# Excluding correlated immune cell and Adding metabolic traits & auto immune traits:

34 representative Immune Cell traits,6 Autoimmune Rheumatoid Arthritis traits, 8 Metabolic traits, Autoimmune\_Ankylosing\_spondylitis, Autoimmune\_Inflammatory\_bowel\_disease, Autoimmune\_thyroid\_Graves\_disease, Autoimmune\_thyroid\_Hashimotos\_disease, Autoimmune\_Celiac

[1] "BAFF-R on CD20- CD38-\_panel\_B cell"

[2] "BAFF-R on memory B cell\_panel\_B cell"

[3] "CD19 on CD20-\_panel\_B cell"

[4] "CD19 on memory B cell\_panel\_B cell"

[5] "CD20 on memory B cell\_panel\_B cell"

[6] "CD24 on memory B cell\_panel\_B cell"

[7] "CD25 on CD24+ CD27+\_panel\_B cell"

[8] "CD27 on sw mem\_panel\_B cell"

[9] "CD38 on IgD+ CD38dim\_panel\_B cell"

[10] "IgD on IgD+ CD38dim\_panel\_B cell"

[11] "CD3 on CD8br\_panel\_Treg"

[12] "CD3 on CD4 Treg\_panel\_Treg"

[13] "HVEM on CD4+\_panel\_Maturation stages of T cell"

[14] "CD28 on CD4 Treg\_panel\_Treg"

[15] "CD86 on granulocyte\_panel\_cDC"

[16] "CCR7 on naive CD4+\_panel\_Maturation stages of T cell"

[17] "CD45 on lymphocyte\_panel\_TBNK"

[18] "CD127 on CD4+\_panel\_Treg"

[19] "CD25 on CD4 Treg\_panel\_Treg"

[20] "CD25 on CD39+ resting Treg\_panel\_Treg"

[21] "CD123 on plasmacytoid DC\_panel\_cDC"

[22] "CD14 on CD14+ CD16+ monocyte\_panel\_Monocyte"

[23] "CD40 on monocytes\_panel\_Monocyte"

[24] "CD64 on CD14+ CD16- monocyte\_panel\_Monocyte"

[25] "CX3CR1 on monocyte\_panel\_Monocyte"

[26] "HLA DR on monocyte\_panel\_Monocyte"

[27] "CCR2 on CD62L+ myeloid DC\_panel\_cDC"

[28] "CD39 on CD39+ CD4+\_panel\_Treg"

[29] "CD8 on CD8br\_panel\_TBNK"

[30] "CD4 on activated Treg\_panel\_Treg"

[31] "CD11c on granulocyte\_panel\_cDC"

[32] "CD45RA on naive CD4+\_panel\_Maturation stages of T cell"

[33] "HLA DR on HLA DR+ T cell\_panel\_TBNK"

[34] "HLA DR on HLA DR+ CD4+\_panel\_TBNK"

[35] "all rheumatoid arthritis multi-ancestry"

[36] "all rheumatoid arthritis EUR"

[37] "all rheumatoid arthritis EAS"

[38] "rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement multi-ancestry"

[39] "rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement EUR"

[40] "rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement EAS"

[41] "diamante\_T2D-European"

[42] "diamante\_T2Dbmiadj-European"

[43] "childhood-bmi\_7years"

[44] "childhood-bmi\_3years"

[45] "MAGIC\_HbA1c-EUR"

[46] "MAGIC\_FI-EUR(negative control trait)"

[47] "MAGIC\_FG-EUR"

[48] "cardio-ukbb\_CAD(negative control trait)"

[49] "Autoimmune\_Ankylosing\_spondylitis"

[50] "Autoimmune\_Inflammatory\_bowel\_disease"

[51] "Autoimmune\_thyroid\_Graves\_disease"

[52] "Autoimmune\_thyroid\_Hashimotos\_disease"

[53] "Autoimmune\_Celiac"

## SECTION 2: PULL SIGNIFICANT VARIANTS FROM MAIN TRAIT GWAS

"Pulling significant SNPs w/ pval<5.0e-08 from 1 T1D GWAS...":

No. total SNPs below pval cutoff: 44761

No. unique SNPs: 44760 -- remove duplicates with the same hm\_variant\_id

No. SNPs excluding indels: 42324---only select SNPs?

mutate(alleles = paste0(REF,ALT)) %>%

subset(nchar(alleles)==2 | (nchar(alleles)<=4 & grepl(",",alleles)))

## SECTION 3: VARIANT PRUNING (LD-BASED) for MAIN TRAIT GWAS

Chr 1 pruned from 914 to 30 SNPs...

Chr2 pruned from 241 to 12 SNPs...

Chr 3 (0 SNPs)

Chr4 pruned from 389 to 4 SNPs...

Chr5 pruned from 50 to 3 SNPs...

Chr 6 (35,746 SNPs): Chromosome has >5000 SNPs; Chr6 pruned from 35746 to 215 SNPs...

Chr7 pruned from 742 to 6 SNPs...

Chr8 pruned from 62 to 3 SNPs...

Chr9 pruned from 32 to 1 SNPs...

Chr10 pruned from 308 to 12 SNPs...

Chr11 pruned from 461 to 28 SNPs...

Chr12 pruned from 968 to 14 SNPs...

Chr13 pruned from 16 to 2 SNPs...

Chr14 pruned from 107 to 4 SNPs...

Chr15 pruned from 34 to 1 SNPs...

Chr16 pruned from 1004 to 11 SNPs...

Chr17 pruned from 278 to 6 SNPs...

Chr18 pruned from 212 to 6 SNPs...

Chr19 pruned from 191 to 4 SNPs...

Chr20 pruned from 70 to 1 SNPs...

Chr21 pruned from 130 to 5 SNPs...

Chr22 pruned from 369 to 3 SNPs...

**T1D SNPs pruned from 42324 to 371...**

## SECTION 4: VARIANT MISSINGNESS: connect Main GWAS and Trait GWASs

[1] "...Reading CD3 on CD8br\_panel\_Treg...: 291 rows, Time taken: 0.607743430137634 min"

[1] "...Reading HLA DR on HLA DR+ CD4+\_panel\_TBNK...: 291 rows, Time taken: 0.622484568754832 min"

[1] "...Reading HLA DR on HLA DR+ T cell\_panel\_TBNK...: 291 rows, Time taken: 0.635582176844279 min"

[1] "...Reading CD38 on IgD+ CD38dim\_panel\_B cell...: 292 rows, Time taken: 0.661892386277517 min"

[1] "...Reading CD19 on CD20-\_panel\_B cell...: 292 rows, Time taken: 0.686374680201213 min"

[1] "...Reading CD3 on CD4 Treg\_panel\_Treg...: 291 rows, Time taken: 0.794898207982381 min"

[1] "...Reading CD123 on plasmacytoid DC\_panel\_cDC...: 291 rows, Time taken: 0.881523362795512 min"

[1] "...Reading CD20 on memory B cell\_panel\_B cell...: 292 rows, Time taken: 0.901710430781047 min"

[1] "...Reading CD24 on memory B cell\_panel\_B cell...: 292 rows, Time taken: 0.957767983277639 min"

[1] "...Reading CD28 on CD4 Treg\_panel\_Treg...: 291 rows, Time taken: 1.01106550693512 min"

[1] "...Reading rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement multi-ancestry...: 325 rows, Time taken: 0.340750702222188 min"

[1] "...Reading HVEM on CD4+\_panel\_Maturation stages of T cell...: 286 rows, Time taken: 1.02799898783366 min"

[1] "...Reading CCR7 on naive CD4+\_panel\_Maturation stages of T cell...: 291 rows, Time taken: 1.03560524781545 min"

[1] "...Reading Autoimmune\_Ankylosing\_spondylitis...: 35 rows, Time taken: 0.040138586362203 min"

[1] "...Reading CD40 on monocytes\_panel\_Monocyte...: 292 rows, Time taken: 1.05376319885254 min"

[1] "...Reading CCR2 on CD62L+ myeloid DC\_panel\_cDC...: 291 rows, Time taken: 1.07615760564804 min"

[1] "...Reading IgD on IgD+ CD38dim\_panel\_B cell...: 292 rows, Time taken: 1.0840557773908 min"

[1] "...Reading BAFF-R on CD20- CD38-\_panel\_B cell...: 292 rows, Time taken: 1.08879172007243 min"

[1] "...Reading BAFF-R on memory B cell\_panel\_B cell...: 292 rows, Time taken: 1.09549127022425 min"

[1] "...Reading HLA DR on monocyte\_panel\_Monocyte...: 292 rows, Time taken: 1.10765644311905 min"

[1] "...Reading CD19 on memory B cell\_panel\_B cell...: 292 rows, Time taken: 1.123550649484 min"

[1] "...Reading CD25 on CD4 Treg\_panel\_Treg...: 292 rows, Time taken: 1.16217503150304 min"

[1] "...Reading CD45 on lymphocyte\_panel\_TBNK...: 292 rows, Time taken: 1.19206965764364 min"

[1] "...Reading CD14 on CD14+ CD16+ monocyte\_panel\_Monocyte...: 292 rows, Time taken: 1.21837398608526 min"

[1] "...Reading CD39 on CD39+ CD4+\_panel\_Treg...: 291 rows, Time taken: 1.21965528329213 min"

[1] "...Reading CD127 on CD4+\_panel\_Treg...: 291 rows, Time taken: 1.24030997355779 min"

[1] "...Reading Autoimmune\_Celiac...: 51 rows, Time taken: 0.0174506545066834 min"

[1] "...Reading CD8 on CD8br\_panel\_TBNK...: 292 rows, Time taken: 1.2628725806872 min"

[1] "...Reading childhood-bmi\_3years...: 282 rows, Time taken: 0.616014365355174 min"

[1] "...Reading CD27 on sw mem\_panel\_B cell...: 292 rows, Time taken: 1.31674334208171 min"

[1] "...Reading CD25 on CD39+ resting Treg\_panel\_Treg...: 292 rows, Time taken: 1.33859004179637 min"

[1] "...Reading CD25 on CD24+ CD27+\_panel\_B cell...: 292 rows, Time taken: 1.34905580679576 min"

[1] "...Reading CD86 on granulocyte\_panel\_cDC...: 291 rows, Time taken: 1.35428594748179 min"

[1] "...Reading CD4 on activated Treg\_panel\_Treg...: 291 rows, Time taken: 1.35354614257812 min"

[1] "...Reading rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement EAS...: 195 rows, Time taken: 0.463932792345683 min"

[1] "...Reading CX3CR1 on monocyte\_panel\_Monocyte...: 292 rows, Time taken: 1.36943566004435 min"

[1] "...Reading CD45RA on naive CD4+\_panel\_Maturation stages of T cell...: 291 rows, Time taken: 1.38881995677948 min"

[1] "...Reading CD64 on CD14+ CD16- monocyte\_panel\_Monocyte...: 292 rows, Time taken: 1.39272385835648 min"

[1] "...Reading CD11c on granulocyte\_panel\_cDC...: 291 rows, Time taken: 1.43731716871262 min"

[1] "...Reading rheumatoid arthritis; anti-citrullinated protein antibody seropositivity; rheumatoid factor seropositivity measurement EUR...: 303 rows, Time taken: 0.329042490323385 min"

[1] "...Reading all rheumatoid arthritis EAS...: 232 rows, Time taken: 0.363469556967417 min"

[1] "...Reading all rheumatoid arthritis EUR...: 306 rows, Time taken: 0.391419355074565 min"

[1] "...Reading all rheumatoid arthritis multi-ancestry...: 329 rows, Time taken: 1.47985031207403 min"

[1] "...Reading MAGIC\_FG-EUR...: 342 rows, Time taken: 0.718753945827484 min"

[1] "...Reading MAGIC\_FI-EUR(negative control trait)...: 341 rows, Time taken: 0.942476801077525 min"

[1] "...Reading diamante\_T2D-European...: 318 rows, Time taken: 0.615927302837372 min"

[1] "...Reading cardio-ukbb\_CAD(negative control trait)...: 265 rows, Time taken: 0.56096894343694 min"

[1] "...Reading childhood-bmi\_7years...: 281 rows, Time taken: 0.386248528957367 min"

[1] "...Reading MAGIC\_HbA1c-EUR...: 341 rows, Time taken: 0.621120897928874 min"

[1] "...Reading diamante\_T2Dbmiadj-European...: 315 rows, Time taken: 0.383619089921315 min"

[1] "...Reading Autoimmune\_thyroid\_Graves\_disease...: 356 rows, Time taken: 0.812950146198273 min"

[1] "...Reading Autoimmune\_Inflammatory\_bowel\_disease...: 333 rows, Time taken: 0.502480598290761 min"

[1] "...Reading Autoimmune\_thyroid\_Hashimotos\_disease...: 356 rows, Time taken: 0.79406483968099 min"

var\_nonmissingness --- 371 variant

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6\_32654016\_G\_T 6\_32654124\_C\_G 6\_32663430\_A\_T 6\_32664759\_G\_T

0.83018868 0.18867925 0.07547170 0.18867925

6\_32665073\_G\_A 6\_32666034\_C\_T 6\_32674140\_G\_A 6\_32678618\_A\_G

0.20754717 0.18867925 0.11320755 0.20754717

6\_32679665\_T\_C 6\_32684214\_A\_G 6\_32689055\_C\_T 6\_32709749\_T\_C

0.81132075 0.75471698 0.16981132 0.11320755

6\_32714887\_C\_T 6\_32719145\_C\_T 6\_32733140\_A\_G 6\_32750491\_G\_A

0.98113208 0.90566038 0.90566038 0.96226415

6\_32764084\_T\_A 6\_32776199\_C\_T 6\_32782386\_T\_C 6\_32800556\_G\_A

0.96226415 0.90566038 0.84905660 0.88679245

6\_32828535\_T\_C 6\_32832146\_T\_C 6\_32840819\_C\_T 6\_32846350\_G\_A

0.13207547 0.96226415 0.86792453 0.96226415

6\_32864260\_T\_C 6\_32888301\_C\_T 6\_32919692\_A\_G 6\_32921245\_T\_C

0.96226415 0.18867925 0.96226415 0.26415094

6\_32932651\_G\_A 6\_32944263\_C\_T 6\_32969254\_C\_T 6\_32976969\_G\_A

0.24528302 0.26415094 0.92452830 0.98113208

6\_32991684\_G\_T 6\_32997190\_A\_G 6\_32997567\_C\_T 6\_33003905\_G\_A

0.13207547 0.96226415 0.94339623 0.90566038

6\_33008408\_G\_A 6\_33011220\_C\_T 6\_33016312\_T\_C 6\_33019058\_G\_C

0.96226415 0.98113208 0.94339623 0.96226415

6\_33048731\_C\_T 6\_33056255\_C\_A 6\_33061632\_T\_G 6\_33072388\_G\_T

0.96226415 0.96226415 0.96226415 0.96226415

6\_33082686\_C\_G 6\_33107429\_C\_T 6\_33139645\_C\_T 6\_33141505\_C\_T

0.96226415 0.84905660 0.96226415 0.79245283

6\_33181602\_G\_A 6\_33187162\_G\_C 6\_33189235\_G\_A 6\_33201504\_G\_A

0.96226415 0.13207547 0.90566038 0.88679245

6\_33255411\_G\_A 6\_33290192\_C\_T 6\_33299744\_C\_T 6\_33308762\_C\_T

0.92452830 0.09433962 0.94339623 0.86792453

6\_33414511\_G\_A 6\_33454056\_G\_A 6\_33529780\_C\_T 6\_33577348\_A\_G

0.96226415 0.96226415 0.73584906 0.96226415

6\_33579472\_C\_T 6\_33606217\_G\_A 6\_33610829\_C\_G 6\_33626164\_G\_A

0.96226415 0.88679245 0.86792453 0.92452830

6\_33629919\_C\_T 6\_33651133\_C\_T 6\_33687396\_T\_C 6\_33760874\_A\_G

0.96226415 0.96226415 0.88679245 0.28301887

6\_33774712\_G\_A 6\_33811187\_A\_G 6\_33833733\_A\_G 6\_33834822\_A\_C

0.92452830 1.00000000 0.96226415 0.28301887

6\_33853345\_G\_A 6\_33877854\_C\_T 6\_33892376\_G\_C 6\_33902222\_A\_G

0.96226415 0.96226415 0.94339623 0.96226415

6\_33928749\_G\_A 6\_33994457\_C\_T 6\_428416\_C\_T 6\_90289744\_G\_A

0.92452830 0.26415094 0.98113208 0.94339623

6\_90305320\_C\_T 7\_117314731\_A\_C 7\_20410918\_T\_C 7\_26853738\_A\_C

1.00000000 0.96226415 0.92452830 0.96226415

7\_50269215\_G\_C 7\_50392217\_G\_A 7\_50965904\_A\_G 8\_119074613\_A\_G

0.96226415 1.00000000 0.92452830 0.96226415

8\_140606084\_T\_C 8\_58959618\_A\_G 9\_4289196\_T\_C

0.96226415 0.96226415 0.98113208

## SECTION 5: DETERMINE VARIANTS NEEDING PROXIES

Choosing variants in need of proxies...

...63 strand-ambiguous variants

...0 multi-allelic variants

...94 variants with excessive missingness **# missing cutoff=0.8**

...140 unique variants in total in need of proxies

Choosing variants in need of proxies...

"...63 strand-ambiguous variants"

"...0 multi-allelic variants"

"...78 variants with excessive missingness" **# missing cutoff=0.5**

"...126 unique variants in total in need of proxies

Choosing variants in need of proxies...

...63 strand-ambiguous variants

...0 multi-allelic variants

...77 variants with excessive missingness **# missing cutoff=0.3**

...126 unique variants in total in need of proxies

**I use missing cutoff=0.3** **as the threshold**

## SECTION 6: PROXY SEARCH - time consuming

No. possible proxies found: 1396

**After finding the proxies, still need to assess variant missingness across traits!**

No proxies needed for 245 variants. # what criterion

No adequate proxies found for 87 variants. # what criterion

Proxies found for 39 variants. **# final\_proxy**

## SECTION 7: Fetch summary statistics for SNPs in trait GWAS

245 original SNPs (=371-126)

39 proxy SNPs...

284 total unique SNPs!

284 of 284 variants are available in the primary GWAS

Max p-value in primary GWAS: 4.630e-08

0 variants with opposite risk allele and above Bonferroni cutoff **# pval\_bonf <- 0.05/nrow(variant\_df)**

0 variants above absolute p-value cutoff **# pval\_cutoff=0.05**

0 unique variants being dropped due to risk allele or p-value

284 variants after p-value and risk allele filter

284 remaining SNPs after p-value filtering

## Section 8: get rsIDs for final variant set

rsIDs found for 284 of 284 SNPs

## Section 9: Fill missing data in z-score and N matrices

Filling missing zscores with trait medians # what criterion

## Section 10.) Generate non-negative z-score matrix

All output in section 10 has been saved to: ./test\_results/section10\_prep\_z\_printoutput.txt

prep\_z\_output has two outputs:

1. The scaled, non-negative z-score matrix
2. Results from the trait filtering (whether the trait is removed or not)

Final matrix: 284 SNPs x 28 traits

## Section 11.) Run bNMF