OpenTargetsDatathonRNotebook

March 7, 2018

1 BioData West Open Targets Datathon

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1.1 Introduction

There has been exponential growth in the genomic data being produced to yield new insights into biology, and particularly with the intent to understand the role of genes and proteins and pathways in disease. Despite this, selecting protein targets for drug discovery still seems more of an art, guided by intuition and influenced by cognitive biases, than a reproducible science. Open Targets was established to bring the data and science together in a pre-competitive environment to help foster better early discovery decision making. In this dual session, we will introduce and engage the participants to the science of target selection. In this datathon, you will be introduced to the evidence types Open Targets is currently using to established relationships between genes and disease to aid in selecting and validating prospective drug targets.

You will be introduced to several genomic and gene-disease data sources. You are tasked with exploring methods for using these data for predicting drug development success. Insights and feedback from among the participants will be collated and shared, and may be used in future development of the Open Targets platform.

Prior to the datathon, you are encouraged to download the data files, view the example analysis notebooks available in R and Python, and review the data documentation. A brief summary will be provided during the introductory session and researchers from Open Targets and GSK will be on hand to answer any questions you may have.

At the datathon, you will be divided into small groups where you can work individually or jointly to explore these data, their relationships to development outcomes, and methods of modeling them to predict outcomes. At the end of the datathon, groups will be invited to share their experiences and discuss potential next steps. You are welcome to use whatever analysis tools you prefer for this analysis exercise.

1.2 Data Import

The three primary datathon files are summarized below. You can find a more complete description of each data file and the variables within them at the datathon Wiki site.

Note about neoplasm versus non-neoplasm indications: Because the genomic evidence that may be important for neoplasms may be very different than for non-neoplasms, we restrict this summary of the data to non-neoplasm data only.

```
In [2]: ## Load packages to use
        library(ggplot2)
        library(tidyr)
        library(dplyr)
```

```
Attaching package: 'dplyr'

The following objects are masked from 'package:stats':

    filter, lag

The following objects are masked from 'package:base':

    intersect, setdiff, setequal, union
```

1.2.1 Pharmaprojects data

The first data file, Pprojects_drugs_TTlabel.csv, is derived from Informa Pharmaprojects, a commercial database tracking the development of over 68,000 drugs over the past several decades. Researchers at GSK have carefully processed and curated this database to create a summary of all target-indication pairs (T-I) that have entered clinical development, tracking the furthest stage of development achieved. A T-I is considered successful if any drug annotated to act through the selected target was approved for the accompanying indication. Further details are available on the See the datathon Wiki site for details. The objective of this datathon is to identify the genomic factors that predict successful T-Is (for example, see the related paper by Nelson et al. 2015). Informa has permitted us to make these data freely available to the datathon participants during the course of this datathon. They must be permanently deleted after the datathon work is completed, as agreed in the survey. We have identified 80%/20% of T-Is as a training set and test set. We encourage any participants interested in exploring predictive models to use them as such.

```
In [3]: pp.data = read.csv("Pprojects_drugs_TTlabel.csv",
                           na.strings = c("NA", ""), header = TRUE) %>%
          filter(DiseaseType %in% "Non-Neoplasm") %>%
          rename(key = target_indication)
```

```
In [4]: summary(pp.data)
```

```
                           key              ensembl_gene_id       disease_id
 ENSG00000000971-EFO_0000253 :   1   ENSG00000113580:  97   EFO_0000685: 171
 ENSG00000001626-EFO_0000555 :   1   ENSG00000073756:  85   EFO_0000676: 158
 ENSG00000001626-HP_0002014  :   1   ENSG00000095303:  79   EFO_0000198: 138
 ENSG00000001626-Orphanet_586:   1   ENSG00000065989:  63   EFO_0003843: 128
 ENSG00000001630-EFO_0003914 :   1   ENSG00000184588:  61   EFO_0000270: 126
 ENSG00000003436-EFO_0001420 :   1   ENSG00000105650:  59   EFO_0000249: 113
 (Other)                     :7874   (Other)        :7436   (Other)    :7046
   entrez_id            MeSH_ID           DiseaseType
```

```
Min.   :        2   D001172: 171   Neoplasm    :   0
1st Qu.:     1815   D011565: 158   Non-Neoplasm:7880
Median :     3596   D009190: 138
Mean   :    35198   D001249: 126
3rd Qu.:     5743   D000544: 113
Max.   :100133941   D003924: 110
                    (Other):7064
           Clinical.Label_PP            Furthest.Phase
Clinical Failure    :4160    Clinical Phase I  :1635
In Progress Clinical:1820    Clinical Phase II :3290
Succeeded           :1900    Clinical Phase III:1005
                             Succeeded         :1900
                             Withdrawn         :  50


     Therapeutic.Direction Indication.with.First.Clinical.Outcome.for.Target
Activator       :1768      N:7165
Inhibitor       :4435      Y: 715
Mixed or Unknown:1677


                           Types.of.Assets Suggested.Dataset.Utility
Non-Selective Assets              :2835   Neither :7167
Selective and Non-Selective Assets:1635   Test    : 154
Selective Assets                  :3410   Training: 559
```

1.2.2 Open Targets Evidence Scores

The second dataset are the evidence scores that are available through the Open Targets Portal. See the datathon Wiki pages for details.

The data file provided includes target evidence scores for all target-indication combinations available in the Open Targets database (over 2.3 million). As the focus of this exercise is to predict clinical success of target-indication pairs, I have imported the large data file and saved the overlap with Pharmaprojects as a separate, much smaller data set.

```
In [5]: ## Create a small dataset matched to pp.data
        #ot.data.all = read.csv("gene_disease_associations_datatypes_with_expression.csv",
        #                        na.strings = c("NA", ""), header = TRUE)
        #write.table(subset(ot.data.all, key %in% pp.data$target_indication),
        #            file = "PP_gene_disease_associations_datatypes_with_expression.csv",
        #            sep = ",", na = "NA",
```

```
#             row.names = FALSE)
```

In [6]:
```
ot.data <- read.csv("PP_gene_disease_associations_datatypes_with_expression.csv",
                    na.strings = c("NA", ""), header = TRUE)
dim(ot.data)
summary(ot.data)
```

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```
                            key         entrez_id
 ENSG00000000971-EFO_0000253   :   1   Min.   :        2
 ENSG00000001626-EFO_0000555   :   1   1st Qu.:     1815
 ENSG00000001626-HP_0002014    :   1   Median :     3588
 ENSG00000001626-Orphanet_586  :   1   Mean   :    29582
 ENSG00000003436-Orphanet_903  :   1   3rd Qu.:     5743
 ENSG00000003436-Orphanet_98878:   1   Max.   :100133941
 (Other)                       :5084
       ensembl_gene_id     symbol           disease_id
 ENSG00000113580:  72   NR3C1  :  72   EFO_0000685: 148
 ENSG00000073756:  71   PTGS2  :  71   EFO_0000676: 135
 ENSG00000095303:  56   PTGS1  :  56   EFO_0000270: 116
 ENSG00000232810:  51   TNF    :  51   EFO_0003843: 115
 ENSG00000149295:  46   DRD2   :  46   EFO_0000198: 102
 ENSG00000113448:  36   PDE4B  :  36   EFO_0000249:  98
 (Other)        :4758   (Other):4758   (Other)    :4376
                  disease_label
 rheumatoid arthritis    : 148
 psoriasis               : 135
 asthma                  : 116
 pain                    : 115
 myelodysplastic syndrome: 102
 Alzheimers disease      :  98
 (Other)                 :4376
                                       therapeutic_area is_direct
 phenotype                                    : 739    False: 311
 nervous system disease; other disease        : 591    True :4779
 cardiovascular disease                       : 471
 immune system disease; skeletal system disease: 300
 respiratory system disease                   : 277
 (Other)                                      :2484
 NA's                                         : 228
 genetic_association somatic_mutation    known_drug       rna_expression
 Min.   :0.0000118   Min.   :0.00000   Min.   :0.000000   Min.   :0.0000
 1st Qu.:0.0563836   1st Qu.:0.00000   1st Qu.:0.000000   1st Qu.:0.0000
 Median :0.2247230   Median :0.00000   Median :0.000000   Median :0.2000
 Mean   :0.4653398   Mean   :0.06326   Mean   :0.005106   Mean   :0.3826
 3rd Qu.:1.0000000   3rd Qu.:0.00000   3rd Qu.:0.000000   3rd Qu.:1.0000
 Max.   :1.5124629   Max.   :1.49410   Max.   :1.010602   Max.   :1.0000
```

```
 affected_pathway     animal_model        literature
 Min.   :0.0000000   Min.   :0.000000   Min.   :0.000000
 1st Qu.:0.0000000   1st Qu.:0.000000   1st Qu.:0.000000
 Median :0.0000000   Median :0.000000   Median :0.000000
 Mean   :0.0001652   Mean   :0.009285   Mean   :0.008681
 3rd Qu.:0.0000000   3rd Qu.:0.000000   3rd Qu.:0.000000
 Max.   :0.0471697   Max.   :1.000000   Max.   :0.314590

                              tissue_label          source
 Unspecified                         :4636   GTExv6     : 454
 Lung                                :  44   Unspecified:4636
 Small Intestine - Terminal Ileum    :  34
 Nerve - Tibial                      :  29
 Skin - Not Sun Exposed (Suprapubic):  29
 Adipose - Subcutaneous              :  25
 (Other)                             : 293
 max_fold_change    expression_score
 Min.   :    0.00   Min.   :0.00000
 1st Qu.:    0.00   1st Qu.:0.00000
 Median :    0.00   Median :0.00000
 Mean   :   31.99   Mean   :0.04244
 3rd Qu.:    0.00   3rd Qu.:0.00000
 Max.   :23708.28   Max.   :0.99000
```

1.2.3 Open Targets Data Broken Down To Specific Data Sources

See the datathon Wiki page for details.

As above, the subset of this data set that overlaps with Pharmaprojects has been saved.

```
In [7]: ## Create a small dataset matched to pp.data
        ##otsource.data.all = read.csv("gene_disease_associations_datasources_with_expression.
        ##                              na.strings = c("NA", ""), header = TRUE)
        ##write.table(subset(otsource.data.all, key %in% pp.data$target_indication),
        ##            file = "PP_gene_disease_associations_datasources_with_expression.csv",
        ##            sep = ",", na = "NA",
        ##            row.names = FALSE)
```

```
In [8]: otsource.data <- read.csv("PP_gene_disease_associations_datasources_with_expression.csv
                                 na.strings = c("NA", ""), header = TRUE)
        dim(otsource.data)
        summary(otsource.data)
```

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```
                              key          entrez_id
 ENSG00000000971-EFO_0000253   :   1   Min.   :        2
```

```
ENSG00000001626-EFO_0000555   :   1   1st Qu.:     1815
ENSG00000001626-HP_0002014    :   1   Median :     3588
ENSG00000001626-Orphanet_586  :   1   Mean   :    29582
ENSG00000003436-Orphanet_903  :   1   3rd Qu.:     5743
ENSG00000003436-Orphanet_98878:   1   Max.   :100133941
(Other)                       :5084
       ensembl_gene_id     symbol           disease_id
ENSG00000113580:  72   NR3C1  :  72   EFO_0000685: 148
ENSG00000073756:  71   PTGS2  :  71   EFO_0000676: 135
ENSG00000095303:  56   PTGS1  :  56   EFO_0000270: 116
ENSG00000232810:  51   TNF    :  51   EFO_0003843: 115
ENSG00000149295:  46   DRD2   :  46   EFO_0000198: 102
ENSG00000113448:  36   PDE4B  :  36   EFO_0000249:  98
(Other)        :4758   (Other):4758   (Other)    :4376
                 disease_label
rheumatoid arthritis    : 148
psoriasis               : 135
asthma                  : 116
pain                    : 115
myelodysplastic syndrome: 102
Alzheimers disease      :  98
(Other)                 :4376
                                       therapeutic_area is_direct
phenotype                                     : 739    False: 311
nervous system disease; other disease         : 591    True :4779
cardiovascular disease                        : 471
immune system disease; skeletal system disease: 300
respiratory system disease                    : 277
(Other)                                       :2484
NA's                                          : 228
expression_atlas       uniprot            gwas_catalog     phewas_catalog
Min.   :0.0000118   Min.   :0.0000000   Min.   :0.00000   Min.   :0.00000
1st Qu.:0.0563836   1st Qu.:0.0000000   1st Qu.:0.00000   1st Qu.:0.00000
Median :0.2247230   Median :0.0000000   Median :0.00000   Median :0.00000
Mean   :0.4653398   Mean   :0.0001652   Mean   :0.01769   Mean   :0.02331
3rd Qu.:1.0000000   3rd Qu.:0.0000000   3rd Qu.:0.00000   3rd Qu.:0.00000
Max.   :1.5124629   Max.   :0.0471697   Max.   :1.00000   Max.   :1.00000

     eva           uniprot_literature genomics_england  gene2phenotype
Min.   :0.000000   Min.   :0.00000    Min.   :0.00000   Min.   :0.00000
1st Qu.:0.000000   1st Qu.:0.00000    1st Qu.:0.00000   1st Qu.:0.00000
Median :0.000000   Median :0.00000    Median :0.00000   Median :0.00000
Mean   :0.000194   Mean   :0.02061    Mean   :0.02338   Mean   :0.02279
3rd Qu.:0.000000   3rd Qu.:0.00000    3rd Qu.:0.00000   3rd Qu.:0.00000
Max.   :0.194296   Max.   :1.00000    Max.   :1.00000   Max.   :1.00000

   reactome          slapenrich         phenodigm        cancer_gene_census
Min.   :0.000000   Min.   :0.000000   Min.   :0.000000   Min.   :0.000000
```

```
 1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.000000
 Median :0.000000   Median :0.000000   Median :0.000000   Median :0.000000
 Mean   :0.006287   Mean   :0.005697   Mean   :0.003588   Mean   :0.008681
 3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.000000
 Max.   :1.000000   Max.   :1.000000   Max.   :0.802229   Max.   :0.314590

  eva_somatic       uniprot_somatic        intogen             chembl
 Min.   :0.000000   Min.   :0.0000000   Min.   :0.0000000   Min.   :0.0000000
 1st Qu.:0.000000   1st Qu.:0.0000000   1st Qu.:0.0000000   1st Qu.:0.0000000
 Median :0.000000   Median :0.0000000   Median :0.0000000   Median :0.0000000
 Mean   :0.004747   Mean   :0.0007955   Mean   :0.0001091   Mean   :0.0001091
 3rd Qu.:0.000000   3rd Qu.:0.0000000   3rd Qu.:0.0000000   3rd Qu.:0.0000000
 Max.   :0.813372   Max.   :0.8131173   Max.   :0.5555556   Max.   :0.4166667

   europepmc                                    tissue_label          source
 Min.   :0.0000   Unspecified                         :4636   GTExv6     : 454
 1st Qu.:0.0000   Lung                                :  44   Unspecified:4636
 Median :0.2000   Small Intestine - Terminal Ileum    :  34
 Mean   :0.3826   Nerve - Tibial                      :  29
 3rd Qu.:1.0000   Skin - Not Sun Exposed (Suprapubic):  29
 Max.   :1.0000   Adipose - Subcutaneous              :  25
                  (Other)                             : 293
 max_fold_change    expression_score
 Min.   :    0.00   Min.   :0.00000
 1st Qu.:    0.00   1st Qu.:0.00000
 Median :    0.00   Median :0.00000
 Mean   :   31.99   Mean   :0.04244
 3rd Qu.:    0.00   3rd Qu.:0.00000
 Max.   :23708.28   Max.   :0.99000
```

1.2.4 Additional Gene Characteristics of Interest

In addition to the current Open Targets evidence scores, we include a number of other genomic characteristics that may be insightful in differentiating between effective and ineffective mechanisms. See the datathon Wiki pages for details.

```
In [9]: ##gene.data.all <- read.csv("gene_info_qtq.csv",
        ##                          na.strings = c("NA", ""), header = TRUE)
        ##write.table(subset(gene.data.all, entrez_id %in% pp.data$entrez_id),
        ##            file = "PP_gene_info_qtq.csv", sep = ",", na = "NA",
        ##            row.names = FALSE)
```

```
In [10]: gene.data <- read.csv("PP_gene_info_qtq.csv",
                               na.strings = c("NA", ""), header = TRUE) %>%
           select(-X, -hgnc_id, -ensembl_gene_id, -uniprot_id)
         dim(gene.data)
```

```
length(unique(gene.data$entrez_id))
summary(gene.data)
```

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1108

```
    symbol        entrez_id                                locus_type
JAK2    :  248   Min.   :        2   endogenous retrovirus     :    7
TGFB1   :  231   1st Qu.:     1815   gene with protein product :40486
CTNNB1  :  218   Median :     3757   immunoglobulin gene       :   17
AKT1    :  179   Mean   :    96704   RNA, micro                :    5
SIRT1   :  177   3rd Qu.:     6387   RNA, misc                 :    1
(Other):39464   Max.   :100133941   T-cell receptor gene      :    1
NA's    :    1                       T-cell receptor pseudogene:    1
             locus_group           go_id
non-coding RNA     :    6   GO:0005886:  842
other              :   25   GO:0005515:  775
protein-coding gene:40486   GO:0005829:  456
pseudogene         :    1   GO:0005576:  390
                            GO:0005887:  358
                            (Other)   :37686
                            NA's      :   11
                                 go_label     evidence_type
plasma membrane                      :  842   IEA    :10934
protein binding                      :  775   IDA    : 9039
cytosol                              :  456   TAS    : 7854
extracellular region                 :  390   ISS    : 3414
integral component of plasma membrane:  358   IMP    : 3058
(Other)                              :37686   (Other): 6208
NA's                                 :   11   NA's   :   11
reported_count                protein_class                target_class
Min.   :  1.000   Enzyme              : 3789   Enzyme_all_others   : 7315
1st Qu.:  1.000   Unclassified protein: 3346   Kinase_Protein      : 6689
Median :  1.000   Secreted protein    : 2175   Extracellular Ligand: 4568
Mean   :  1.673   Membrane receptor   : 1548   Receptor_all_others : 4324
3rd Qu.:  1.000   Transcription factor:  693   7TM_Group1          : 3613
Max.   :453.000   (Other)             :22284   (Other)             :14001
NA's   :11        NA's                : 6683   NA's                :    8
   topology_type    target_location              ExAC_LoF
Membrane  : 4314   Exposed  :15753   Intolerant to LoF:14716
MultiTM   : 8653   Nucleus  : 8200   Missing          :  794
Secreted  : 7519   Free     : 7519   Tolerant to LoF  : 6810
SingleTM  : 6962   Organelle: 4123   Unclassified     :18190
Unattached:13062   Cytoplasm: 3255   NA's             :    8
NA's      :    8   (Other)  : 1660
                   NA's     :    8
pc_mouse_gene_identity GTEX_median_all_tissues
Min.   :  0.00         Min.   :    0.00
```

```
 1st Qu.: 77.62         1st Qu.:    0.50
 Median : 88.10         Median :    3.77
 Mean   : 83.37         Mean   :   28.21
 3rd Qu.: 94.59         3rd Qu.:   17.74
 Max.   :100.00         Max.   :10056.00
 NA's   :8              NA's   :8
                            description
 Janus kinase 2                    :  248
 transforming growth factor beta 1:  231
 catenin beta 1                    :  218
 AKT serine/threonine kinase 1     :  179
 sirtuin 1                         :  177
 (Other)                           :39457
 NA's                              :    8
```

Most of the descriptors in this data set have a single value for each gene. We create a simplified version for analysis by reducing this data set to the first occurance of each each.

```
In [11]: ugene.data <- gene.data %>%
             subset(!duplicated(symbol))
```

1.2.5 Merge data into single data frame for analysis

```
In [12]: all.data <- pp.data %>%
             filter(Clinical.Label_PP %in% c("Clinical Failure",
                                             "Succeeded")) %>%
             inner_join(ot.data) %>%
             left_join(otsource.data) %>%
             left_join(ugene.data)
         all.data = all.data %>%
             mutate(clinical.outcome =
                    droplevels(recode_factor(Clinical.Label_PP,
                                             `Clinical Failure` = "Failure",
                                             `Succeeded` = "Success")))
         dim(all.data)
         summary(all.data)
```

```
Joining, by = c("key", "ensembl_gene_id", "disease_id", "entrez_id")
Warning message:
"Column `key` joining factors with different levels, coercing to character vector"Warning messa
"Column `ensembl_gene_id` joining factors with different levels, coercing to character vector"
"Column `disease_id` joining factors with different levels, coercing to character vector"Joini
Warning message:
"Column `key` joining character vector and factor, coercing into character vector"Warning messa
"Column `ensembl_gene_id` joining character vector and factor, coercing into character vector"
"Column `disease_id` joining character vector and factor, coercing into character vector"Joini
Warning message:
"Column `symbol` joining factors with different levels, coercing to character vector"
```

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```
    key            ensembl_gene_id     disease_id          entrez_id
Length:4047        Length:4047        Length:4047        Min.   :        2
Class :character   Class :character   Class :character   1st Qu.:     1813
Mode  :character   Mode  :character   Mode  :character   Median :     3559
                                                         Mean   :    33468
                                                         3rd Qu.:     5742
                                                         Max.   :100133941

   MeSH_ID           DiseaseType              Clinical.Label_PP
D001172: 128   Neoplasm    :   0   Clinical Failure    :2757
D011565: 114   Non-Neoplasm:4047   In Progress Clinical:   0
D001249: 104                       Succeeded           :1290
D000544:  73
D003924:  73
D006973:  68
(Other):3487
           Furthest.Phase      Therapeutic.Direction
Clinical Phase I  : 777   Activator       : 845
Clinical Phase II :1492   Inhibitor       :2239
Clinical Phase III: 454   Mixed or Unknown: 963
Succeeded         :1290
Withdrawn         :  34


Indication.with.First.Clinical.Outcome.for.Target
N:3528
Y: 519




                         Types.of.Assets Suggested.Dataset.Utility
Non-Selective Assets              :1237   Neither :3528
Selective and Non-Selective Assets:1242   Test    : 116
Selective Assets                  :1568   Training: 403




   symbol                             disease_label
Length:4047        rheumatoid arthritis     : 128
Class :character   psoriasis                : 114
Mode  :character   asthma                   : 104
                   pain                     : 102
                   Alzheimers disease       :  73
```

```
                  type II diabetes mellitus:  73
                  (Other)                   :3453
                                        therapeutic_area is_direct
phenotype                                        : 634    False: 258
nervous system disease; other disease            : 517    True :3789
cardiovascular disease                           : 406
immune system disease; skeletal system disease: 230
respiratory system disease                       : 222
(Other)                                          :1839
NA's                                             : 199
genetic_association somatic_mutation    known_drug       rna_expression
Min.   :0.0000118   Min.   :0.00000   Min.   :0.000000   Min.   :0.0000
1st Qu.:0.0612497   1st Qu.:0.00000   1st Qu.:0.000000   1st Qu.:0.0000
Median :0.2611111   Median :0.00000   Median :0.000000   Median :0.2000
Mean   :0.5048597   Mean   :0.06269   Mean   :0.004864   Mean   :0.4255
3rd Qu.:1.0049113   3rd Qu.:0.00000   3rd Qu.:0.000000   3rd Qu.:1.0000
Max.   :1.5124629   Max.   :1.49410   Max.   :1.010602   Max.   :1.0000

affected_pathway     animal_model       literature
Min.   :0.0000000   Min.   :0.00000   Min.   :0.000000
1st Qu.:0.0000000   1st Qu.:0.00000   1st Qu.:0.000000
Median :0.0000000   Median :0.00000   Median :0.000000
Mean   :0.0001736   Mean   :0.01034   Mean   :0.009063
3rd Qu.:0.0000000   3rd Qu.:0.00000   3rd Qu.:0.000000
Max.   :0.0313116   Max.   :1.00000   Max.   :0.314590

                            tissue_label          source
Unspecified                       :3671   GTExv6     : 376
Lung                              :  35   Unspecified:3671
Nerve - Tibial                    :  24
Skin - Not Sun Exposed (Suprapubic):  23
Artery - Aorta                    :  22
Brain - Frontal Cortex (BA9)      :  22
(Other)                           : 250
max_fold_change    expression_score  expression_atlas       uniprot
Min.   :    0.00   Min.   :0.00000   Min.   :0.0000118   Min.   :0.0000000
1st Qu.:    0.00   1st Qu.:0.00000   1st Qu.:0.0612497   1st Qu.:0.0000000
Median :    0.00   Median :0.00000   Median :0.2611111   Median :0.0000000
Mean   :   26.19   Mean   :0.04418   Mean   :0.5048597   Mean   :0.0001736
3rd Qu.:    0.00   3rd Qu.:0.00000   3rd Qu.:1.0049113   3rd Qu.:0.0000000
Max.   :10791.95   Max.   :0.98000   Max.   :1.5124629   Max.   :0.0313116

 gwas_catalog     phewas_catalog         eva             uniprot_literature
Min.   :0.00000   Min.   :0.00000   Min.   :0.0000000   Min.   :0.0000
1st Qu.:0.00000   1st Qu.:0.00000   1st Qu.:0.0000000   1st Qu.:0.0000
Median :0.00000   Median :0.00000   Median :0.0000000   Median :0.0000
Mean   :0.01858   Mean   :0.02261   Mean   :0.0002321   Mean   :0.0203
3rd Qu.:0.00000   3rd Qu.:0.00000   3rd Qu.:0.0000000   3rd Qu.:0.0000
```

```
Max.   :1.00000   Max.   :1.00000   Max.   :0.1942961   Max.   :1.0000

genomics_england  gene2phenotype       reactome          slapenrich
Min.   :0.00000   Min.   :0.00000   Min.   :0.000000   Min.   :0.00000
1st Qu.:0.00000   1st Qu.:0.00000   1st Qu.:0.000000   1st Qu.:0.00000
Median :0.00000   Median :0.00000   Median :0.000000   Median :0.00000
Mean   :0.02347   Mean   :0.02224   Mean   :0.006177   Mean   :0.00593
3rd Qu.:0.00000   3rd Qu.:0.00000   3rd Qu.:0.000000   3rd Qu.:0.00000
Max.   :1.00000   Max.   :1.00000   Max.   :1.000000   Max.   :1.00000

  phenodigm        cancer_gene_census  eva_somatic       uniprot_somatic
Min.   :0.000000   Min.   :0.000000   Min.   :0.000000   Min.   :0.0000000
1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.000000   1st Qu.:0.0000000
Median :0.000000   Median :0.000000   Median :0.000000   Median :0.0000000
Mean   :0.004409   Mean   :0.009063   Mean   :0.004562   Mean   :0.0004755
3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.000000   3rd Qu.:0.0000000
Max.   :0.802229   Max.   :0.314590   Max.   :0.813372   Max.   :0.8131173

   intogen             chembl            europepmc
Min.   :0.0000000   Min.   :0.0000000   Min.   :0.0000
1st Qu.:0.0000000   1st Qu.:0.0000000   1st Qu.:0.0000
Median :0.0000000   Median :0.0000000   Median :0.2000
Mean   :0.0001373   Mean   :0.0001373   Mean   :0.4255
3rd Qu.:0.0000000   3rd Qu.:0.0000000   3rd Qu.:1.0000
Max.   :0.5555556   Max.   :0.4166667   Max.   :1.0000

                     locus_type                locus_group          go_id
endogenous retrovirus     :   0   non-coding RNA     :   0   GO:0009897: 188
gene with protein product :4042   other              :   5   GO:0005737: 178
immunoglobulin gene       :   5   protein-coding gene:4042   GO:0004252: 153
RNA, micro                :   0   pseudogene         :   0   GO:0000187: 128
RNA, misc                 :   0                              GO:0005088:  85
T-cell receptor gene      :   0                              (Other)   :3310
T-cell receptor pseudogene:   0                              NA's      :   5
                                          go_label    evidence_type
external side of plasma membrane             : 188   IEA    :1254
cytoplasm                                    : 178   IDA    : 790
serine-type endopeptidase activity           : 153   TAS    : 741
activation of MAPK activity                  : 128   ISS    : 459
Ras guanyl-nucleotide exchange factor activity:  85   IMP    : 252
(Other)                                      :3310   (Other): 546
NA's                                         :   5   NA's   :   5
reported_count              protein_class                target_class
Min.   : 1.000   Secreted protein  : 238   7TM_Group1          : 994
1st Qu.: 1.000   Oxidoreductase    : 225   Enzyme_all_others   : 535
Median : 1.000   Membrane receptor : 219   Receptor_all_others : 440
Mean   : 1.192   Enzyme            : 184   Ion Channel         : 384
3rd Qu.: 1.000   Serotonin receptor: 145   Extracellular Ligand: 310
```

```
Max.   :15.000   (Other)           :2747   Kinase_Protein      : 240
NA's   :5        NA's              : 289   (Other)             :1144
   topology_type       target_location             ExAC_LoF
Membrane  : 354   Cytoplasm    : 212   Intolerant to LoF:1164
MultiTM   :1744   Exposed      :2172   Missing          :  95
Secreted  : 594   Free         : 594   Tolerant to LoF  : 696
SingleTM  : 605   Mitochondrion: 155   Unclassified     :2092
Unattached: 750   Nucleus      : 430
                  Organelle    : 484
                  Unknown      :   0
pc_mouse_gene_identity GTEX_median_all_tissues
Min.   :  0.00         Min.   :   0.00
1st Qu.: 77.87         1st Qu.:   0.11
Median : 87.31         Median :   0.87
Mean   : 82.68         Mean   :  10.69
3rd Qu.: 93.49         3rd Qu.:   5.20
Max.   :100.00         Max.   :1488.58

                                        description   clinical.outcome
nuclear receptor subfamily 3 group C member 1:  68   Failure:2757
prostaglandin-endoperoxide synthase 2        :  68   Success:1290
prostaglandin-endoperoxide synthase 1        :  54
tumor necrosis factor                        :  49
dopamine receptor D2                         :  41
5-hydroxytryptamine receptor 1A              :  33
(Other)                                      :3734
```

1.3 Data Exploration

1.3.1 Quantitative Open Targets scores

Put data into a long format to permit trellised ggplots

```
In [13]: id.vars = c('key', 'symbol', 'disease_label')
         outcome.vars = c('Clinical.Label_PP', 'Furthest.Phase',
                          'Therapeutic.Direction', 'clinical.outcome')
         ot.scores = c('genetic_association',
                       'known_drug', 'rna_expression',
                     'affected_pathway', 'animal_model', 'literature')
         otsrc.scores = c('expression_atlas', 'uniprot', 'gwas_catalog',
                          'phewas_catalog',
                          'eva', 'uniprot_literature', 'genomics_england',
                          'gene2phenotype',
                          'reactome', 'slapenrich', 'phenodigm', 'europepmc',
                          'expression_score')
         gene.qvars = c('pc_mouse_gene_identity', 'GTEX_median_all_tissues')
         gene.cvars = c('protein_class', 'target_class', 'topology_type',
                        'target_location', 'ExAC_LoF')
```

```
In [14]: all.long = gather(all.data[, c(id.vars, outcome.vars, ot.scores,
                                        otsrc.scores, gene.qvars)],
                           datasource, score,
                           genetic_association:GTEX_median_all_tissues,
                           factor_key = TRUE)
         ot.long = gather(all.data[, c(id.vars, outcome.vars, ot.scores,
                                       otsrc.scores)],
                          datasource, score,
                          genetic_association:expression_score,
                          factor_key = TRUE)
```

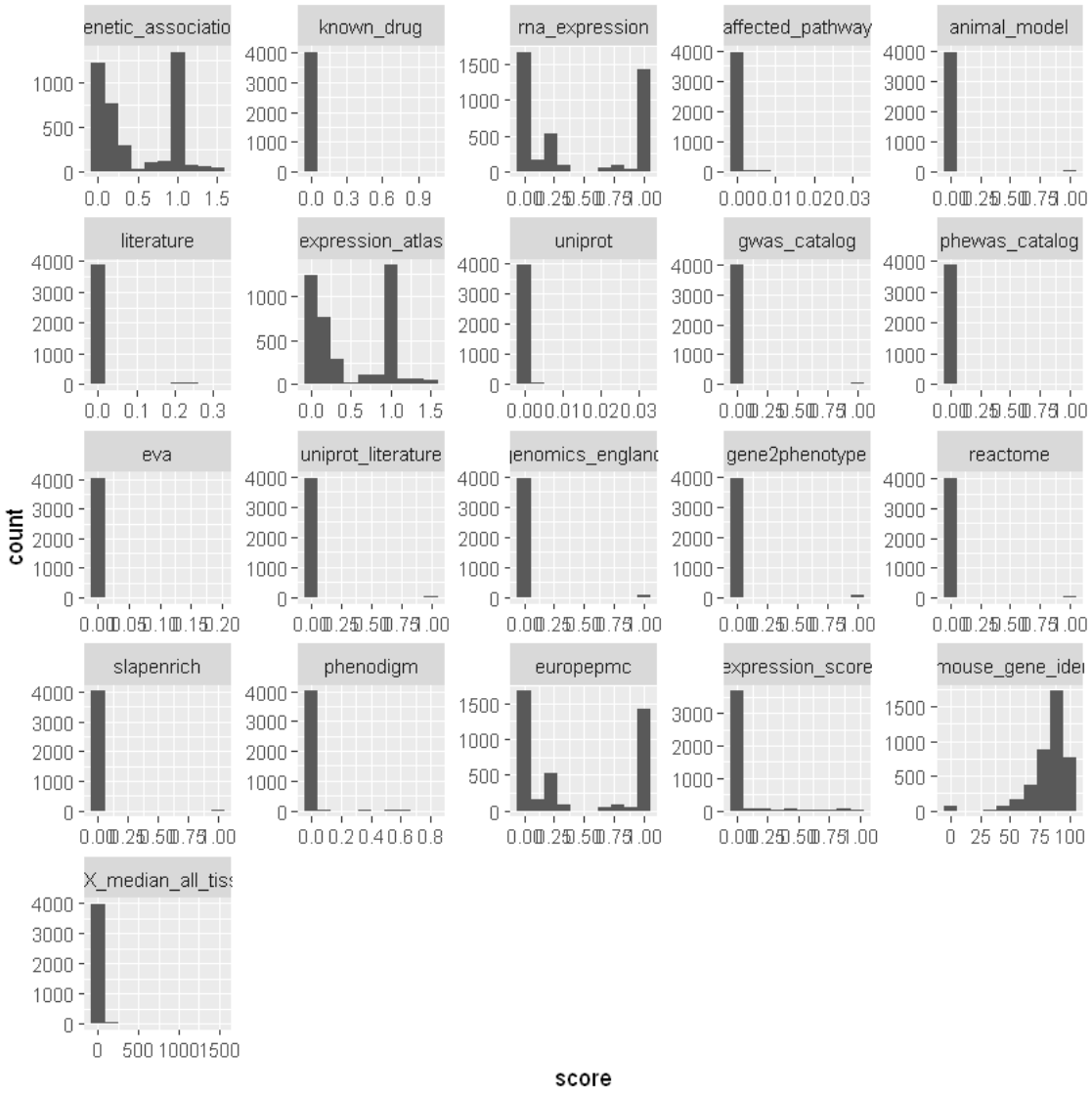
```
In [15]: dim(ot.long)
         summary(ot.long)
```

1. 76893 2. 9

```
     key                symbol                            disease_label
 Length:76893       Length:76893       rheumatoid arthritis     : 2432
 Class :character   Class :character   psoriasis                : 2166
 Mode  :character   Mode  :character   asthma                   : 1976
                                       pain                     : 1938
                                       Alzheimers disease       : 1387
                                       type II diabetes mellitus: 1387
                                       (Other)                  :65607
            Clinical.Label_PP            Furthest.Phase
 Clinical Failure    :52383   Clinical Phase I  :14763
 In Progress Clinical:    0   Clinical Phase II :28348
 Succeeded           :24510   Clinical Phase III: 8626
                              Succeeded         :24510
                              Withdrawn         :  646


      Therapeutic.Direction clinical.outcome               datasource
 Activator       :16055     Failure:52383    genetic_association: 4047
 Inhibitor       :42541     Success:24510    known_drug         : 4047
 Mixed or Unknown:18297                      rna_expression     : 4047
                                             affected_pathway   : 4047
                                             animal_model       : 4047
                                             literature         : 4047
                                             (Other)            :52611
     score
 Min.   :0.0000
 1st Qu.:0.0000
 Median :0.0000
 Mean   :0.1081
 3rd Qu.:0.0000
 Max.   :1.5125
```

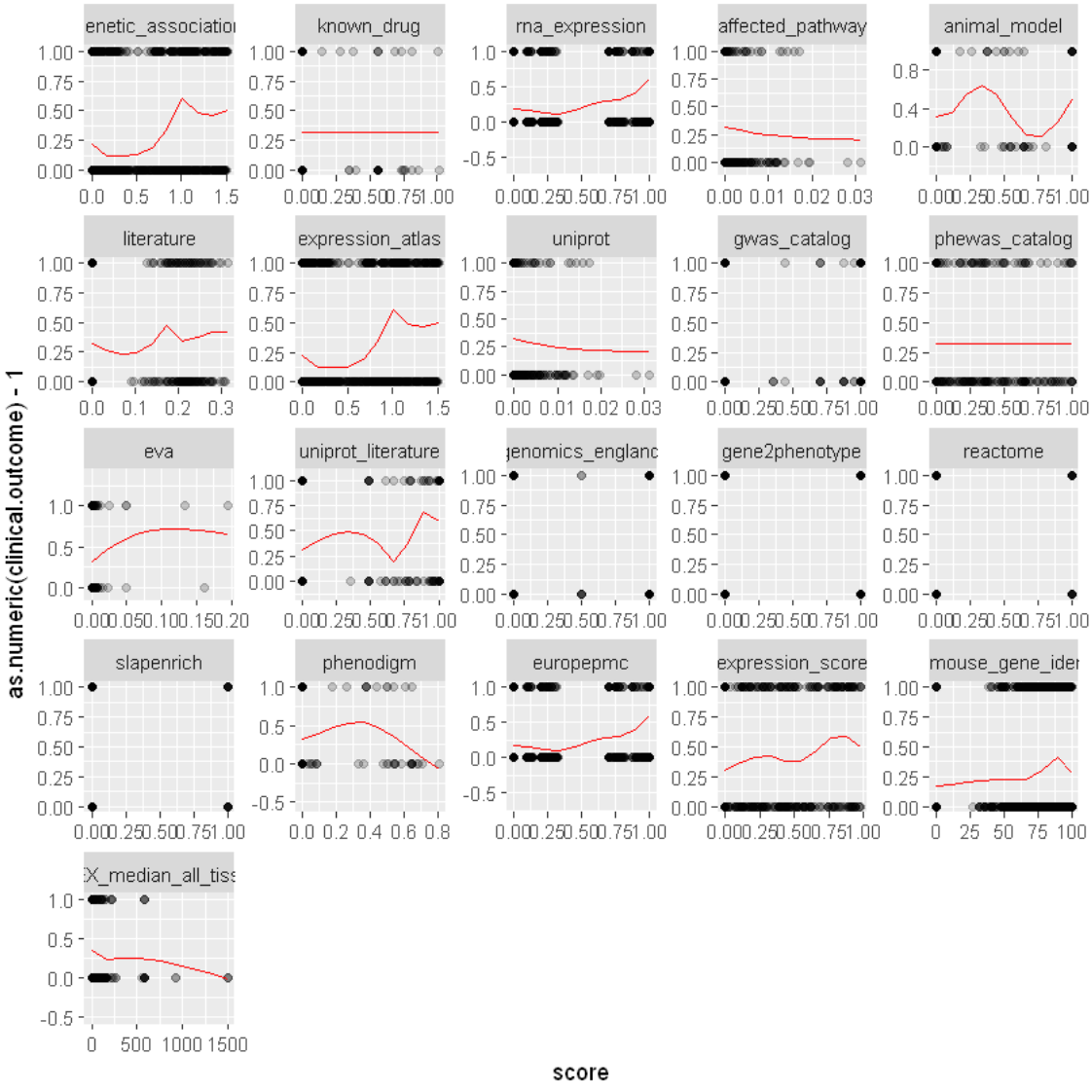
```
In [16]: g = ggplot(all.long, aes(score)) +
           geom_histogram(bins = 10) +
           facet_wrap(~datasource, scales = "free")
         print(g)
```




```
In [17]: g = ggplot(all.long, aes(score, as.numeric(clinical.outcome) - 1)) +
             geom_point(alpha = 0.2) +
             stat_smooth(geom = "line", n = 10, color = "red") +
             facet_wrap(~datasource, scales = "free")
         print(g)
```

```
`geom_smooth()` using method = 'gam'
Warning message:
```

```
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."Warning message:
"Computation failed in `stat_smooth()`:
x has insufficient unique values to support 10 knots: reduce k."
```



Looking at the relationship between the various Open Targets scores and T-I success, it appears that score values below 0.25 are generally associated with lower success rates, though this varies

for many score types. Let's set a threshold value of 0.1 and call everything that exceeds that as having positive evidence.

```
In [18]: pos.score.vars = paste(c(ot.scores, otsrc.scores), ".pos", sep = "")
         names(pos.score.vars) = c(ot.scores, otsrc.scores)
         for(i in names(pos.score.vars)) {
             all.data[, pos.score.vars[i]] = cut(all.data[, i], c(0, 0.1, 100),
                                                 labels = c("Negative", "Positive"),
                                                 include.lowest = TRUE)
         }
         do.call("rbind", apply(all.data[, pos.score.vars], 2, table))
```

	Negative	Positive
genetic_association.pos	1346	2701
known_drug.pos	4014	33
rna_expression.pos	1780	2267
affected_pathway.pos	4047	4047
animal_model.pos	3990	57
literature.pos	3879	168
expression_atlas.pos	1346	2701
uniprot.pos	4047	4047
gwas_catalog.pos	3965	82
phewas_catalog.pos	3871	176
eva.pos	4044	3
uniprot_literature.pos	3949	98
genomics_england.pos	3948	99
gene2phenotype.pos	3957	90
reactome.pos	4022	25
slapenrich.pos	4023	24
phenodigm.pos	4014	33
europepmc.pos	1780	2267
expression_score.pos	3694	353

```
In [19]: or.mat = matrix(NA, ncol = 3, nrow = length(pos.score.vars),
                         dimnames = list(pos.score.vars,
                                         c("OR", "Lower", "Upper")))
         or.list = list()
         for(i in pos.score.vars) {
             or.list[[i]][["Table"]] = table(all.data[, "clinical.outcome"],
                                             all.data[, i])
             or.list[[i]][["Test"]] = fisher.test(or.list[[i]][["Table"]])
             or.mat[i,] = unlist(or.list[[i]][["Test"]][c("estimate", "conf.int")])
         }
         or.mat
```

	OR	Lower	Upper
genetic_association.pos	3.4523682	2.9222694	4.090734
known_drug.pos	0.9286864	0.3933594	2.035838
rna_expression.pos	3.7144895	3.1949489	4.325741
affected_pathway.pos	0.0000000	0.0000000	Inf
animal_model.pos	1.5646741	0.8808883	2.741718
literature.pos	1.3671568	0.9789196	1.897862
expression_atlas.pos	3.4523682	2.9222694	4.090734
uniprot.pos	0.0000000	0.0000000	Inf
gwas_catalog.pos	1.7792583	1.1137054	2.827303
phewas_catalog.pos	0.9436282	0.6669673	1.320463
eva.pos	4.2777800	0.2225089	252.170065
uniprot_literature.pos	1.7672575	1.1524474	2.697760
genomics_england.pos	2.0502396	1.3448570	3.121098
gene2phenotype.pos	1.9879581	1.2759333	3.090268
reactome.pos	2.3281882	0.9763370	5.599475
slapenrich.pos	2.1474860	0.8797479	5.242341
phenodigm.pos	1.2232484	0.5468556	2.612753
europepmc.pos	3.7144895	3.1949489	4.325741
expression_score.pos	1.8808130	1.4977330	2.359559

Repeat categorization for human-mouse protein sequence identity and GTEx median tissue (not currently in Open Targets).

```
In [20]: pos.gene.qvars = paste(gene.qvars, ".pos", sep = "")
         all.data = all.data %>%
             mutate(pc_mouse_gene_identity.pos =
                    ifelse(pc_mouse_gene_identity > 70, "Positive", "Negative")) %>%
             mutate(GTEX_median_all_tissues.pos =
                    ifelse(GTEX_median_all_tissues < 0.5, "Positive", "Negative"))
         apply(all.data[, pos.gene.qvars], 2, table)
```

	pc_mouse_gene_identity.pos	GTEX_median_all_tissues.pos
Negative	593	2317
Positive	3454	1730

```
In [21]: or.mat = matrix(NA, ncol = 3, nrow = length(pos.gene.qvars),
                         dimnames = list(pos.gene.qvars, c("OR", "Lower", "Upper")))
         or.list = list()
         for(i in pos.gene.qvars) {
             or.list[[i]][["Table"]] = table(all.data[, "clinical.outcome"],
                                             all.data[, i])
             or.list[[i]][["Test"]] = fisher.test(or.list[[i]][["Table"]])
             or.mat[i,] = unlist(or.list[[i]][["Test"]][c("estimate", "conf.int")])
         }
         or.mat
```

	OR	Lower	Upper
pc_mouse_gene_identity.pos	1.761191	1.429009	2.181400
GTEX_median_all_tissues.pos	1.287073	1.124078	1.473687

1.3.2 Categorical gene features

```
In [22]: summary((all.data[, gene.cvars]))
```

```
            protein_class                target_class     topology_type
 Secreted protein  : 238   7TM_Group1           : 994   Membrane  : 354
 Oxidoreductase    : 225   Enzyme_all_others    : 535   MultiTM   :1744
 Membrane receptor : 219   Receptor_all_others : 440   Secreted  : 594
 Enzyme            : 184   Ion Channel          : 384   SingleTM  : 605
 Serotonin receptor: 145   Extracellular Ligand: 310   Unattached: 750
 (Other)           :2747   Kinase_Protein       : 240
 NA's              : 289   (Other)              :1144
     target_location              ExAC_LoF
 Cytoplasm    : 212   Intolerant to LoF:1164
 Exposed      :2172   Missing          :  95
 Free         : 594   Tolerant to LoF  : 696
 Mitochondrion: 155   Unclassified     :2092
 Nucleus      : 430
 Organelle    : 484
 Unknown      :   0
```

```
In [23]: protein.classes = table(all.data$protein_class)
         common.protein.classes = names(protein.classes[protein.classes >= 50])
         all.data$pcred = as.character(all.data$protein_class)
         all.data$pcred[!(all.data$pcred %in% common.protein.classes)] = "Other"
         g = glm(clinical.outcome ~ pcred, all.data, family = binomial(link = "logit"))
         summary(g)
         anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ pcred, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
   Min      1Q  Median      3Q     Max
-1.665  -0.693  -0.693   1.114   2.797

Coefficients:
                                                    Estimate Std. Error
(Intercept)                                           0.8842     0.2727
pcredAdrenergic receptor                             -0.4395     0.3274
pcredCC chemokine receptor                           -4.7760     1.0463
pcredDopamine receptor                               -1.1355     0.3416
pcredEnzyme                                          -2.7813     0.3497
pcredGABA-A receptor                                 -0.7431     0.3619
pcredHistamine receptor                              -1.0993     0.3829
pcredHydrolase                                       -0.8465     0.3871
```

```
pcredMembrane receptor                                        -1.3202     0.3058
pcredNuclear hormone receptor subfamily 3 group C member 1     0.2144     0.3909
pcredOpioid receptor                                          -0.8543     0.3662
pcredOther                                                    -2.1882     0.2782
pcredOxidoreductase                                           -0.7328     0.3037
pcredProstanoid receptor                                      -2.4482     0.4569
pcredSecreted protein                                         -1.7800     0.3079
pcredSerine protease S1A subfamily                            -0.4787     0.3406
pcredSerotonin receptor                                       -1.3475     0.3217
pcredSLC06 neurotransmitter transporter family                -0.9565     0.3502
pcredUnclassified protein                                     -1.9828     0.3674
pcredVoltage-gated sodium channel                             -0.8568     0.3594
                                                             z value Pr(>|z|)
(Intercept)                                                   3.242 0.001186 **
pcredAdrenergic receptor                                     -1.342 0.179453
pcredCC chemokine receptor                                   -4.565 5.00e-06 ***
pcredDopamine receptor                                       -3.324 0.000887 ***
pcredEnzyme                                                  -7.954 1.81e-15 ***
pcredGABA-A receptor                                         -2.053 0.040048 *
pcredHistamine receptor                                      -2.871 0.004094 **
pcredHydrolase                                               -2.187 0.028778 *
pcredMembrane receptor                                       -4.317 1.58e-05 ***
pcredNuclear hormone receptor subfamily 3 group C member 1    0.549 0.583346
pcredOpioid receptor                                         -2.333 0.019640 *
pcredOther                                                   -7.867 3.64e-15 ***
pcredOxidoreductase                                          -2.413 0.015835 *
pcredProstanoid receptor                                     -5.358 8.39e-08 ***
pcredSecreted protein                                        -5.782 7.39e-09 ***
pcredSerine protease S1A subfamily                           -1.405 0.159904
pcredSerotonin receptor                                      -4.189 2.80e-05 ***
pcredSLC06 neurotransmitter transporter family               -2.732 0.006304 **
pcredUnclassified protein                                    -5.397 6.78e-08 ***
pcredVoltage-gated sodium channel                            -2.384 0.017129 *
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5066.3  on 4046  degrees of freedom
Residual deviance: 4593.0  on 4027  degrees of freedom
AIC: 4633

Number of Fisher Scoring iterations: 6
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4046	5066.255	NA
pcred	19	473.2993	4027	4592.955	2.205321e-88

```
In [24]: g = glm(clinical.outcome ~ target_class, all.data,
                 family = binomial(link = "logit"))
         summary(g)
         anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ target_class, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.1542  -0.9553  -0.7705   1.4020   2.0729

Coefficients:
                                                Estimate Std. Error z value
(Intercept)                                     -1.26976    0.22635  -5.610
target_class7TM_Group1                           0.75571    0.23565   3.207
target_classEnzyme_all_others                    0.72188    0.24349   2.965
target_classEnzyme_Esterase                      0.26010    0.28331   0.918
target_classEnzyme_Transferase                   0.06579    0.51759   0.127
target_classExtracellular Ligand                -0.19923    0.26916  -0.740
target_classExtracellular_all_others            -0.21832    0.37255  -0.586
target_classIon Channel                          0.69168    0.25009   2.766
target_classKinase_Protein                      -0.75462    0.30276  -2.492
target_classNuclear Receptor                     1.14520    0.26542   4.315
target_classOther                                0.50762    0.30519   1.663
target_classProtease                             0.64878    0.26589   2.440
target_classReceptor_all_others                  0.20719    0.25128   0.825
target_classTranscriptional_Factor_all_others -0.35948    0.41333  -0.870
target_classTransporter                          1.21495    0.28045   4.332
                                                Pr(>|z|)
(Intercept)                                     2.03e-08 ***
target_class7TM_Group1                           0.00134 **
target_classEnzyme_all_others                    0.00303 **
target_classEnzyme_Esterase                      0.35859
target_classEnzyme_Transferase                   0.89886
target_classExtracellular Ligand                 0.45919
target_classExtracellular_all_others             0.55787
target_classIon Channel                          0.00568 **
target_classKinase_Protein                       0.01269 *
target_classNuclear Receptor                    1.60e-05 ***
target_classOther                                0.09625 .
target_classProtease                             0.01469 *
```

```
target_classReceptor_all_others                 0.40964
target_classTranscriptional_Factor_all_others  0.38446
target_classTransporter                       1.48e-05 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5066.3  on 4046  degrees of freedom
Residual deviance: 4892.7  on 4032  degrees of freedom
AIC: 4922.7

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4046	5066.255	NA
target_class	14	173.5554	4032	4892.699	1.30849e-29

```
In [25]: g = glm(clinical.outcome ~ topology_type, all.data,
                 family = binomial(link = "logit"))
         summary(g)
         anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ topology_type, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0359  -0.9563  -0.7636   1.4160   1.6699

Coefficients:
                        Estimate Std. Error z value Pr(>|z|)
(Intercept)              -0.3423     0.1079  -3.173  0.00151 **
topology_typeMultiTM     -0.2029     0.1188  -1.709  0.08746 .
topology_typeSecreted    -0.6216     0.1416  -4.389 1.14e-05 ***
topology_typeSingleTM    -0.7410     0.1428  -5.190 2.10e-07 ***
topology_typeUnattached  -0.7670     0.1371  -5.597 2.19e-08 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5066.3  on 4046  degrees of freedom
Residual deviance: 4997.7  on 4042  degrees of freedom
AIC: 5007.7
```

```
Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4046	5066.255	NA
topology_type	4	68.54075	4042	4997.714	4.612921e-14

```
In [26]: g = glm(clinical.outcome ~ target_location, all.data,
                 family = binomial(link = "logit"))
         summary(g)
         anova(g, test = "Chisq")


Call:
glm(formula = clinical.outcome ~ target_location, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0854  -0.8921  -0.8039   1.4926   1.7734

Coefficients:
                            Estimate Std. Error z value Pr(>|z|)
(Intercept)                  -1.3398     0.1694  -7.911 2.55e-15 ***
target_locationExposed        0.6237     0.1754   3.556 0.000377 ***
target_locationFree           0.3759     0.1926   1.951 0.051025 .
target_locationMitochondrion  1.1195     0.2341   4.782 1.73e-06 ***
target_locationNucleus        0.1845     0.2036   0.906 0.364686
target_locationOrganelle      0.9635     0.1930   4.993 5.95e-07 ***
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5066.3  on 4046  degrees of freedom
Residual deviance: 5006.7  on 4041  degrees of freedom
AIC: 5018.7

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4046	5066.255	NA
target_location	5	59.59673	4041	5006.658	1.472514e-11

```
In [27]: g = glm(clinical.outcome ~ ExAC_LoF, all.data,
                 family = binomial(link = "logit"))
```

```
summary(g)
anova(g, test = "Chisq")
```

```
Call:
glm(formula = clinical.outcome ~ ExAC_LoF, family = binomial(link = "logit"),
    data = all.data)

Deviance Residuals:
    Min       1Q   Median       3Q      Max
-1.0455  -0.8971  -0.8891   1.4865   1.6548

Coefficients:
                        Estimate Std. Error z value Pr(>|z|)
(Intercept)             -0.72424    0.06251 -11.587  < 2e-16 ***
ExAC_LoFMissing          0.40578    0.21700   1.870  0.06149 .
ExAC_LoFTolerant to LoF -0.35152    0.10716  -3.280  0.00104 **
ExAC_LoFUnclassified     0.02175    0.07788   0.279  0.77998
---
Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1

(Dispersion parameter for binomial family taken to be 1)

    Null deviance: 5066.3  on 4046  degrees of freedom
Residual deviance: 5046.2  on 4043  degrees of freedom
AIC: 5054.2

Number of Fisher Scoring iterations: 4
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	4046	5066.255	NA
ExAC_LoF	3	20.0475	4043	5046.207	0.0001659382

1.4 Save the main analysis dataset as an RData file

```
In [28]: save(all.data, file = "datathon_OTdata.RData", compress = TRUE)
```

1.5 Example prediction model

1.5.1 Backwards stepwise regression

```
In [29]: set.seed(6475250)
         train.select = sample(1:nrow(all.data), size = nrow(all.data) * 0.8,
                               replace = FALSE)
         train.data = all.data[train.select,]
         test.data = subset(all.data, !(key %in% train.data$key))
```

```
In [30]: indep.vars = c(pos.score.vars, pos.gene.qvars,
                        "pcred", "target_class", "topology_type",
                        "target_location", "ExAC_LoF")
         ## Eliminate those that are too rare to be robust
         indep.vars = indep.vars[!(indep.vars %in%
                                   c("known_drug.pos", "affected_pathway.pos",
                                    "uniprot.pos", "eva.pos"))]
         full.glm = glm(clinical.outcome ~ ., train.data[, c("clinical.outcome", indep.vars)],
                        family = binomial)
         anova(full.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3236	4073.523	NA
genetic_association.pos	1	187.00174950	3235	3886.521	1.434865e-42
rna_expression.pos	1	56.30752972	3234	3830.214	6.197762e-14
animal_model.pos	1	2.09263477	3233	3828.121	1.480106e-01
literature.pos	1	5.62038805	3232	3822.501	1.775272e-02
expression_atlas.pos	0	0.00000000	3232	3822.501	NA
gwas_catalog.pos	1	8.39894942	3231	3814.102	3.754379e-03
phewas_catalog.pos	1	0.49742863	3230	3813.605	4.806321e-01
uniprot_literature.pos	1	0.01838811	3229	3813.586	8.921353e-01
genomics_england.pos	1	3.50979134	3228	3810.076	6.100714e-02
gene2phenotype.pos	1	3.33373132	3227	3806.743	6.787273e-02
reactome.pos	1	0.63036421	3226	3806.112	4.272217e-01
slapenrich.pos	1	0.66277879	3225	3805.449	4.155806e-01
phenodigm.pos	0	0.00000000	3225	3805.449	NA
europepmc.pos	0	0.00000000	3225	3805.449	NA
expression_score.pos	1	31.40812248	3224	3774.041	2.091043e-08
pc_mouse_gene_identity.pos	1	5.09596022	3223	3768.945	2.398163e-02
GTEX_median_all_tissues.pos	1	4.69376069	3222	3764.252	3.027232e-02
pcred	19	281.10965197	3203	3483.142	1.461416e-48
target_class	14	51.08710495	3189	3432.055	4.010326e-06
topology_type	4	32.62960919	3185	3399.425	1.422289e-06
target_location	4	3.84241991	3181	3395.583	4.277518e-01
ExAC_LoF	3	0.61465682	3178	3394.968	8.930690e-01

```
In [31]: back.glm = step(full.glm, trace = 0)
         anova(back.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3236	4073.523	NA
rna_expression.pos	1	238.941390	3235	3834.582	6.691628e-54
literature.pos	1	9.196914	3234	3825.385	2.424234e-03
genomics_england.pos	1	13.533569	3233	3811.851	2.343340e-04
gene2phenotype.pos	1	3.139484	3232	3808.712	7.641799e-02
slapenrich.pos	1	0.794998	3231	3807.917	3.725931e-01
expression_score.pos	1	30.301628	3230	3777.615	3.698154e-08
pcred	19	289.203412	3211	3488.412	3.245276e-50
target_class	14	50.900158	3197	3437.512	4.311790e-06
topology_type	4	33.267613	3193	3404.244	1.052872e-06

```
In [32]: null.glm = glm(clinical.outcome ~ 1, train.data, family = binomial)
         forward.glm = step(null.glm,
                            scope = list(lower = formula(null.glm),
                                         upper = formula(full.glm)),
                            direction = "forward", trace = 0)
         anova(forward.glm, test = "Chisq")
```

	Df	Deviance	Resid. Df	Resid. Dev	Pr(>Chi)
NULL	NA	NA	3236	4073.523	NA
pcred	19	381.274021	3217	3692.249	3.406007e-69
rna_expression.pos	1	132.258684	3216	3559.991	1.313396e-30
expression_score.pos	1	39.700947	3215	3520.290	2.959820e-10
target_class	14	56.177001	3201	3464.113	5.429065e-07
topology_type	4	30.824909	3197	3433.288	3.323760e-06
gene2phenotype.pos	1	18.967162	3196	3414.320	1.329876e-05
genomics_england.pos	1	4.505366	3195	3409.815	3.378866e-02
literature.pos	1	2.923172	3194	3406.892	8.731604e-02
slapenrich.pos	1	2.647904	3193	3404.244	1.036865e-01

```
In [33]: test.data$pred.prob = predict(forward.glm, newdata = test.data,
                                       type = "response")
         train.data$pred.prob = predict(forward.glm, newdata = train.data,
                                        type = "response")
```

```
In [34]: by(train.data[, "pred.prob"], list(train.data$clinical.outcome), summary)
```

```
: Failure
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.007595 0.119277 0.217781 0.259889 0.372693 0.878485
------------------------------------------------------------
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.03032 0.28901 0.46292 0.45562 0.61303 0.93493
```

```
In [35]: by(test.data[, "pred.prob"], list(test.data$clinical.outcome), summary)
```

```
: Failure
    Min.  1st Qu.   Median     Mean  3rd Qu.     Max.
0.007595 0.119627 0.233484 0.264122 0.375751 0.876388
------------------------------------------------------------
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.05236 0.28901 0.46339 0.44858 0.60247 0.92494
```

```
In [36]: lVec = test.data$Indication.with.First.Clinical.Outcome.for.Target %in% "Y"
         by(test.data[lVec, "pred.prob"], list(test.data$clinical.outcome[lVec]), summary)
```

```
: Failure
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.04419 0.11693 0.15367 0.23191 0.32192 0.65320
------------------------------------------------------------
: Success
   Min. 1st Qu.  Median    Mean 3rd Qu.    Max.
0.05236 0.25069 0.37275 0.39818 0.54082 0.77218
```

```
In [37]: train.data = train.data %>%
             mutate(pred.outcome = ifelse(pred.prob >= 0.5, "Success", "Failure"))
         test.data = test.data %>%
             mutate(pred.outcome = ifelse(pred.prob >= 0.5, "Success", "Failure"))
```

```
In [38]: xtabs(~ clinical.outcome + pred.outcome, train.data)
         xtabs(~ clinical.outcome + pred.outcome, test.data)
```

```
                pred.outcome
clinical.outcome Failure Success
         Failure    1915     276
         Success     581     465


                pred.outcome
clinical.outcome Failure Success
         Failure     485      81
         Success     145      99
```

```
In [40]: simple_roc <- function(labels, scores){
           labels <- labels[order(scores, decreasing=TRUE)]
           data.frame(TPR=cumsum(labels)/sum(labels), FPR=cumsum(!labels)/sum(!labels), labels)
         }
         roc.train = simple_roc(train.data$clinical.outcome %in% "Success",
                                train.data$pred.prob)
         roc.test = simple_roc(test.data$clinical.outcome %in% "Success",
                               test.data$pred.prob)
```

```
plot(TPR ~ 1 - FPR, roc.train, type = "l", lwd = 2, col = "blue")
lines(TPR ~ 1 - FPR, roc.test, lwd = 2, col = "red")
abline(0, 1)
```