GWAS_catalog_EDA_and_normalization

April 23, 2022

[1]:
```
from typing import Any, Dict, List, Mapping, Sequence, Set, Text

import pandas as pd
import numpy as np
import math
import json
import re
import requests
import time
```

[2]:
```
SKIP_MAFS = True
```

1 Exploratory analysis of CSV data retrieved from GWAS Catalog.

This specific data is for Schizophrenia, but other data in GWAS catalog can be retrieved in the same format.

1.1 Exploring raw data types, range of data, etc.

1.1.1 Overall

[3]:
```
raw_schizo_df = pd.read_csv('schizophrenia_gwas_catalog_2022.csv')
raw_schizo_df.head()
```

[3]:

	Variant and risk allele	P-value	P-value annotation	RAF	OR Beta	\
0	rs11265461-C	2 x 10-7	NaN	0.41	1.45	'-
1	rs230529-T	2 x 10-7	NaN	0.47	1.45	'-
2	rs2237457-T	6 x 10-7	(Recessive model)	0.36	1.74	'-
3	rs2269372-A	4 x 10-8	NaN	NR	1.313	'-
4	rs7597593-T	9 x 10-11	NaN	NR	1.066	'-

	CI	Mapped gene	Reported trait	\
0	[1.26-1.67]	SLAMF1, SETP9	Schizophrenia (treatment resistant)	
1	[1.26-1.66]	NFKB1	Schizophrenia (treatment resistant)	

```
2         [NR]          GRB10  Schizophrenia (treatment resistant)
3         [NR]          RENBP                          Schizophrenia
4  [1.05-1.09]         ZNF804A                          Schizophrenia

                             Trait(s) Background trait(s) Study accession  \
0  treatment refractory schizophrenia                   '-      GCST001458
1  treatment refractory schizophrenia                   '-      GCST001458
2  treatment refractory schizophrenia                   '-      GCST002604
3                       schizophrenia                   '-      GCST002190
4                       schizophrenia                   '-      GCST004946

      Location
0  1:160660353
1  4:102536261
2   7:50658447
3  X:153942092
4  2:184668853
```

[4]:
```
total_rows = len(raw_schizo_df)
print(total_rows)
```

```
3849
```

1.2 According to https://www.ebi.ac.uk/gwas/docs/methods/curation

"RISK ALLELE FREQUENCY: Reported risk/effect allele frequency associated with strongest SNP in controls (if not available among all controls, among the control group with the largest sample size). If the associated locus is a haplotype the haplotype frequency will be extracted." So RAF is not global AF, but rather that of the study group. Since this are less comparable across studies, we'll lookup global AF for variants.

1.2.1 Variants

[5]:
```
num_unique_variants = len(raw_schizo_df['Variant and risk allele'].unique())
print(f"{num_unique_variants} unique variants out of {total_rows} records.")

variant_counts = raw_schizo_df['Variant and risk allele'].value_counts()
```

```
2739 unique variants out of 3849 records.
```

[6]:
```
# Explore entries for one repeated variant to assess differences.
duplicates = raw_schizo_df.groupby('Variant and risk allele').filter(lambda x:␣
 ↪len(x) > 1)
one_variant = duplicates.iloc[0]['Variant and risk allele']
duplicates[duplicates['Variant and risk allele'] == one_variant]
```

[6]:
```
      Variant and risk allele    P-value          P-value annotation   RAF  \
4          rs7597593-<b>T</b>  9 x 10-11                         NaN    NR
747        rs7597593-<b>T</b>  2 x 10-11                         NaN    NR
2878       rs7597593-<b>T</b>  3 x 10-12                         NaN  0.62
3625       rs7597593-<b>T</b>   8 x 10-6  (5 degree of freedom test)    NR

          OR Beta           CI Mapped gene  \
4     1.066   '-  [1.05-1.09]     ZNF804A
747   1.069   '-  [1.05-1.09]     ZNF804A
2878    '-    '-           '-     ZNF804A
3625  1.055   '-  [1.03-1.08]     ZNF804A

                                       Reported trait  \
4                                       Schizophrenia
747                                     Schizophrenia
2878                 Broad depression or schizophrenia
3625  Autism spectrum disorder, attention deficit-hy…

                                            Trait(s) Background trait(s)  \
4                                       schizophrenia                  '-
747                                     schizophrenia                  '-
2878                unipolar depression, schizophrenia                  '-
3625  attention deficit hyperactivity disorder, unip…                 '-

     Study accession     Location
4         GCST004946  2:184668853
747       GCST007201  2:184668853
2878      GCST007257  2:184668853
3625      GCST001877  2:184668853
```

1.2.2 P-values

[7]:
```
raw_schizo_df['P-value'].describe()
```

[7]:
```
count         3849
unique         163
top       2 x 10-8
freq            201
Name: P-value, dtype: object
```

[8]:
```
len(raw_schizo_df['Mapped gene'].unique())
```

[8]:
```
1427
```

1.2.3 Genes

[9]:
```
def has_multiple_genes(mapped_gene):
  return "," in mapped_gene


multi_gene_index = raw_schizo_df['Mapped gene'].apply(has_multiple_genes)
len(raw_schizo_df[multi_gene_index])
```

[9]:
```
913
```

1.2.4 Reported trait / Trait(s)

[10]:
```
raw_schizo_df['Reported trait'].unique()
```

[10]:
```
array(['Schizophrenia (treatment resistant)', 'Schizophrenia',
       'Schizophrenia (MTAG)', 'Schizophrenia or bipolar disorder',
       'Schizophrenia (negative symptoms)', 'Methamphetamine dependence',
       'Early-onset schizophrenia',
       'Autism spectrum disorder or schizophrenia',
       'Gray matter volume (schizophrenia interaction)',
       'Schizophrenia (inflammation and infection response interaction)',
       'Broad depression or schizophrenia',
       'Dentate gyrus volume x schizophrenia interaction',
       'Schizophrenia vs type 2 diabetes',
       'Schizophrenia and type 2 diabetes',
       'Autism and schizophrenia (MTAG)',
       'Left superior temporal gyrus thickness (schizophrenia interaction)',
       'Bipolar disorder and schizophrenia',
       'Schizophrenia (cytomegalovirus infection interaction)',
       'Schizophrenia (age at onset)',
       'Schizophrenia or schizoaffective disorder',
       'Schizophrenia vs autism spectrum disorder (ordinary least squares
(OLS))',
       'Schizophrenia vs bipolar disorder (ordinary least squares (OLS))',
       'Schizophrenia vs anorexia nervosa (ordinary least squares (OLS))',
       'Schizophrenia vs ADHD (ordinary least squares (OLS))',
       'Schizophrenia vs major depressive disorder (ordinary least squares
(OLS))',
       "Schizophrenia vs Tourette's syndrome and other tic disorders (ordinary
least squares (OLS))",
       'Schizophrenia x sex interaction',
       'Bipolar disorder lithium response (continuous) or schizophrenia',
       'Bipolar disorder lithium response (categorical) or schizophrenia',
       'Cognitive ability, years of educational attainment or schizophrenia
(pleiotropy)',
```

```
       'Brain imaging in schizophrenia (dorsolateral prefrontal cortex
interaction)',
       'Schizophrenia, schizoaffective disorder or bipolar disorder',
       'Schizophrenia, bipolar disorder or recurrent major depressive disorder x
sex interaction (3df)',
       'Schizophrenia, bipolar disorder or recurrent major depressive disorder',
       'Schizophrenia, bipolar disorder or major depressive disorder x sex
interaction',
       'Schizophrenia, bipolar disorder or major depressive disorder',
       'Schizophrenia, bipolar disorder or major depressive disorder x sex
interaction (3df)',
       'Neuropsychiatric disorders',
       'Autism spectrum disorder, attention deficit-hyperactivity disorder,
bipolar disorder, major depressive disorder, and schizophrenia (combined)',
       'Psychiatric diseases (pleiotropy) (HIPO component 1)',
       'Schizophrenia, bipolar disorder or recurrent major depressive disorder x
sex interaction',
       'Anorexia nervosa, attention-deficit/hyperactivity disorder, autism
spectrum disorder, bipolar disorder, major depression, obsessive-compulsive
disorder, schizophrenia, or Tourette syndrome (pleiotropy)'],
      dtype=object)
```

[11]:
```
raw_schizo_df['Trait(s)'].unique()
```

[11]:
```
array(['treatment refractory schizophrenia', 'schizophrenia',
       'autism spectrum disorder, schizophrenia',
       'schizophrenia, grey matter volume measurement',
       'schizophrenia, cytomegalovirus seropositivity',
       'schizophrenia, HSV1 seropositivity',
       'schizophrenia, Toxoplasma gondii seropositivity',
       'unipolar depression, schizophrenia',
       'dentate gyrus volume measurement, schizophrenia',
       'schizophrenia, type 2 diabetes mellitus',
       'schizophrenia, bipolar disorder',
       'schizophrenia, left superior temporal gyrus thickness measurement',
       'schizophrenia, cytomegalovirus infection',
       'schizophrenia, age at onset',
       'schizophrenia, schizoaffective disorder',
       'anorexia nervosa, schizophrenia',
       'attention deficit hyperactivity disorder, schizophrenia',
       'Tourette syndrome, schizophrenia',
       'schizophrenia, sex interaction measurement',
       'schizophrenia, bipolar disorder, response to lithium ion',
       'schizophrenia, intelligence, self reported educational attainment',
       'schizophrenia, dorsolateral prefrontal cortex functional measurement,
brain measurement',
       'schizophrenia, bipolar disorder, schizoaffective disorder',
```

```
       'unipolar depression, schizophrenia, sex interaction measurement, bipolar
disorder',
       'disease recurrence, unipolar depression, schizophrenia, bipolar
disorder',
       'unipolar depression, schizophrenia, bipolar disorder',
       'attention deficit hyperactivity disorder, autism spectrum disorder,
schizophrenia, bipolar disorder, major depressive disorder',
       'attention deficit hyperactivity disorder, unipolar depression, autism
spectrum disorder, schizophrenia, bipolar disorder',
       'disease recurrence, unipolar depression, schizophrenia, sex interaction
measurement, bipolar disorder',
       'anorexia nervosa, obsessive-compulsive disorder, attention deficit
hyperactivity disorder, Tourette syndrome, unipolar depression, autism spectrum
disorder, schizophrenia, bipolar disorder'],
      dtype=object)
```

[12]:
```
num_just_schizo = len(raw_schizo_df[raw_schizo_df['Trait(s)'] ==␣
↪'schizophrenia'])
print(f"{num_just_schizo} / {total_rows} rows are for the trait schizophrenia␣
↪only.")
```

```
2564 / 3849 rows are for the trait schizophrenia only.
```

1.2.5 Initial observations:

- 3849 records total
- P-values are currently objects/strings
- A lot of genes - 1427 unique values, although some normalization seems to be required (e.g. to fix ”SLAMF1, SETP9”). After normalizing it may be good to analyze counts per gene - maybe genes only implicated once are less signficant than others which appear multiple times.
- Many records have multiple traits in addition to schizophrenia (e.g. one trait value is ”anorexia nervosa, obsessive-compulsive disorder, attention deficit hyperactivity disorder, Tourette syndrome, unipolar depression, autism spectrum disorder, schizophrenia, bipolar disorder”). I assume these studies examined patients with either condition, but it’s not entirely clear without checking the studies themselves. To make this a scalable approach, it may be best to omit records that are for more than just schizophrenia to avoid any potential biases in the future similarity analysis.
- A fair amount of the variants in the dataset appear multiple times (e.g. reported by different studies). It’s worth noting this, although at the moment it’s unclear what the best way to handle this is. Maybe subsequent analysis should only focus on variants identified multiple time; maybe for each repeated variant, only the lowest p-value should be retained. However, some care should be applied given the above point about traits (maybe want the lowest p-value among records for just the trait schizophrenia).

1.3 Cleaning/normalizing data

[13]:
```
# Create copy of DF to hold normalized data and leave raw DF untouched.
schizo_df = raw_schizo_df.copy()
```

1.3.1 P-values

[14]:
```
def pval_to_num(pval):
  parts = pval.split(" x 10-")
  return float(parts[0]) * pow(10, -float(parts[1]))


print(pval_to_num("2 x 10-7"))
```

```
2e-07
```

[15]:
```
schizo_df['P-value_norm'] = raw_schizo_df['P-value'].apply(pval_to_num)
```

[16]:
```
schizo_df['P-value_norm'].describe()
```

[16]:
```
count    3.849000e+03
mean     1.072234e-06
std      2.255918e-06
min      2.000000e-44
25%      3.000000e-10
50%      2.000000e-08
75%      6.000000e-07
max      1.000000e-05
Name: P-value_norm, dtype: float64
```

1.3.2 Traits

[17]:
```
# As mentioned above, it may be best to use the subset of data which focused
# solely on the trait of interest (schizophrenia).
# There are some others that are probably fine to include (e.g. treatment
# refractory schizophrenia), but for the sake of simplicity and
# generalizability, we'll assume there is one canonical GWAS catalog trait of
# interest for each condition to be analyzed.
canonical_trait = 'schizophrenia'
filtered_df = schizo_df[schizo_df['Trait(s)'] == canonical_trait]
print(f"Filtered from {len(schizo_df)} rows to {len(filtered_df)} rows.")
```

```
Filtered from 3849 rows to 2564 rows.
```

[18]:
```
# The majority of the data is retained, so we'll use just this subset.
schizo_df = filtered_df
```

1.3.3 Variants

[19]:
```
# Sanity-check that all duplicated variants are reported to map to same gene(s)
# before we split multi-gene associations into separate rows.
# If all repeated variants map to same gene, we can just retain the entry with
# lowest p-value (or any really, since subsequent analysis just cares about
# variant ID and implicated genes).
duplicate_variants = schizo_df.groupby('Variant and risk allele').filter(lambda␣
↪x: len(x) > 1)['Variant and risk allele'].unique()
all_good = True
for variant in duplicate_variants:
  all_mapped_genes = schizo_df[schizo_df['Variant and risk allele'] ==␣
↪variant]['Mapped gene'].unique()
  if len(all_mapped_genes) > 1:
    print(f"Found variant, {variant}, with differing mapped gene values.")
    all_good = False


if all_good:
  print("No repeated variants with differing mapped gene values.")
```

```
No repeated variants with differing mapped gene values.
```

[20]:
```
# Proceed with just choosing the record with the lowest p-value.
# It may later be useful to revisit this step and retain these duplicates -
# maybe only focusing on those associations that have been found in multiple
# independent studies will lead to better results in the subsequent analysis.
min_indices = schizo_df.groupby('Variant and risk allele')['P-value_norm'].
↪idxmin()
schizo_df = schizo_df.loc[min_indices]
```

[21]:
```
# Sanity-check duplicates are gone:
num_unique_variants = len(schizo_df['Variant and risk allele'].unique())
num_total = len(schizo_df)
print(f"{num_unique_variants} unique variants of {num_total} records")
```

```
1822 unique variants of 1822 records
```

1.3.4 Genes

[22]:
```
# Genes are comma-separated so `explode` can be used to create a new row for
# each gene (with all other columns identical).
# https://pandas.pydata.org/docs/reference/api/pandas.DataFrame.explode.html
schizo_df['gene_norm'] = raw_schizo_df['Mapped gene'].apply(lambda val: val.
 ↪split(", "))
exploded_schizo_df = schizo_df.explode('gene_norm')
len(exploded_schizo_df)
```

[22]:
```
2201
```

[23]:
```
# Sanity check that the final number of rows is expected:
schizo_df['gene_norm'].apply(lambda x: len(x)).value_counts()
```

[23]:
```
1    1444
2     377
3       1
Name: gene_norm, dtype: int64
```

[24]:
```
# 1444 entries with one gene + 2 * 377 entries with two + 3 * 1 entries with␣
 ↪three
assert len(exploded_schizo_df) == 1444 + 2 * 377 + 3 * 1
```

[25]:
```
# Sanity-check passes so set schizo_df to the exploded version.
schizo_df = exploded_schizo_df
```

[26]:
```
schizo_df['gene_norm'].value_counts()
```

[26]:
```
'-           251
LINC01470     21
CACNA1C       15
Y_RNA         15
VRK2          11
             ...
ARHGAP31       1
ADAMTS6        1
NLRC5          1
VN1R18P        1
NRIP1          1
Name: gene_norm, Length: 1118, dtype: int64
```

[27]:
```
# 491 / 4764 entries have "'-" for their gene; I'm assuming this indicates an
# unknown/unconfirmed gene association. According to curation site, it says
# 'NR' is used for not reported and 'intergenic' is used to denote intergenic
# regions, but neither of these appear in this data
UNKNOWN_GENE = "UNKNOWN"
```

```
def replace_unknown_gene(gene):
  return UNKNOWN_GENE if gene == "'-" else gene


schizo_df['gene_norm'] = schizo_df['gene_norm'].apply(replace_unknown_gene)
schizo_df['gene_norm'].value_counts()
```

[27]:
```
UNKNOWN      251
LINC01470     21
CACNA1C       15
Y_RNA         15
VRK2          11
              …
ARHGAP31       1
ADAMTS6        1
NLRC5          1
VN1R18P        1
NRIP1          1
Name: gene_norm, Length: 1118, dtype: int64
```

[28]:
```
unique_genes = schizo_df['gene_norm'].unique()
'NR' in unique_genes or 'intergenic' in unique_genes
```

[28]:
```
False
```

1.3.5 Location

[29]:
```
# Location is mostly fine. Some associations don't report an rs ID in 'Variant
# and risk allele' and instead report in the format 'chrX:location-<b>?</b>',
# and then their Location value is 'Mapping not available'. Just copy over the
# location info in same format as other variants. Note some rs ID variants also
# use 'Mapping not available' though, so leave those as is.
NON_RSVAR_FORMAT_LOCATION_VALUE = 'Mapping not available'


def try_fix_variant_location(variant_row: pd.Series) -> Text:
  """Given variants of form 'chr6:55564517-<b>?</b>' returns '6:55564517'."""
  if variant_row['Location'] != NON_RSVAR_FORMAT_LOCATION_VALUE:
    return variant_row['Location']
  variant = variant_row['Variant and risk allele']
  if 'rs' in variant:
    return NON_RSVAR_FORMAT_LOCATION_VALUE
  parts = variant.split(":")
  chr_num = parts[0][3]
  location = parts[1].split("-")[0]
```

```
  return f'{chr_num}:{location}'


nonstandard_variants_df = schizo_df.loc[schizo_df['Location'] ==␣
↪NON_RSVAR_FORMAT_LOCATION_VALUE]
print(f'{len(nonstandard_variants_df)} variants missing location info.')
schizo_df['Location'] = schizo_df.apply(try_fix_variant_location, axis=1)

still_missing_count = len(schizo_df.loc[schizo_df['Location'] ==␣
↪NON_RSVAR_FORMAT_LOCATION_VALUE])
print(f'{still_missing_count} variants still missing location info.')
```

```
130 variants missing location info.
129 variants still missing location info.
```

1.4 Output

Finally, write out the normalized version of the data for use in further analysis.

[30]:
```
schizo_df.head()
```

[30]:

	Variant and risk allele	P-value	P-value annotation	RAF	OR	\
2388	chr6:55564517-?	3 x 10-6	(female)	0.5665	'-	
1176	rs1001780-G	8 x 10-6	NaN	NR	1.0752687	
2036	rs10043984-?	5 x 10-8	NaN	'-	'-	
615	rs10043984-T	4 x 10-8	NaN	0.2614	'-	
236	rs10046758-?	9 x 10-8	NaN	NR	'-	

	Beta	CI	Mapped gene	\
2388	0.1622 unit increase	[0.094-0.23]	'-	
1176	'-	[NR]	DLX2-DT	
2036	'-	'-	KDM3B	
615	0.067151085 unit increase	[0.043-0.091]	KDM3B	
236	'-	'-	CSMD1	

	Reported trait	Trait(s)	Background trait(s)	Study accession	\
2388	Schizophrenia	schizophrenia	'-	GCST012309	
1176	Schizophrenia	schizophrenia	'-	GCST003048	
2036	Schizophrenia (MTAG)	schizophrenia	'-	GCST010640	
615	Schizophrenia (MTAG)	schizophrenia	'-	GCST012089	
236	Schizophrenia	schizophrenia	'-	GCST008459	

	Location	P-value_norm	gene_norm
2388	6:55564517	3.000000e-06	UNKNOWN
1176	2:172107630	8.000000e-06	DLX2-DT
2036	5:138376432	5.000000e-08	KDM3B

```
615   5:138376432  4.000000e-08     KDM3B
236     8:4326648  9.000000e-08     CSMD1
```

[31]:
```
# Keep only the relevant, normalized columns for brevity. This can always be
# updated later to retain more if there's a use for it.

out_df = schizo_df[['Variant and risk allele', 'P-value_norm', 'Trait(s)',␣
↪'gene_norm', 'Location']]
column_remapping = {
    'Variant and risk allele': 'variant_and_allele',
    'P-value_norm': 'p_value',
    'Trait(s)': 'trait',
    'gene_norm': 'gene',
    'Location': 'location',
}
out_df = out_df.rename(columns=column_remapping)
out_df.head()
```

[31]:
```
          variant_and_allele       p_value          trait     gene  \
2388  chr6:55564517-<b>?</b>  3.000000e-06  schizophrenia  UNKNOWN
1176      rs1001780-<b>G</b>  8.000000e-06  schizophrenia  DLX2-DT
2036     rs10043984-<b>?</b>  5.000000e-08  schizophrenia    KDM3B
615      rs10043984-<b>T</b>  4.000000e-08  schizophrenia    KDM3B
236      rs10046758-<b>?</b>  9.000000e-08  schizophrenia    CSMD1

         location
2388   6:55564517
1176  2:172107630
2036  5:138376432
615   5:138376432
236     8:4326648
```

[32]:
```
out_df.to_csv('schizophrenia_gwas_catalog_2022_cleaned.csv')
```

2 Load auxiliary data from dbSNP

[33]:
```
DB_SNP = 'snp'

# dbsnp efetch max refsnp results:
MAX_DBSNP_QUERIES = 15

# dbsnp API min time between requests.
SLEEP_SECONDS = 3

SUBCOL_DELIM = ';'
```

```
# Use this study for reporting population mean allele frequency (MAF).
PREFFERED_AF_STUDY = 'dbGaP_PopFreq'

# Given a dbSNP ID, fetches allele frequency data about the SNP from dbSNP.
# Returns a dict of dicts, where outer key is SNP ID, inner dict key is allele,
# and value is MAF for that allele for that SNP.
def get_mafs_for_refsnps(snp_ids):
    start = 0
    stop = len(snp_ids)
    data = {}
    while start < stop:
        cutoff = start + MAX_DBSNP_QUERIES
        cutoff = min(stop, cutoff)
        time.sleep(SLEEP_SECONDS)
        data_batch = _get_mafs_for_refsnps_internal(snp_ids[start:cutoff])
        # Pythonic way to merge dicts (3.5+)
        data = {**data, **data_batch}
        start += MAX_DBSNP_QUERIES
    return data


# Wrapped to avoid exceeding API request/response size limitations.
def _get_mafs_for_refsnps_internal(snp_ids):
    url = 'https://eutils.ncbi.nlm.nih.gov/entrez/eutils/efetch.fcgi'
    params = {
        'db': DB_SNP,
        'id': snp_ids,
        'rettype': 'json',
        'retmode': 'text',
    }

    maf_dicts = {}
    request = requests.get(url=url, params=params)
    parseable_json = '[{' + request.text[1:].replace('{"refsnp_id":',␣
↪',{"refsnp_id":') + ']'
    response = json.loads(parseable_json)
    for snp_response in response:
        if 'primary_snapshot_data' not in snp_response:
            continue

        snp_id = 'rs' + snp_response['refsnp_id']
        allele_to_maf = {}
        allele_annotations =␣
↪snp_response['primary_snapshot_data']['allele_annotations']
        for allele_annotation in allele_annotations:
            frequencies = allele_annotation['frequency']
```

```
            pop_freq_entries = [entry for entry in frequencies if␣
↪entry['study_name'] == PREFFERED_AF_STUDY]
            if len(pop_freq_entries) == 0:
              continue
            pop_freq_entry = pop_freq_entries[0]
            pop_maf = pop_freq_entry['allele_count'] /␣
↪pop_freq_entry['total_count']
            allele = pop_freq_entry['observation']['inserted_sequence']
            allele_to_maf[allele] = pop_maf
        # Sometimes all alleles are reported, even with 0.0 values.
        # Drop those, assuming they are truly 0 and should be ignored.
        allele_to_maf = {key: value for key, value in allele_to_maf.items() if␣
↪value > 0.0}
        maf_dicts[snp_id] = allele_to_maf

    return maf_dicts
```

[34]:
```
all_variants = out_df['variant_and_allele'].tolist()
rs_variants_and_alleles = [var for var in all_variants if 'rs' in var]
other_variants = [var for var in all_variants if var not in␣
↪rs_variants_and_alleles]

print(f"{len(rs_variants_and_alleles)} rs variants out of {len(all_variants)}␣
↪total variants")
```

```
2200 rs variants out of 2201 total variants
```

[35]:
```
print(other_variants)
```

```
['chr6:55564517-<b>?</b>']
```

[36]:
```
ALLELE_REGEX_PATTERN = r"<b>(.*)</b>"


def parse_variant_and_allele(variant_and_allele):
  """Given a string like 'rs1001780-<b>G</b>', returns ('rs1001780', 'G')."""
  parts = variant_and_allele.split("-")
  variant = parts[0]
  allele = re.findall(ALLELE_REGEX_PATTERN, parts[1], flags=0)[0]
  return (variant, allele)


def parse_variant(variant_and_allele):
  """Given a string like 'rs1001780-<b>G</b>', returns 'rs1001780'."""
  return parse_variant_and_allele(variant_and_allele)[0]
```

```
rs_variants = [parse_variant(var) for var in rs_variants_and_alleles]
```

[37]:
```
rs_variants[0:10]
```

[37]:
```
['rs1001780',
 'rs10043984',
 'rs10043984',
 'rs10046758',
 'rs10052004',
 'rs1006737',
 'rs1006737',
 'rs10077591',
 'rs10077591',
 'rs10083370']
```

[38]:
```
# Demo
mafs = get_mafs_for_refsnps(rs_variants[0:5])
mafs
```

[38]:
```
{'rs1001780': {'G': 0.907379924446843, 'T': 0.09262007555315704},
 'rs10043984': {'C': 0.745363299149029, 'T': 0.25463670085097095},
 'rs10046758': {'C': 0.8966909848879625, 'G': 0.10330901511203752},
 'rs10052004': {'A': 0.29921583447493977, 'G': 0.700784165525060 2}}
```

[39]:
```
# Takes ~45 minutes to run :|
mafs = get_mafs_for_refsnps(rs_variants)
```

[40]:
```
UNKNOWN_AF = -1.0
# From https://www.ebi.ac.uk/gwas/docs/methods/curation
# "? for unknown risk allele"
UNKNOWN_ALLELE = '?'


def try_get_maf_for_variant_and_allele(variant_and_allele):
  variant, allele = parse_variant_and_allele(variant_and_allele)
  if variant not in mafs:
    return UNKNOWN_AF

  var_mafs = mafs[variant]
  if allele == UNKNOWN_ALLELE:
    # Assume the significant association to be with the allele with min value if
    # not reported explicitly when there are only two alleles.
    if len(var_mafs.keys()) == 2:
      return min(var_mafs.values())
    print(f'Found variant with no reported allele for non-biallelic variant.')
    return UNKNOWN_AF
```

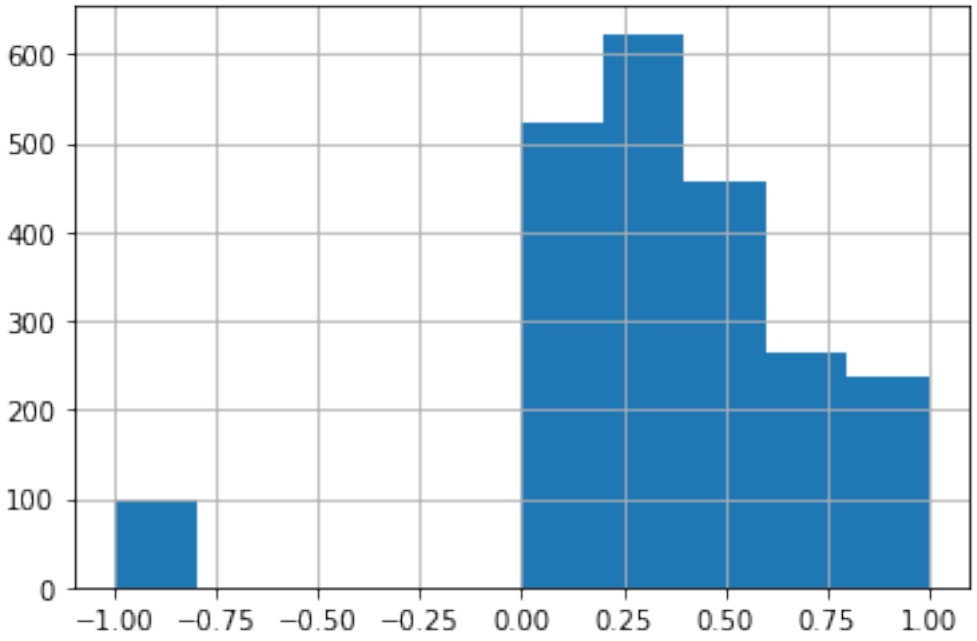
```
  if allele not in var_mafs:
    return UNKNOWN_AF

  return var_mafs[allele]


out_df['maf'] = out_df['variant_and_allele'].
 ↪map(try_get_maf_for_variant_and_allele)
out_df['maf'].describe()
```

```
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
Found variant with no reported allele for non-biallelic variant.
```

[40]:
```
count    2201.000000
mean        0.346703
std         0.387918
min        -1.000000
25%         0.179093
50%         0.355426
75%         0.560081
max         1.000000
Name: maf, dtype: float64
```

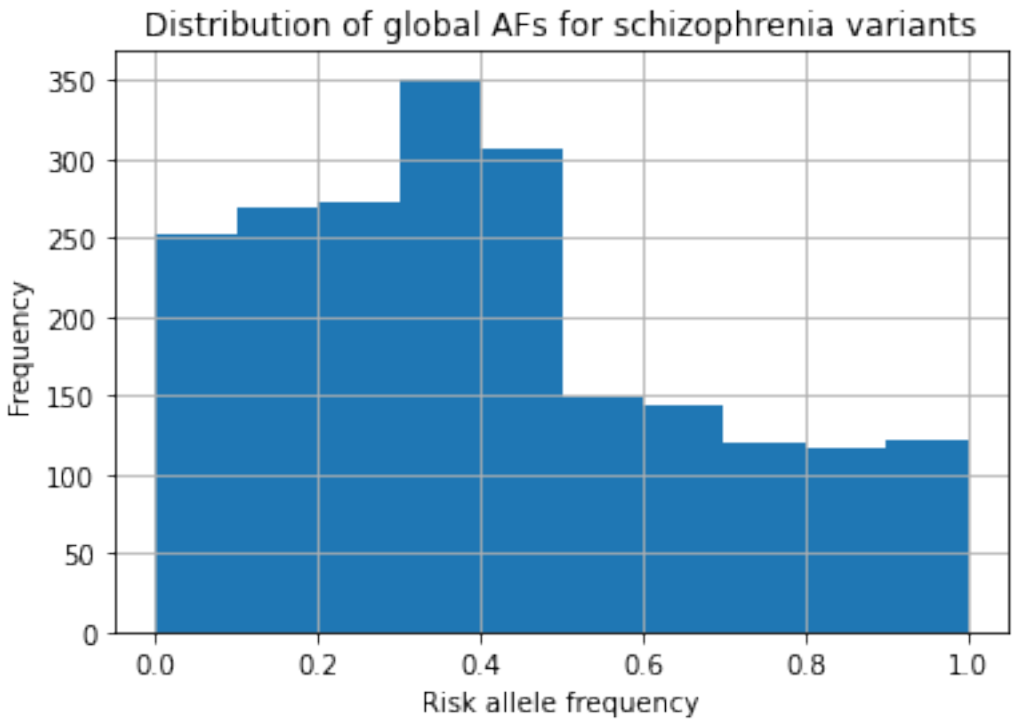
[41]:
```
out_df['maf'].hist()
```

[41]:
```
<matplotlib.axes._subplots.AxesSubplot at 0x7f652b4d3cd0>
```



[42]:
```
ax = out_df[out_df['maf'] > 0]['maf'].plot(kind='hist',
                                           grid=True,
                                           title='Distribution of global AFs for␣
 ↪schizophrenia variants')
ax.set_xlabel('Risk allele frequency')
```

[42]:
```
Text(0.5, 0, 'Risk allele frequency')
```



Check out the alleles with unknown AFs:

[43]:
```
unknowns = out_df[out_df['maf'] < 0.0]
len(unknowns)
```

[43]:
```
99
```

[44]:
```
unknowns.head()
```

[44]:

	variant_and_allele	p_value	trait	gene	location	maf
2388	chr6:55564517-?	3.000000e-06	schizophrenia	UNKNOWN	6:55564517	-1.0
2008	rs1023330-?	9.000000e-09	schizophrenia	TLCD4-RWDD3	1:95121217	-1.0
2008	rs1023330-?	9.000000e-09	schizophrenia	TLCD4	1:95121217	-1.0
2083	rs1023497-?	9.000000e-09	schizophrenia	CENPM	22:41944504	-1.0
1847	rs10489202-A	1.000000e-08	schizophrenia	UNKNOWN	Mapping not available	-1.0

[45]:
```
mafs['rs1023330']
```

[45]:
```
{'A': 8.575226171590276e-06, 'C': 0.6589289542511684, 'T': 0.34106247052266003}
```

[46]:
```
mafs['rs1023497']
```

[46]:
```
{'C': 0.9115666616788868, 'G': 0.08805925482567709, 'T': 0.0003740834954361814}
```

[47]:
```
mafs['rs10489202']
```

[47]:
```
{'G': 0.7572409986349701, 'T': 0.24275900136502987}
```

Most seem to be tri-allelic and risk allele is not specified. Some don't appear to have data for the risk allele.

Also inspect the ones with AFs close to 1:

[48]:
```
ones = out_df[out_df['maf'] > 0.99]
len(ones)
```

[48]:
```
8
```

[49]:
```
ones.head()
```

[49]:

	variant_and_allele	p_value	trait	gene	location	maf
1230	rs117509195-G	5.000000e-06	schizophrenia	LINC00301	11:60619545	0.995525
575	rs12620761-C	2.000000e-06	schizophrenia	MGAT5	2:134096560	0.998044
1339	rs148114321-T	9.000000e-06	schizophrenia	RALGAPA1	14:35744236	0.992117
1412	rs190474885-C	1.000000e-06	schizophrenia	NT5C2	10:103213560	0.991070
894	rs60005721-A	8.000000e-09	schizophrenia	CMAHP	6:25262991	1.000000

[50]:
```
mafs['rs60005721']
```

[50]:
```
{'A': 1.0}
```

[51]:
```
mafs['rs117509195']
```

[51]:
```
{'C': 0.004475005457323728, 'G': 0.9955249945426763}
```

Interestingly, some of the reported risk alleles appear to be the dominant allele, not the minor alleles.

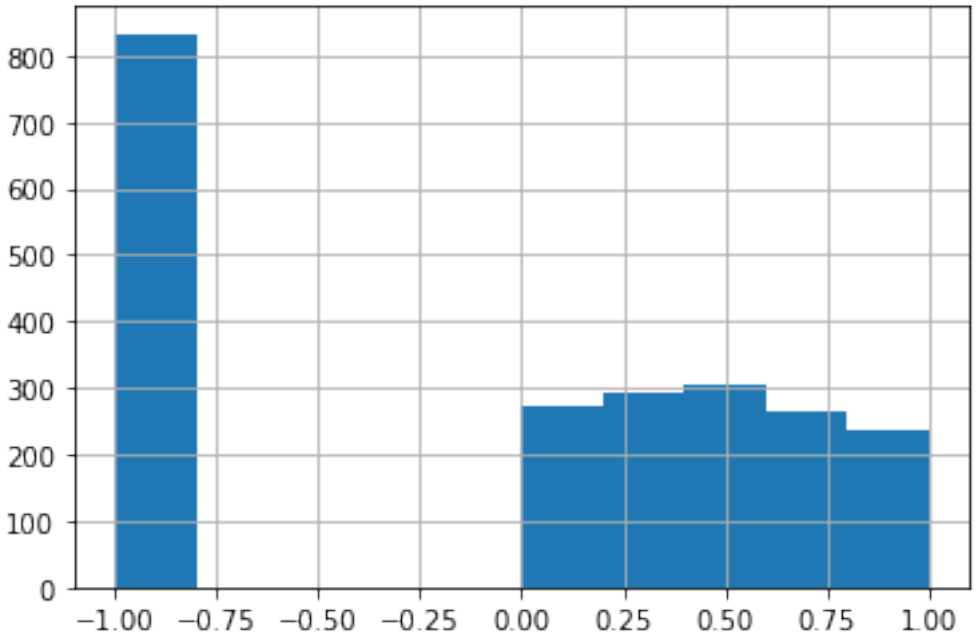
This means the assumption to choose the min AF for biallelic variants may not be correct. Fix that, even though a significant number of variants do not report the risk allele:

[52]:
```
def try_get_maf_for_variant_and_allele(variant_and_allele):
  variant, allele = parse_variant_and_allele(variant_and_allele)
  if variant not in mafs:
    return UNKNOWN_AF

  var_mafs = mafs[variant]
  if allele == UNKNOWN_ALLELE or allele not in var_mafs:
    return UNKNOWN_AF

  return var_mafs[allele]


out_df['maf'] = out_df['variant_and_allele'].
 ↪map(try_get_maf_for_variant_and_allele)
out_df['maf'].describe()
```

[52]:
```
count    2201.000000
mean       -0.075961
std         0.753832
min        -1.000000
25%        -1.000000
50%         0.196713
75%         0.560081
max         1.000000
Name: maf, dtype: float64
```

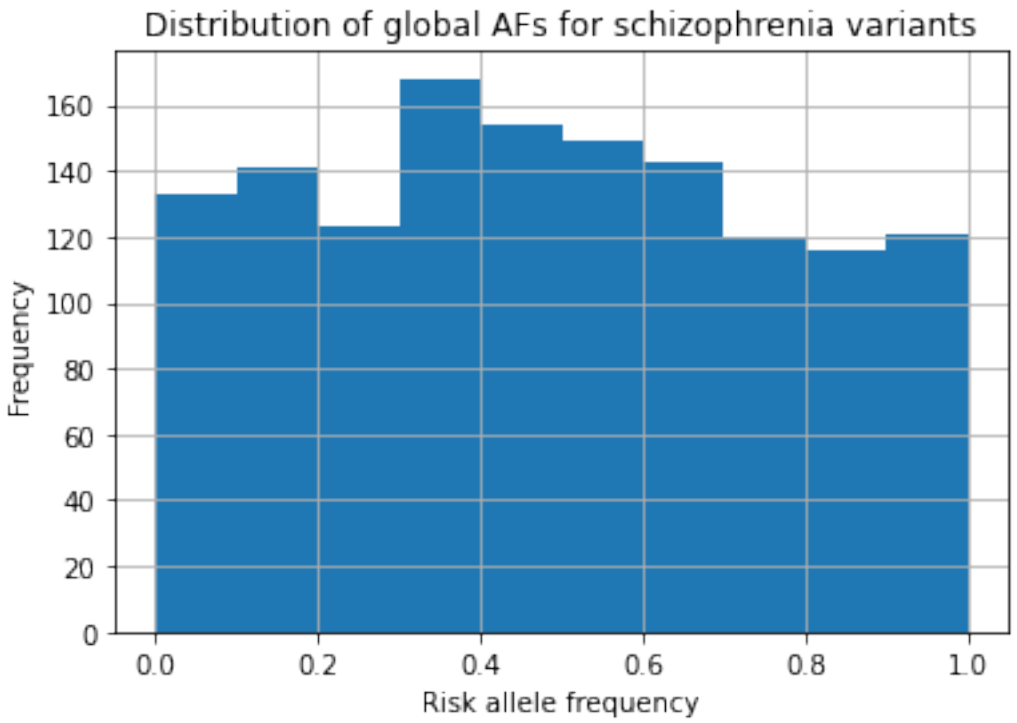
[53]:
```
out_df['maf'].hist()
```

[53]:
```
<matplotlib.axes._subplots.AxesSubplot at 0x7f652b15a890>
```



[54]:
```
ax = out_df[out_df['maf'] > 0]['maf'].plot(kind='hist',
                                           grid=True,
                                           title='Distribution of global AFs for␣
 ↪schizophrenia variants')
ax.set_xlabel('Risk allele frequency')
```

[54]: Text(0.5, 0, 'Risk allele frequency')



[55]:
```
unknowns = out_df[out_df['maf'] < 0.0]
print(f'{len(unknowns)} variants with unknown risk alleles out of {len(out_df)}␣
 ↪total variants')
```

```
833 variants with unknown risk alleles out of 2201 total variants
```

3 Join with cis-eQTL data

Join with processed lists of variants signficantly associated with genes in select tissues.

[56]:
```
tissue_files = [
  'Adipose_Subcutaneous.significant_variant_locations.txt',
  'Adipose_Visceral_Omentum.significant_variant_locations.txt',
  'Adrenal_Gland.significant_variant_locations.txt',
  'Artery_Aorta.significant_variant_locations.txt',
  'Artery_Coronary.significant_variant_locations.txt',
  'Artery_Tibial.significant_variant_locations.txt',
  'Brain_Amygdala.significant_variant_locations.txt',
  'Brain_Anterior_cingulate_cortex_BA24.significant_variant_locations.txt',
  'Brain_Caudate_basal_ganglia.significant_variant_locations.txt',
  'Brain_Cerebellar_Hemisphere.significant_variant_locations.txt',
  'Brain_Cerebellum.significant_variant_locations.txt',
```

```
  'Brain_Cortex.significant_variant_locations.txt',
  'Brain_Frontal_Cortex_BA9.significant_variant_locations.txt',
  'Brain_Hippocampus.significant_variant_locations.txt',
  'Brain_Hypothalamus.significant_variant_locations.txt',
  'Brain_Nucleus_accumbens_basal_ganglia.significant_variant_locations.txt',
]
```

[57]:
```
NON_RSVAR_FORMAT_LOCATION_VALUE = 'Mapping not available'
INVALID_LOCATION = 'Invalid variant location'


def gtex_location_to_gwas_location(gtex_location: Text) -> Text:
  """Converts variant locations in GWAS catalog format to GTEx format.

  i.e. given 'chr1_64764_C_T_b38', returns '4:79296443'.
  """
  parts = gtex_location.split("_")
  chr = parts[0][3]
  return f'{chr}:{parts[1]}'


def find_tissue_associations(variant_pos_set: Set, tissue_filepath: Text) ->␣
 ↪Dict[Text, Text]:
  """Identifies variants with significant tissue associations.

  Returns:
      A dict mapping variant locations to tissue. Always same tissue per
      function invocation, but idea is to merge later.
  """
  tissue_associations = {}
  tissue = tissue_filepath.split(".")[0]
  with open(tissue_filepath) as tissue_file:
    for variant_pos_with_allele in tissue_file.readlines():
      gwas_variant_pos = gtex_location_to_gwas_location(variant_pos_with_allele)
      if gwas_variant_pos in variant_pos_set:
        tissue_associations[gwas_variant_pos] = tissue
  return tissue_associations


variant_positions = set(out_df['location'])
variant_positions.remove(NON_RSVAR_FORMAT_LOCATION_VALUE)
for tissue_file in tissue_files:
  tas = find_tissue_associations(variant_positions, tissue_file)
  num_associations = len(tas.keys())
  tissue = tissue_file.split(".")[0]
  print(f'Found {num_associations} associations with tissue {tissue}')
```

```
Found 314 associations with tissue Adipose_Subcutaneous
Found 260 associations with tissue Adipose_Visceral_Omentum
Found 173 associations with tissue Adrenal_Gland
Found 275 associations with tissue Artery_Aorta
Found 134 associations with tissue Artery_Coronary
Found 316 associations with tissue Artery_Tibial
Found 76 associations with tissue Brain_Amygdala
Found 112 associations with tissue Brain_Anterior_cingulate_cortex_BA24
Found 172 associations with tissue Brain_Caudate_basal_ganglia
Found 179 associations with tissue Brain_Cerebellar_Hemisphere
Found 218 associations with tissue Brain_Cerebellum
Found 182 associations with tissue Brain_Cortex
Found 157 associations with tissue Brain_Frontal_Cortex_BA9
Found 125 associations with tissue Brain_Hippocampus
Found 111 associations with tissue Brain_Hypothalamus
Found 157 associations with tissue Brain_Nucleus_accumbens_basal_ganglia
```