumB
Normal−like
Normal


METABRIC Discovery
METABRIC Validation
TCGA RNA−seq
TCGA Microarray
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HER2
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LumB
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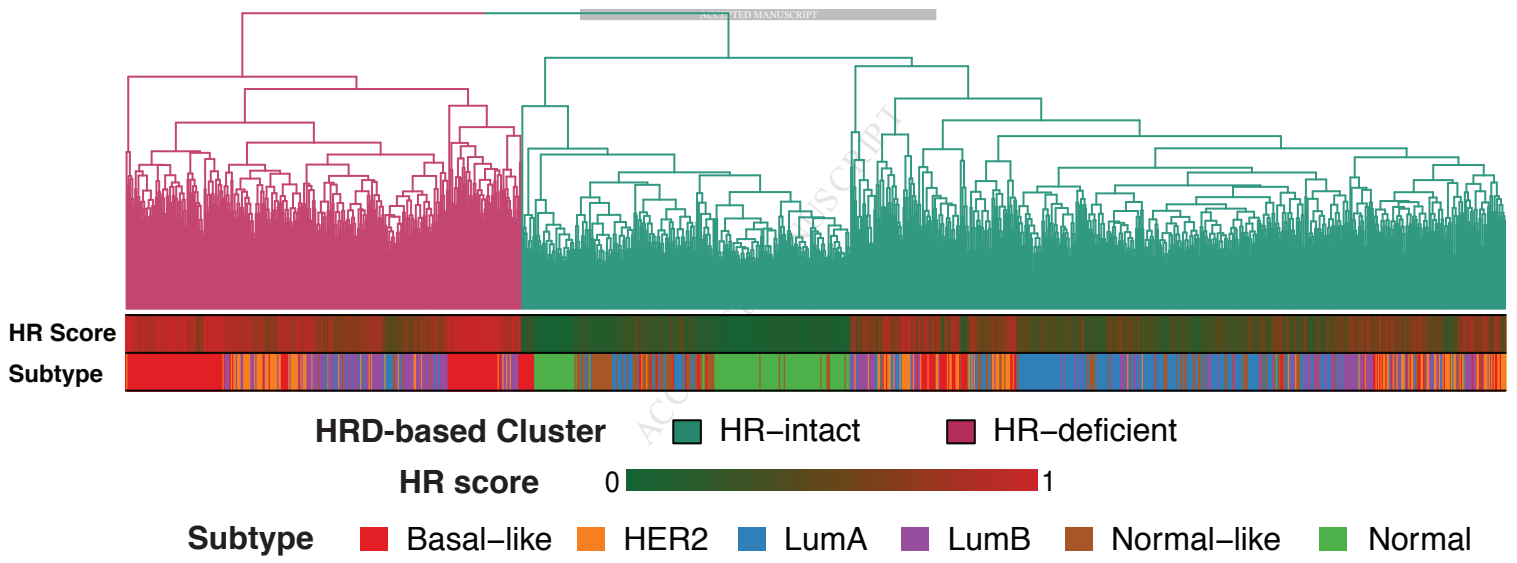
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HER2
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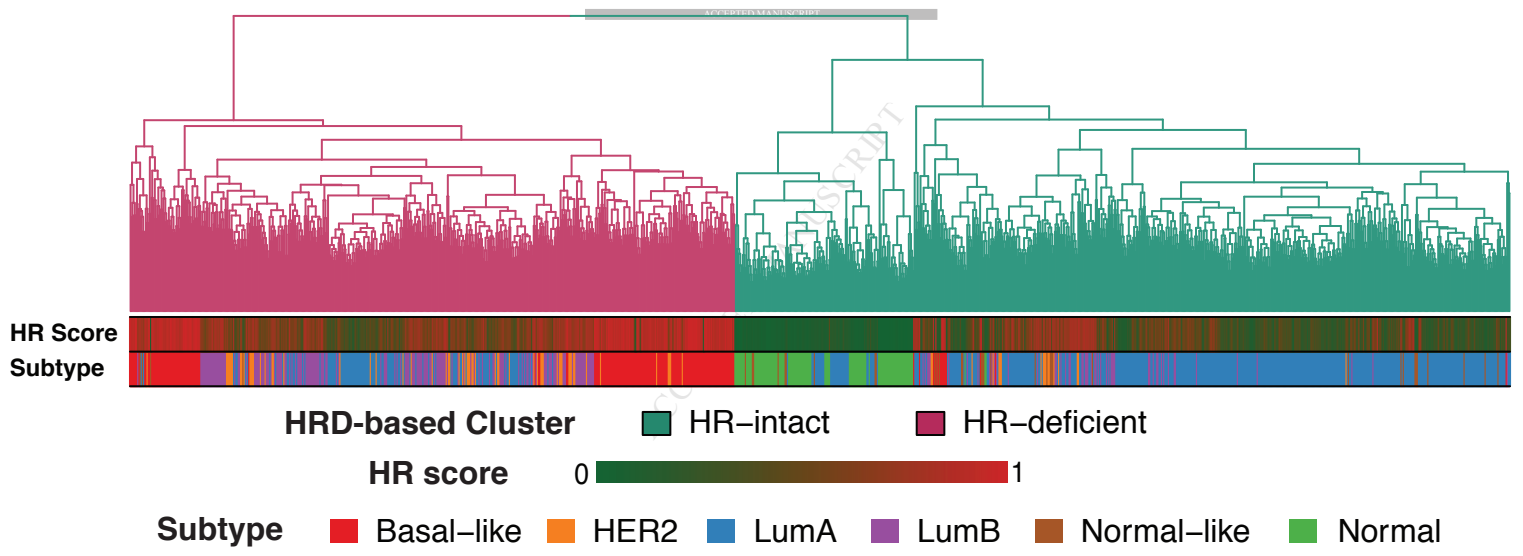
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Subtype
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HER2
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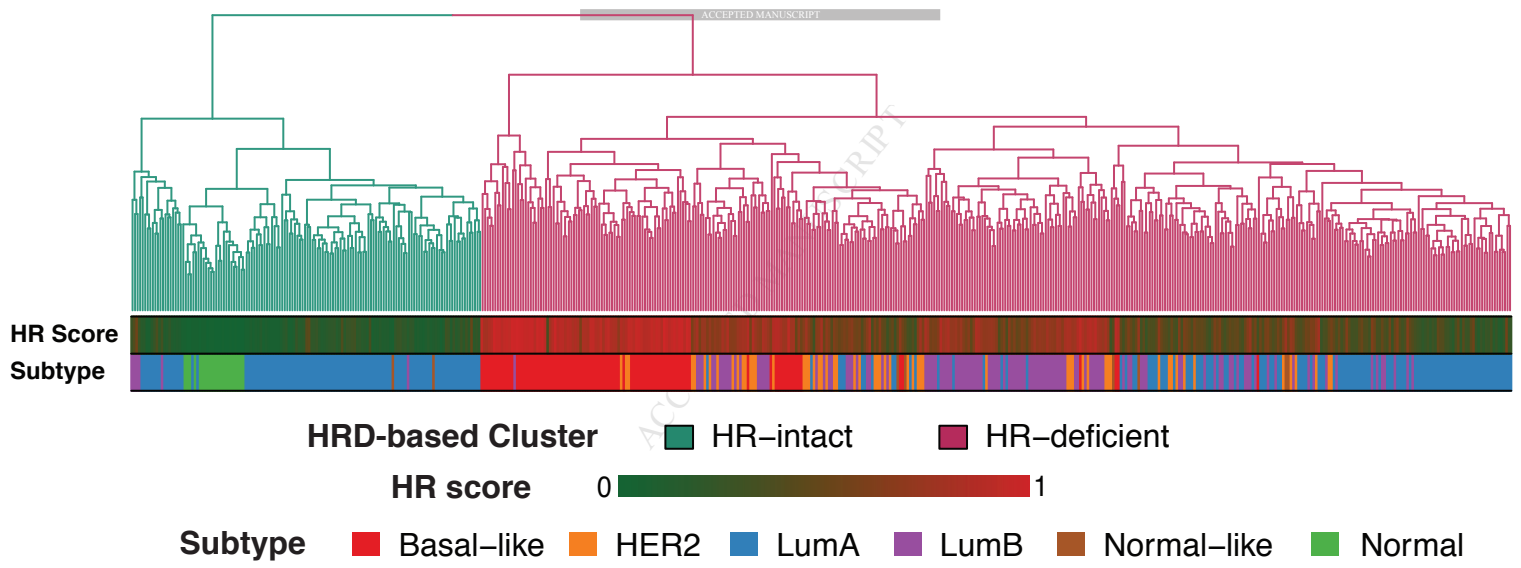
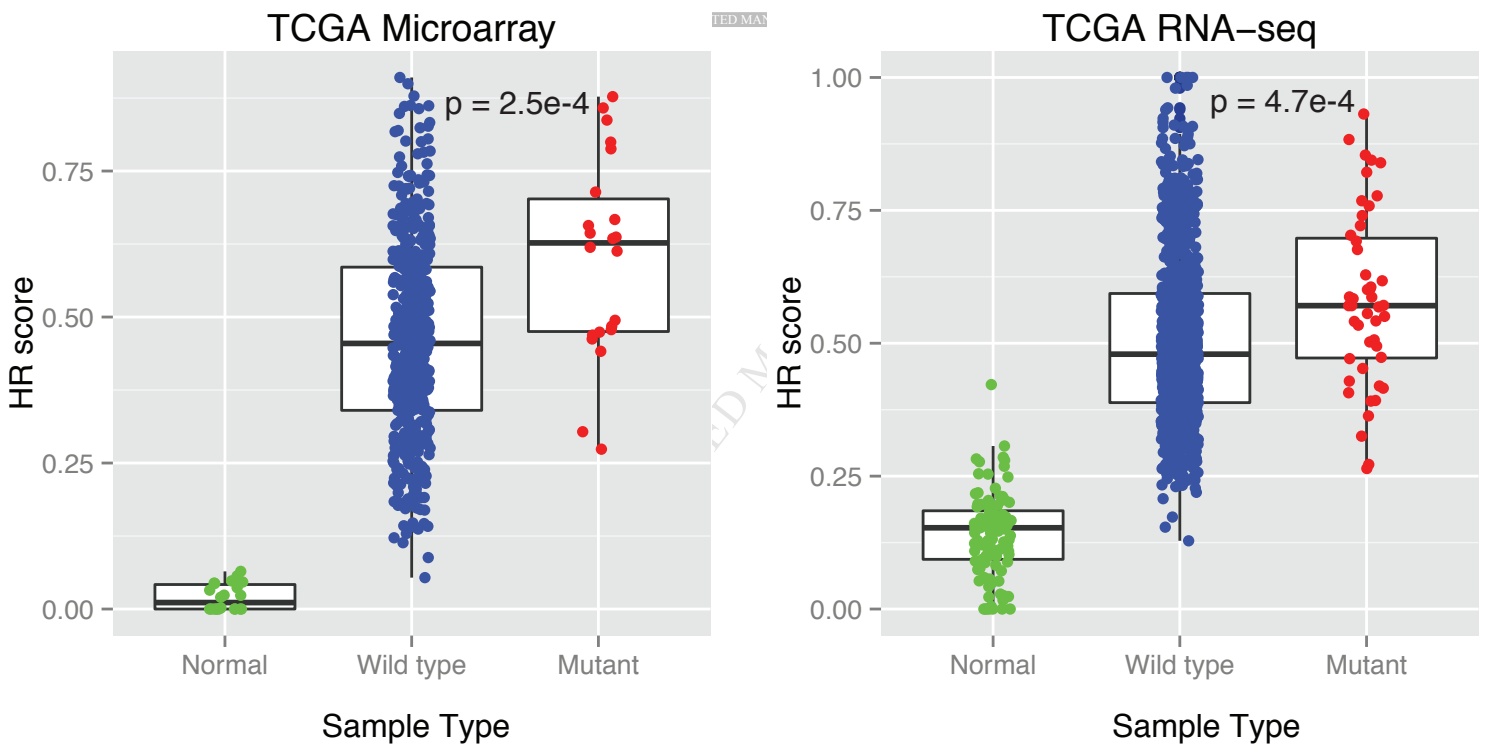
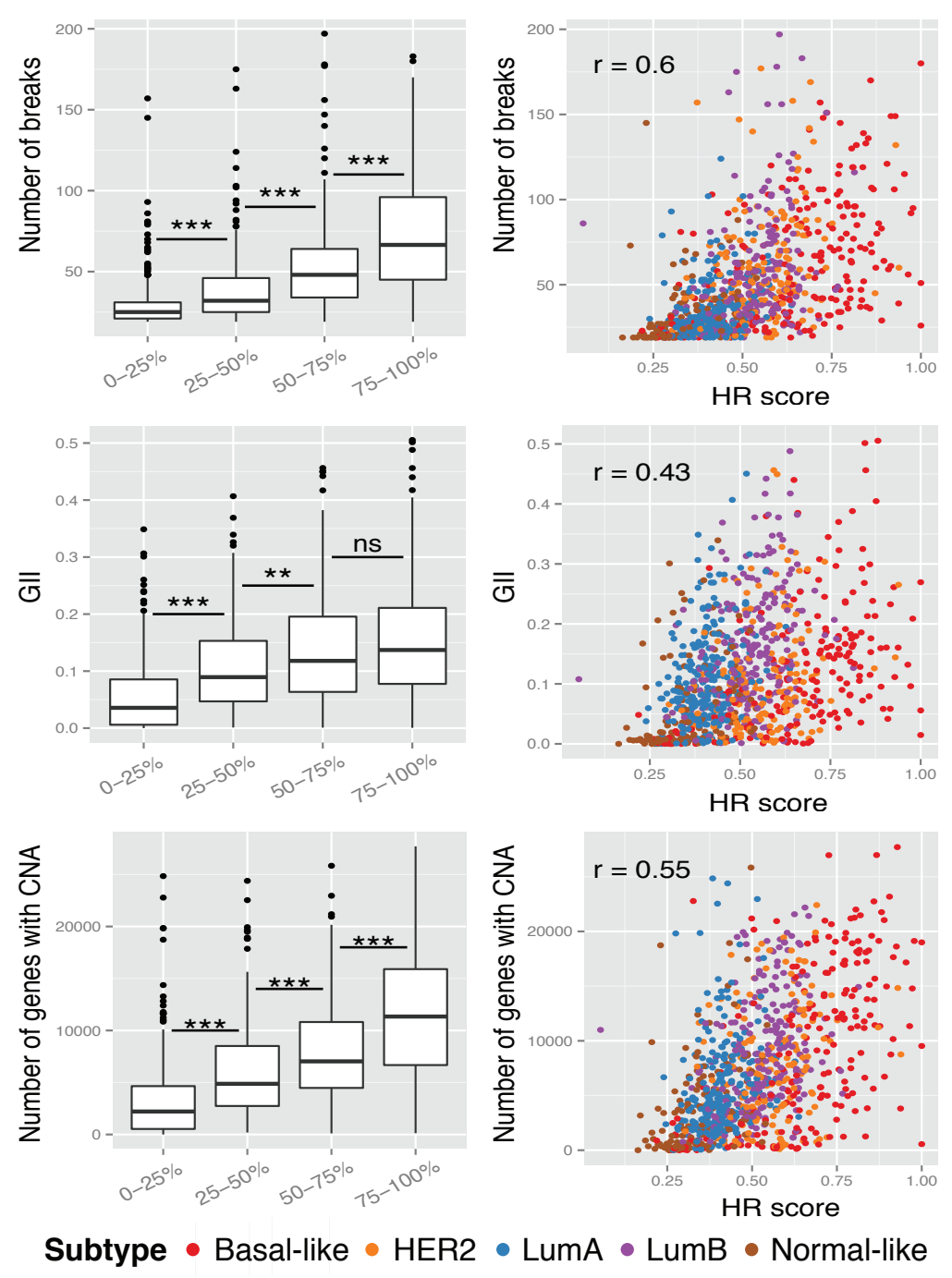
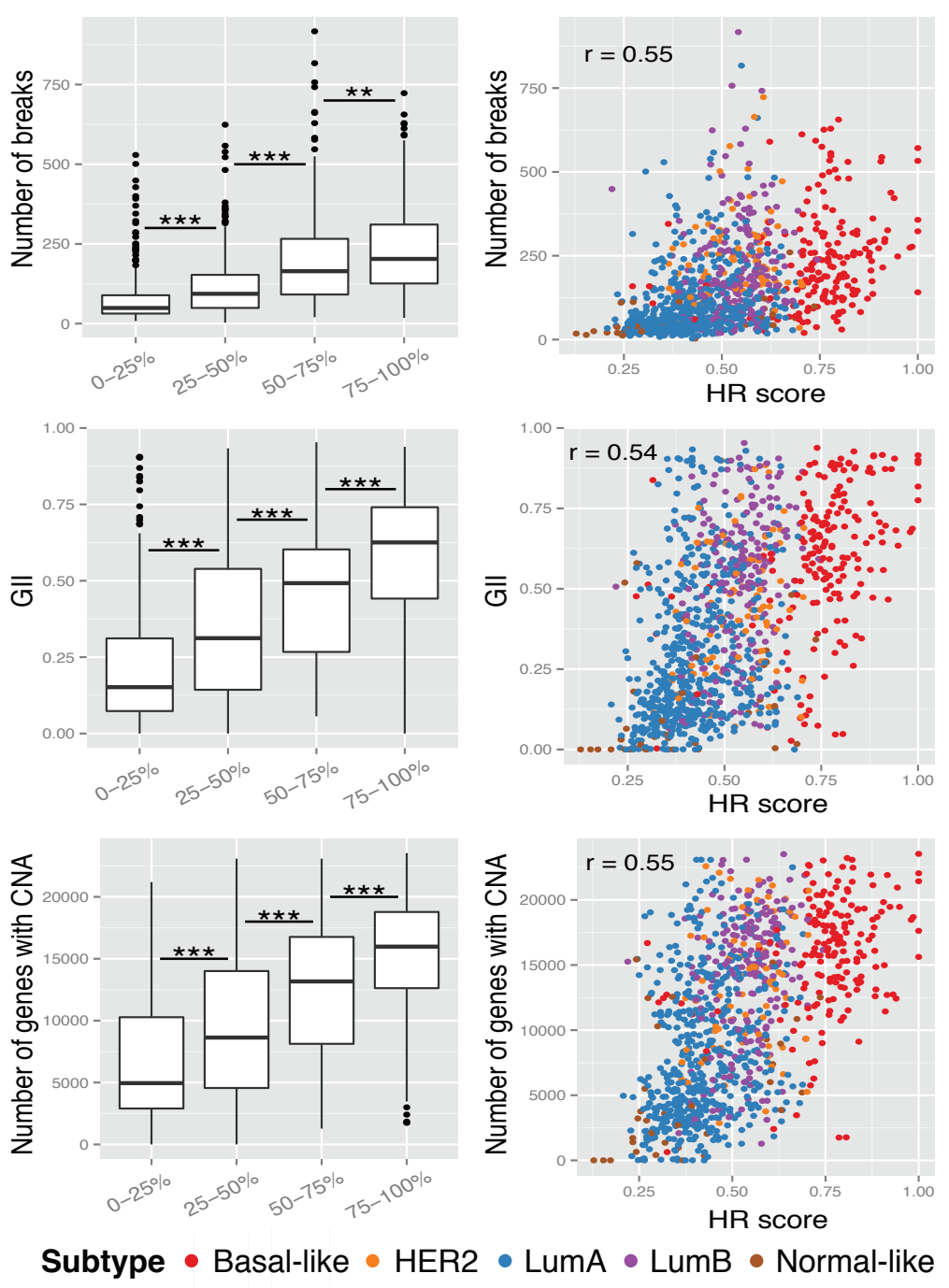
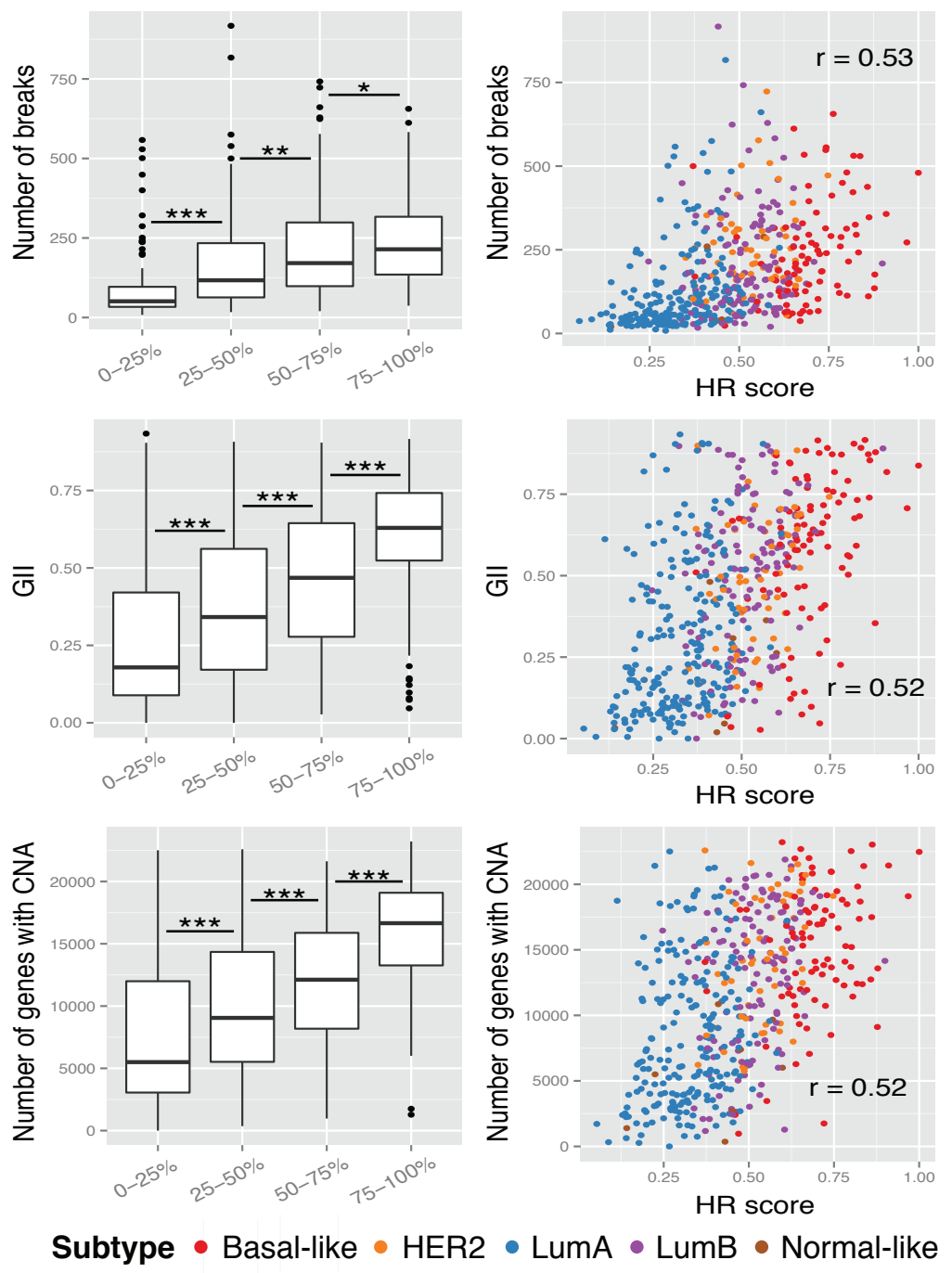
Normal

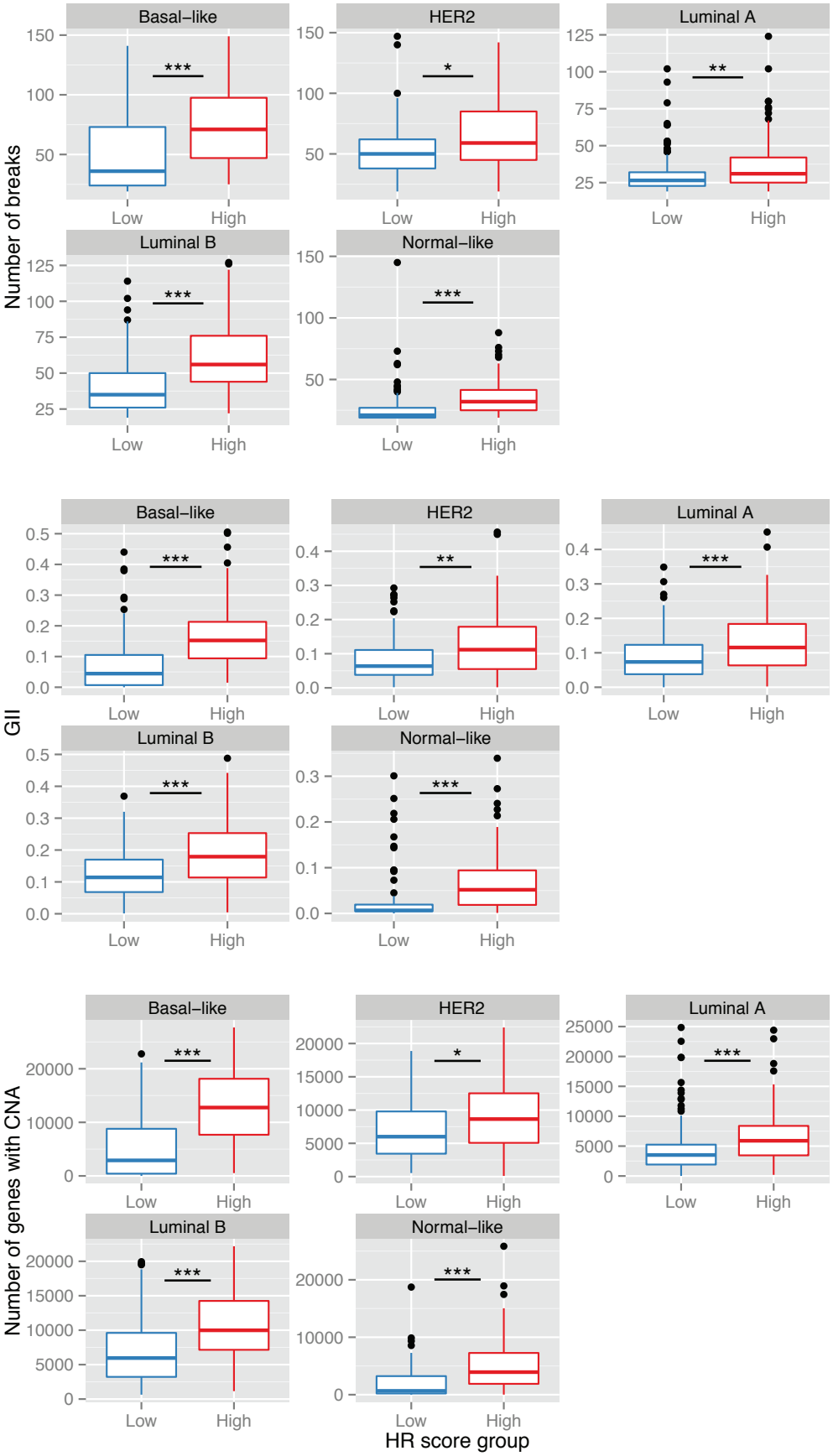


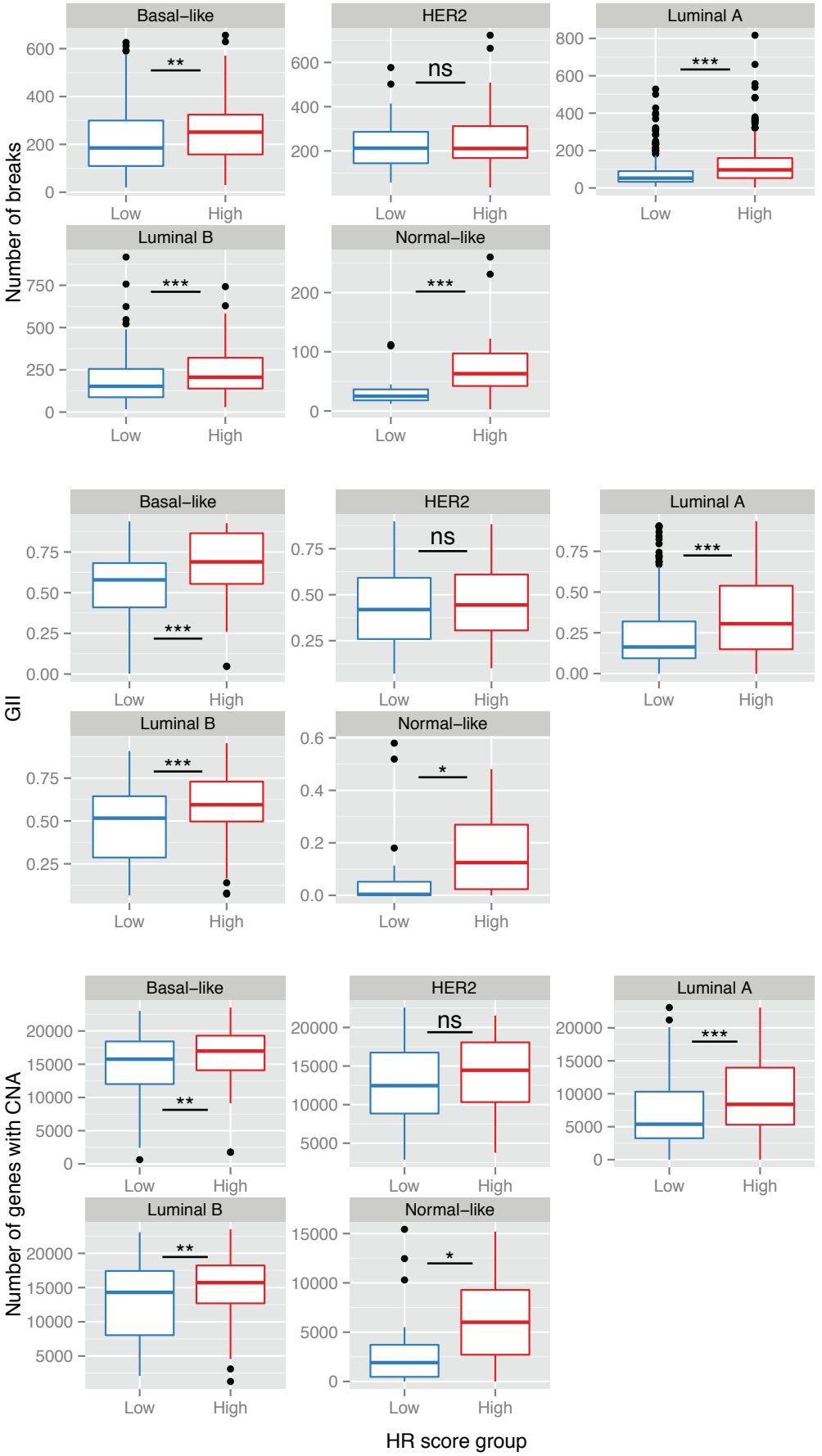

TCGA Microarray
p = 2.5e-4
HR score
0.00
0.25
0.50
0.75
Normal
Wild type
Mutant
Sample Type
TCGA RNA−seq
p = 4.7e-4
HR score
0.00
0.25
0.50
0.75
1.00
Normal
Wild type
Mutant
Sample Type

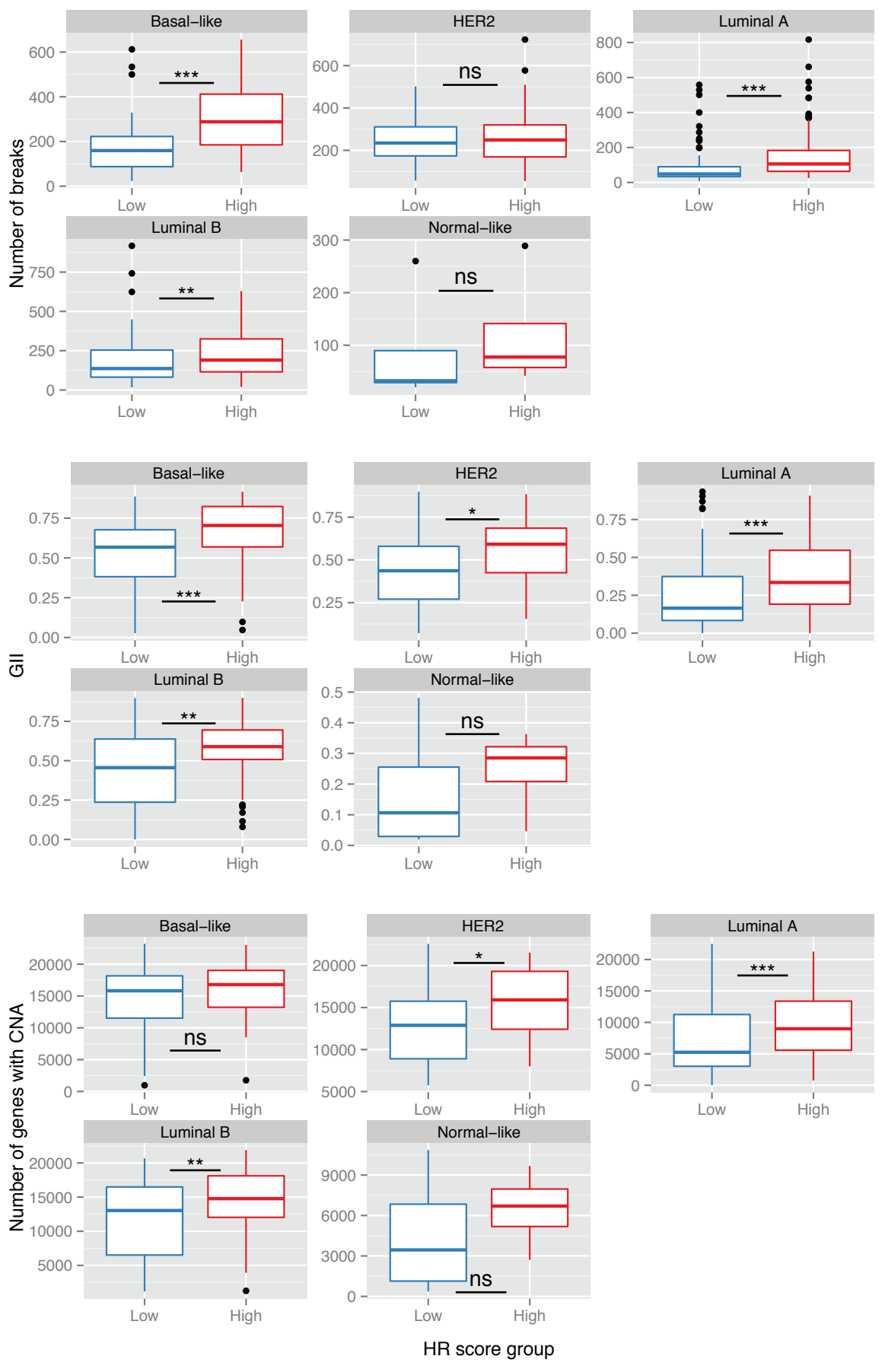

Number of breaks
200
150
100
50
***
***
***
0–25%
25–50%
50–75%
75–100%
r = 0.6
HR score
GII
0.5
0.4
0.3
0.2
0.1
0.0
***
**
ns
r = 0.43
Number of genes with CNA
20000
10000
0
r = 0.55
0.25
0.50
0.75
1.00
Subtype
Basal-like
HER2
LumA
LumB
Normal-like

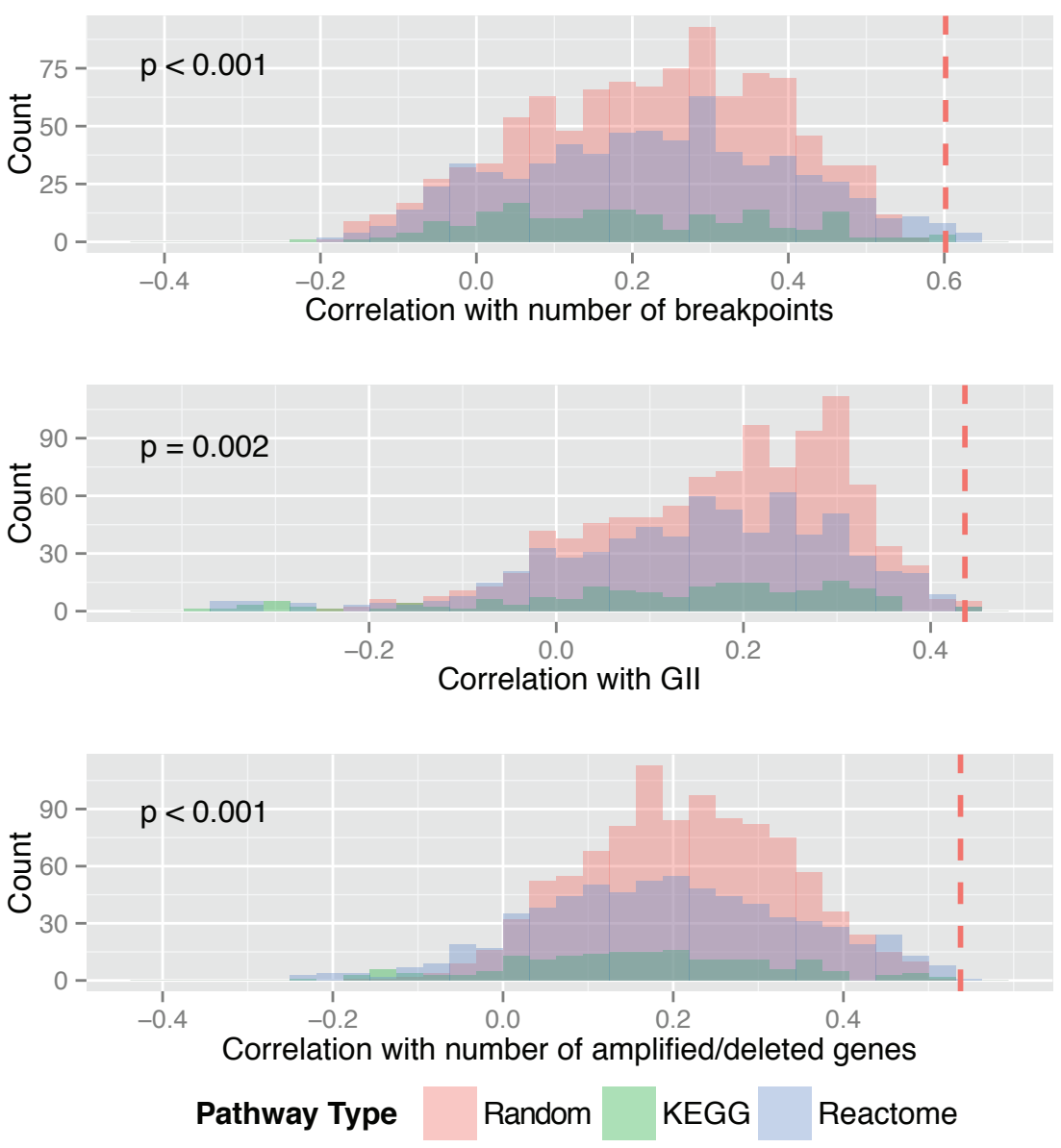

Number of breaks
0
250
500
750
**
***
***
0–25%
25–50%
50–75%
75–100%
r = 0.55
HR score
GII
0.00
0.25
0.50
0.75
1.00
r = 0.54
Number of genes with CNA
0
5000
10000
15000
20000
r = 0.55
Subtype
Basal-like
HER2
LumA
LumB
Normal-like

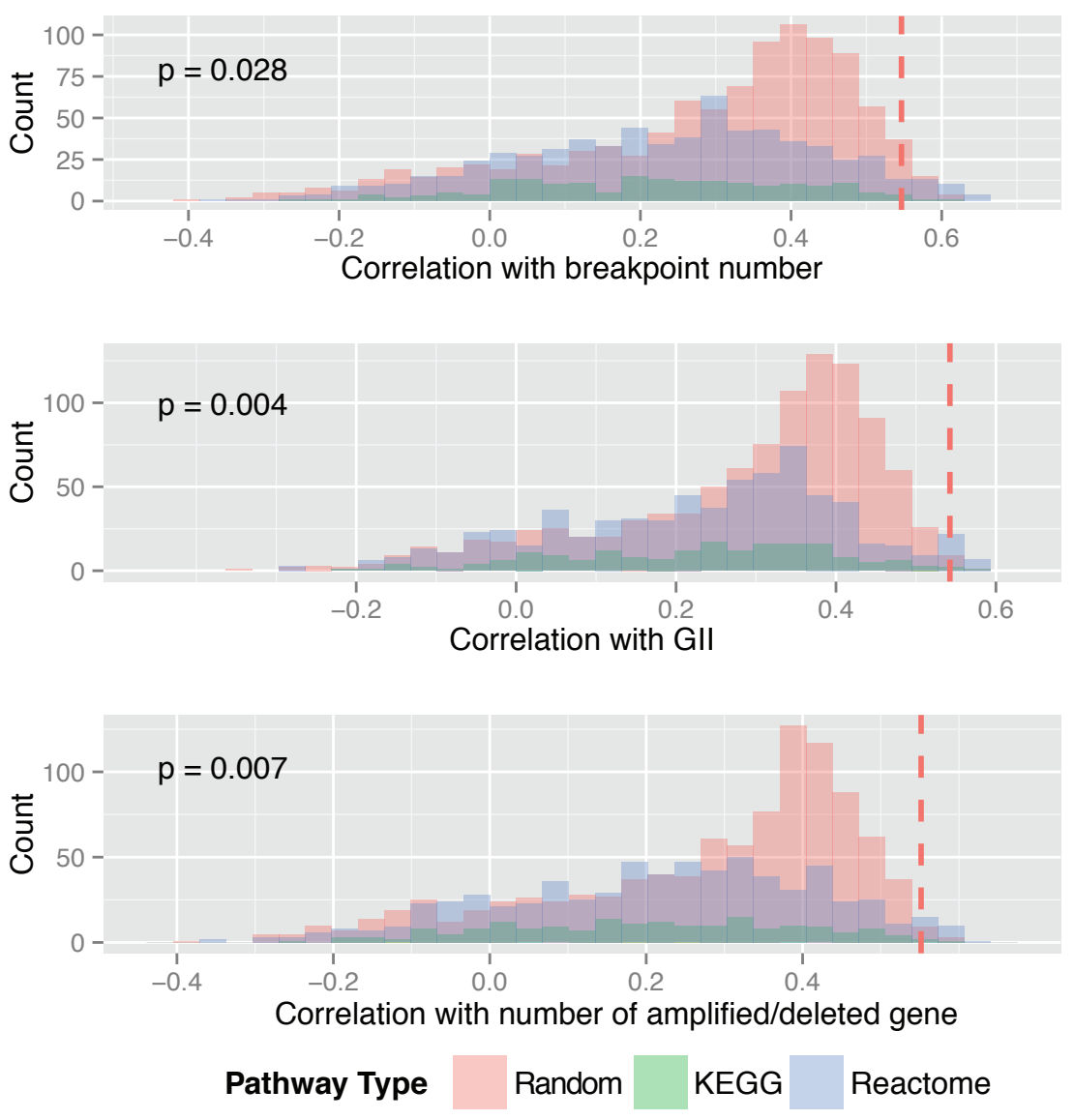

Number of breaks
750
500
250
0
***
**
*
0–25%
25–50%
50–75%
75–100%
Number of breaks
r = 0.53
0.25
0.50
0.75
1.00
HR score
GII
0.75
0.50
0.25
0.00
***
***
***
0–25%
25–50%
50–75%
75–100%
GII
r = 0.52
0.25
0.50
0.75
1.00
HR score
Number of genes with CNA
20000
15000
10000
5000
0
***
***
***
0–25%
25–50%
50–75%
75–100%
Number of genes with CNA
r = 0.52
0.25
0.50
0.75
1.00
HR score
Subtype
Basal-like
HER2
LumA
LumB
Normal-like

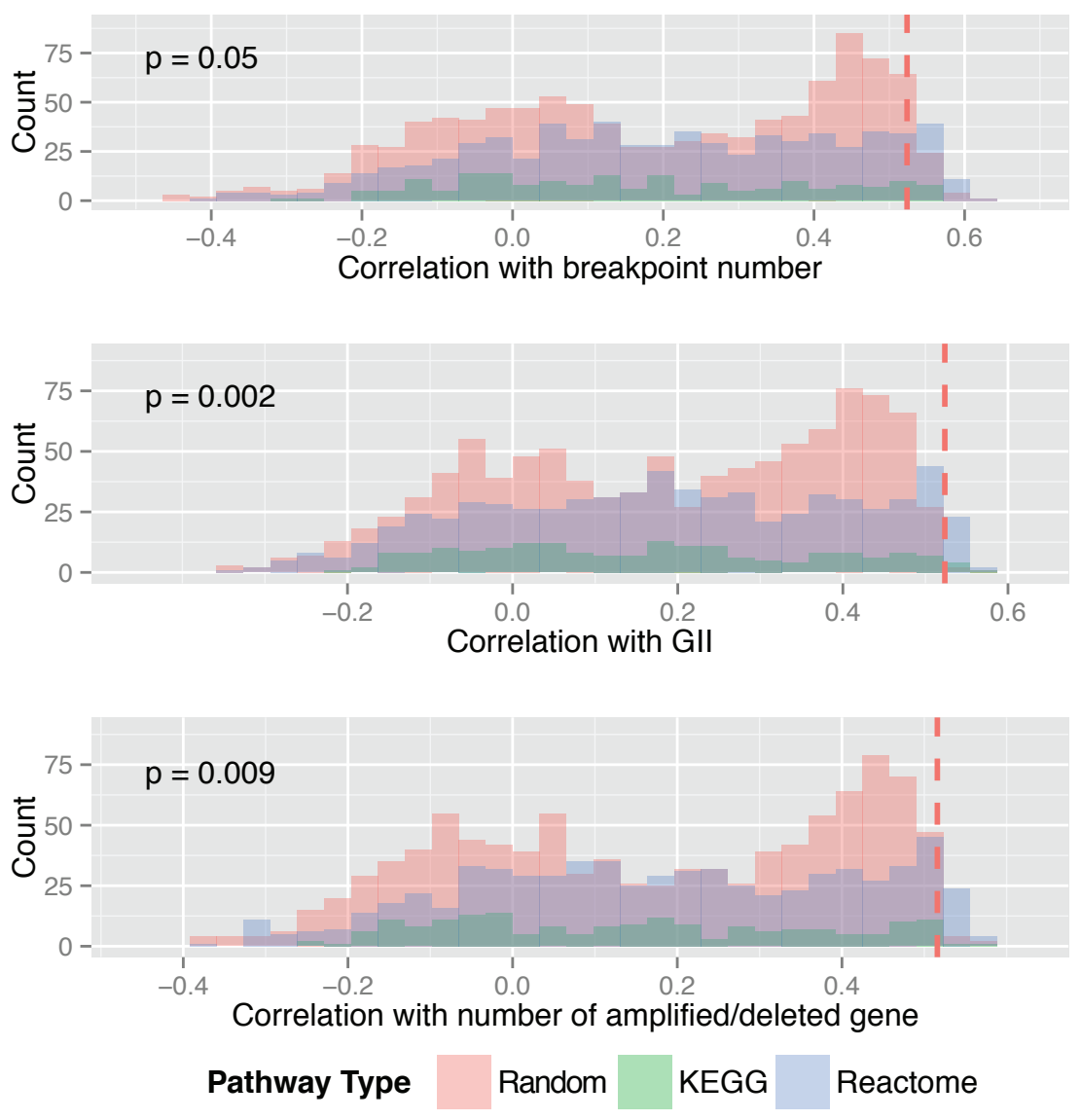

Basal−like
HER2
Luminal A
Luminal B
Normal−like
Number of breaks
GII
Number of genes with CNA
Low
High
HR score group


Basal−like
HER2
Luminal A
Luminal B
Normal−like
Number of breaks
GII
Number of genes with CNA
Low
High
ns
HR score group


Basal−like
HER2
Luminal A
Luminal B
Normal−like
Number of breaks
GII
Number of genes with CNA
Low
High
***
**
*
ns
HR score group


p < 0.001
Count
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
0.6
Correlation with number of breakpoints
p = 0.002
Count
90
60
30
0
−0.2
0.0
0.2
0.4
Correlation with GII
p < 0.001
Count
90
60
30
0
−0.4
−0.2
0.0
0.2
0.4
Correlation with number of amplified/deleted genes
Pathway Type
Random
KEGG
Reactome


p = 0.028
Count
100
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
0.6
Correlation with breakpoint number
p = 0.004
Count
100
50
0
−0.2
0.0
0.2
0.4
0.6
Correlation with GII
p = 0.007
Count
100
50
0
−0.4
−0.2
0.0
0.2
0.4
Correlation with number of amplified/deleted gene
Pathway Type
Random
KEGG
Reactome


p = 0.05
Count
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
0.6
Correlation with breakpoint number
p = 0.002
Count
75
50
25
0
−0.2
0.0
0.2
0.4
0.6
Correlation with GII
p = 0.009
Count
75
50
25
0
−0.4
−0.2
0.0
0.2
0.4
Correlation with number of amplified/deleted gene
Pathway Type
Random
KEGG
Reactome