# Biological Large-scale data analysis —SNPs Disease-association Predictor

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# Outline

- Background
- Database
- Data
- Methods and Results
- Acknowledgement

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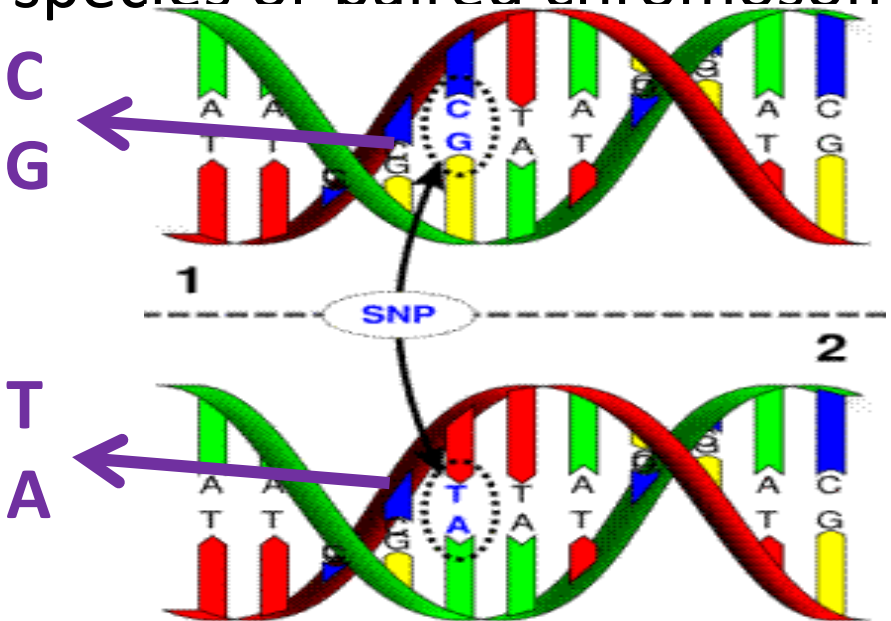
# Background

- **SNP(single nucleotide polymorphism)** is a DNA sequence variation occurring when a single nucleotide — A, T, C or G — in the genome (or other shared sequence) differs between members of a biological species or paired chromosomes in a human.

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# Background

- **The difference between the SNP and the mutation**

SNP ——the variant frequency > = 1%

Mutation ——the variant frequency < 1%

- **There are many SNPs in the human genome**

Every 1000 basic groups appear a SNP

$3x10^6$ SNPs in human genome

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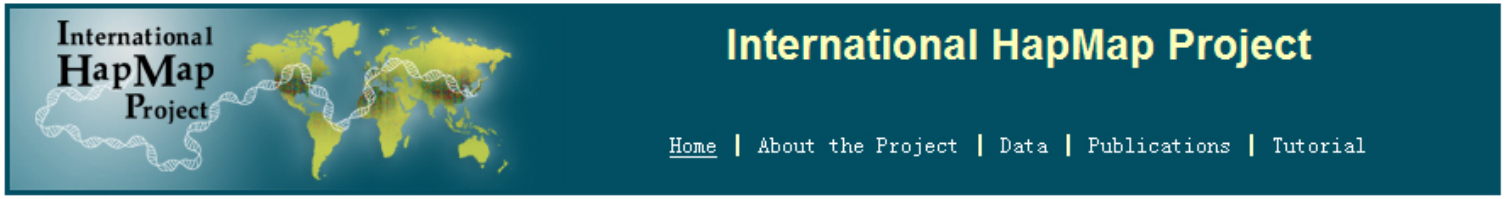
# Background

## ➢ The International HapMap Project

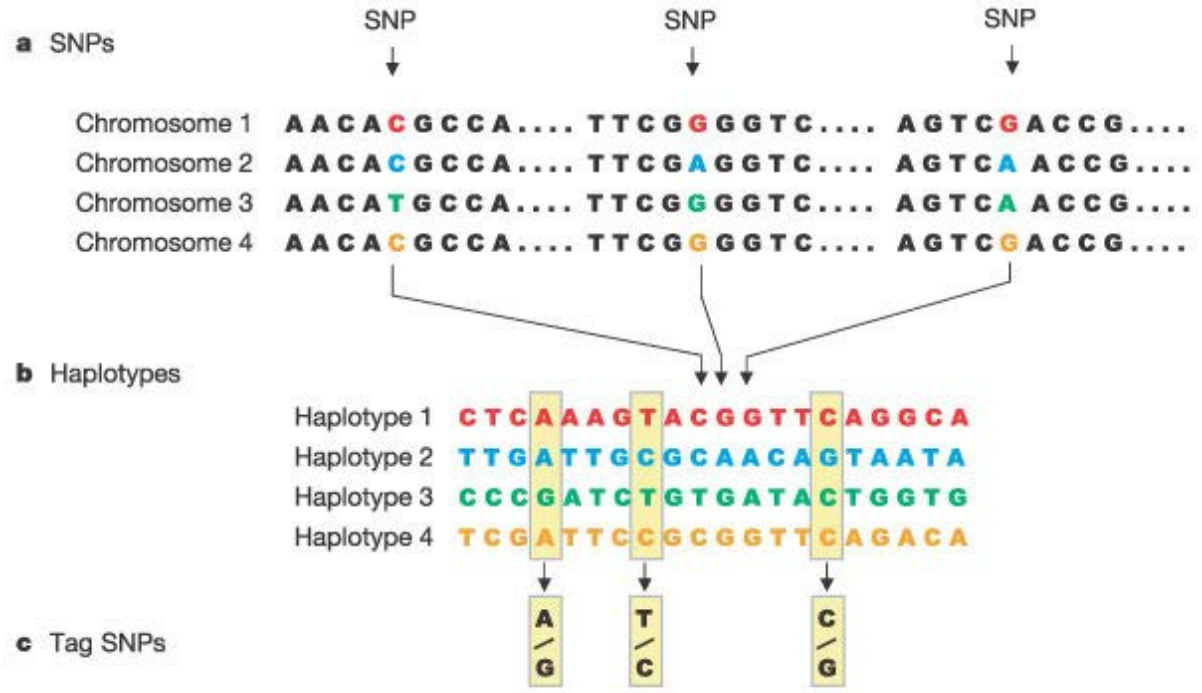
HapMap ( Haplotype Map )




http://hapmap.ncbi.nlm.nih.gov/index.html.en

# Background

## ➢SNPs haplotypes and tag SNPs

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# Background

## ➢1000 Genomes


The Phase 1 publication, an Integrated map of genetic variation from 1092 human genomes.

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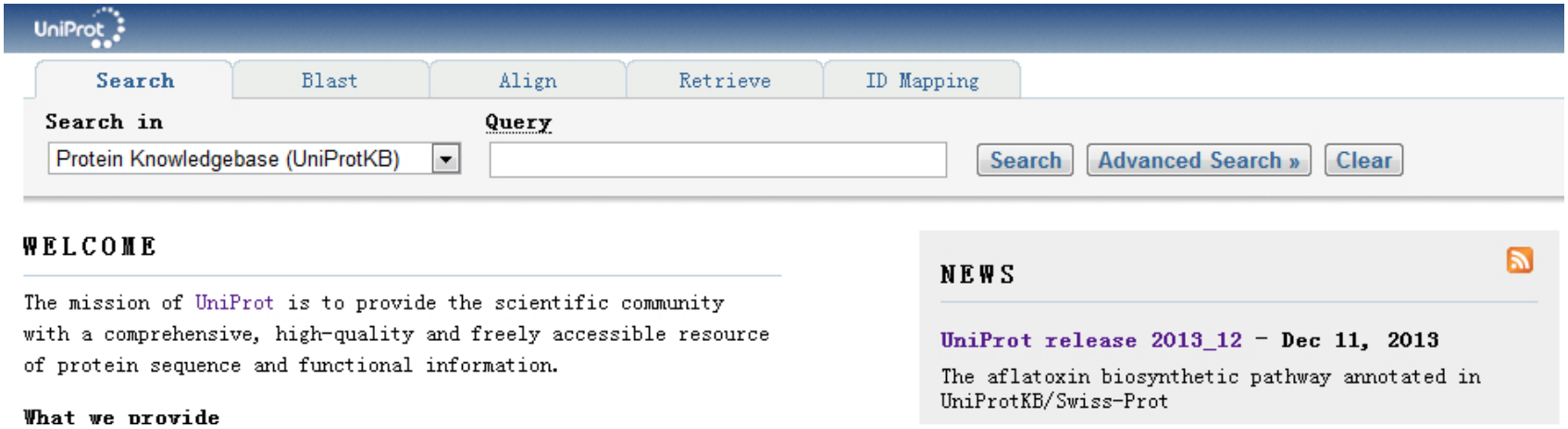
# Database

## ➢Uniprot




http://www.uniprot.org/

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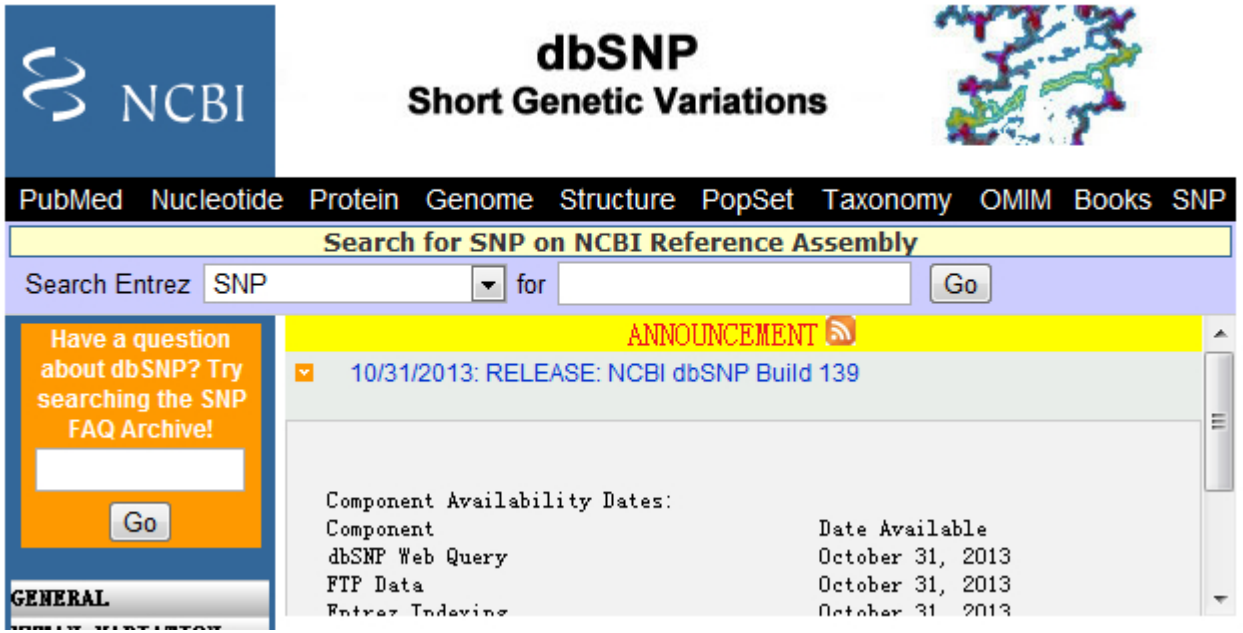
# Database

## ➢dbSNP




http://www.ncbi.nlm.nih.gov/projects/SNP/

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# Database

## ➢SwissVar


HOME | SEARCH | STATISTICS | DOCUMENTATION | USEFUL LINKS | CONTACT | PUBLICATIONS

**Search for disease - protein - variant associations**

search

Enter a disease (e.g.: cataract), a protein or gene name (e.g.: Plasminogen)

A portal to Swiss-Prot diseases and variants

http://swissvar.expasy.org/

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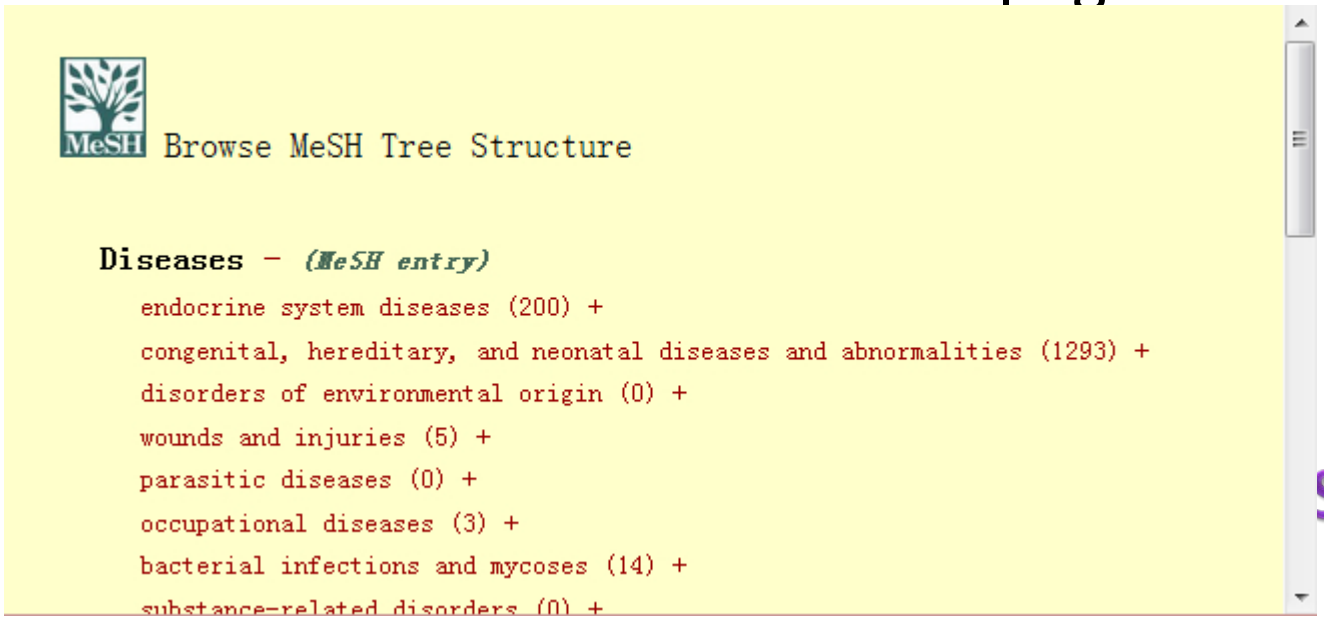
# Database

## ➢SwissVar

SwissVar is a portal to search variants in Swiss-Prot entries of the UniProt Knowledgebase (UniProtKB), and gives direct access to the Swiss-Prot Variant pages.



# Database

## ➢SwissVar

| Accession | Entry name | Disease | Variants | 3D mapping (variant position) |
|---|---|---|---|---|
| P31947 | 1433S_HUMAN | | p.Met155Ile | |
| Q96QU6 | 1A1L1_HUMAN | breast cancer | p.Gly221Glu<br>p.Ser393Leu | |
| P13746 | 1A11_HUMAN | | p.Glu43Lys<br>p.Arg89Gly<br>p.Gln94His | 1Q94D (19)<br>1QVOA (65)<br>1Q94A (70) |

Uniprot

National Library of Medicine - Medical Subject Headings(MeSH)

ExPASy-UniProtKB/Swiss-Prot variant pages

PDB

http://swissvar.expasy.org/

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# Database

**SwissVar**

search categories

- Disease
- Protein name / Gene name
- variant type or structure/function features

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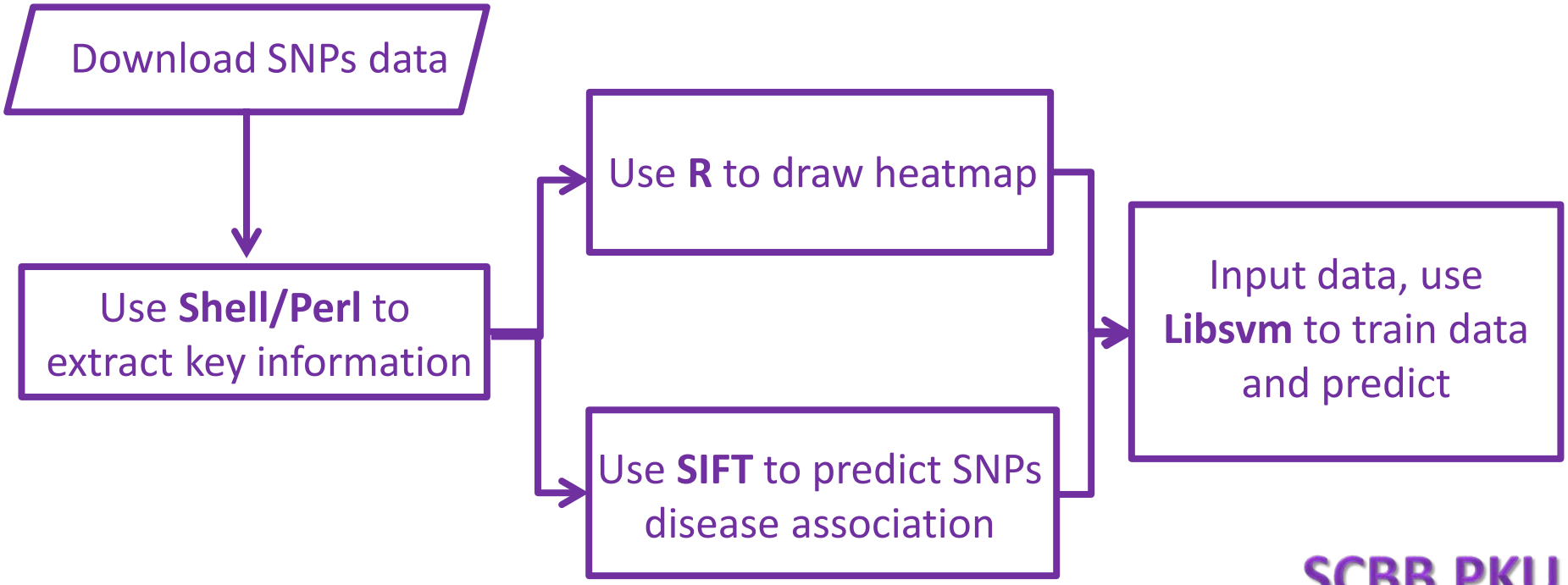
# Data

- Download previous knowledgebase
- Get the file name “humsavar.txt”

| 字段 | 字段说明 | 字节 |
|---|---|---|
| Main gene name | 主要基因的名字 | 1-10 [10] |
| Swiss-Prot AC | Swiss-Prot登录号（Accession Number） | 11-21 [11] |
| FTId | Swiss-Prot特征标识符 | 22-33 [12] |
| AAchange | 格式为：p.突变前+位置+突变后 | 34-48 [15] |
| Type of variant | 变异的类型属于Polymorphism、Disease或Unclassified | 49-62 [14] |
| dbSNP | dbSNP的rs号 | 63-74 [12] |
| Disease name | 涉及的疾病的名称（有些只是sample） | 75-End [...] |

# Methods and Results

## Analysis flow

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# Methods and Results

## ➢ Statistics and analysis data

- Linux shell script commonly used commands

| | |
|---|---|
| ✓ mkdir | Create a directory |
| ✓ cd | Enter the directory |
| ✓ lftp/get | download the files |
| ✓ ls | View the files in the current directory |
| ✓ tar | Compression and decompression command |
| ✓ cat | View the files |
| ✓ less/more | Selectively view |
| ✓ rm | Delete files or directories |

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# Methods and Results

## ➢ Statistics and analysis data

- Linux shell script commonly used commands

| | |
|---|---|
| ✓ pwd | Display the current directory path |
| ✓ cp | Copy the file |
| ✓ mv | Move or change the file and directory name |
| ✓ grep | Search a specific string in the files |
| ✓ cut | Interception of a column |
| ✓ perl | Write a perl program at the command line |
| ✓ awk | Write an awk program at the command line |
| ✓ man | View command Manual |

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# Methods and Results

## ➢ Statistics and analysis data

- Linux Perl script figure out 20*20 amino acids substitution table

After substitution

Before substitution

| | Ala | Arg | Asp | Asn | Cys | Gln | Glu | Gly | His | Ile | Leu | Lys | Met | Phe | Pro | Ser | Thr | Trp | Tyr | Val |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ala | 0 | 1 | 116 | 0 | 0 | 0 | 117 | 251 | 0 | 1 | 4 | 1 | 1 | 0 | 237 | 308 | 1261 | 0 | 0 | 996 |
| Arg | 4 | 0 | 2 | 1 | 700 | 1160 | 6 | 358 | 1005 | 38 | 177 | 312 | 30 | 0 | 144 | 213 | 78 | 572 | 0 | 0 |
| Asp | 77 | 4 | 0 | 525 | 0 | 2 | 346 | 234 | 143 | 0 | 2 | 0 | 0 | 0 | 0 | 5 | 0 | 0 | 108 | 92 |
| Asn | 0 | 0 | 274 | 0 | 0 | 0 | 5 | 0 | 90 | 49 | 0 | 241 | 0 | 1 | 0 | 642 | 98 | 0 | 44 | 0 |
| Cys | 0 | 201 | 0 | 0 | 0 | 1 | 0 | 43 | 0 | 0 | 0 | 1 | 0 | 42 | 0 | 136 | 0 | 41 | 174 | 0 |
| Gln | 0 | 541 | 2 | 0 | 0 | 0 | 187 | 1 | 334 | 0 | 72 | 124 | 0 | 0 | 104 | 0 | 0 | 3 | 0 | 0 |
| Glu | 132 | 2 | 401 | 3 | 0 | 248 | 0 | 310 | 0 | 0 | 4 | 726 | 0 | 0 | 0 | 1 | 2 | 0 | 0 | 85 |
| Gly | 229 | 545 | 291 | 1 | 68 | 1 | 245 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 570 | 0 | 42 | 0 | 189 |
| His | 0 | 420 | 55 | 68 | 0 | 203 | 1 | 0 | 0 | 0 | 42 | 0 | 0 | 0 | 63 | 1 | 0 | 0 | 241 | 0 |
| Ile | 1 | 15 | 0 | 65 | 0 | 0 | 0 | 0 | 0 | 0 | 120 | 11 | 210 | 73 | 0 | 34 | 504 | 0 | 0 | 891 |
| Leu | 3 | 114 | 2 | 0 | 0 | 63 | 1 | 0 | 48 | 135 | 0 | 0 | 150 | 431 | 425 | 148 | 3 | 36 | 4 | 440 |
| Lys | 2 | 427 | 0 | 254 | 0 | 133 | 358 | 0 | 0 | 16 | 0 | 0 | 37 | 0 | 0 | 0 | 106 | 0 | 0 | 1 |
| Met | 0 | 31 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 234 | 132 | 32 | 0 | 0 | 0 | 0 | 316 | 0 | 0 | 444 |
| Phe | 0 | 0 | 1 | 2 | 51 | 0 | 0 | 1 | 1 | 47 | 380 | 0 | 0 | 0 | 0 | 149 | 0 | 0 | 62 | 54 |
| Pro | 244 | 209 | 0 | 0 | 0 | 99 | 0 | 0 | 102 | 1 | 919 | 0 | 0 | 0 | 0 | 685 | 213 | 0 | 0 | 0 |
| Ser | 211 | 221 | 2 | 467 | 204 | 0 | 0 | 347 | 2 | 97 | 318 | 0 | 0 | 247 | 346 | 0 | 298 | 23 | 101 | 1 |
| Thr | 744 | 80 | 1 | 121 | 0 | 0 | 5 | 1 | 0 | 492 | 2 | 83 | 584 | 0 | 177 | 307 | 0 | 0 | 0 | 0 |
| Trp | 0 | 152 | 0 | 0 | 48 | 4 | 0 | 26 | 0 | 0 | 33 | 0 | 0 | 0 | 1 | 19 | 0 | 0 | 0 | 0 |
| Tyr | 0 | 0 | 38 | 27 | 266 | 1 | 0 | 1 | 204 | 1 | 5 | 0 | 0 | 75 | 0 | 54 | 1 | 0 | 0 | 1 |
| Val | 562 | 1 | 38 | 0 | 0 | 0 | 60 | 131 | 0 | 1068 | 392 | 0 | 706 | 83 | 0 | 1 | 0 | 0 | 1 | 0 |

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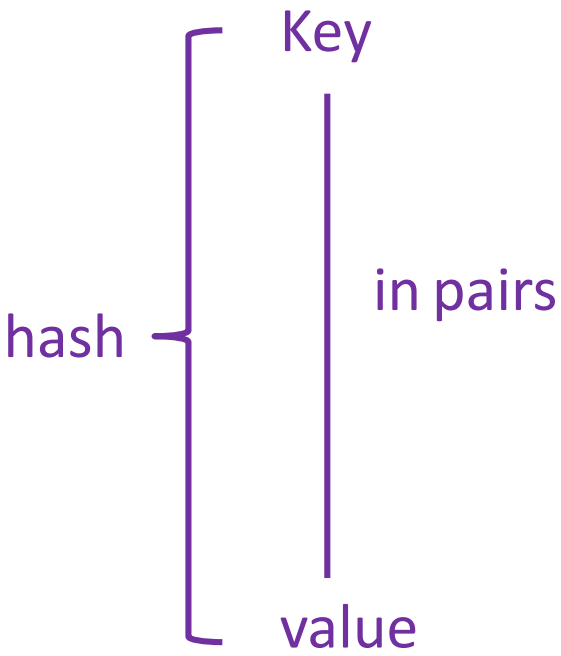
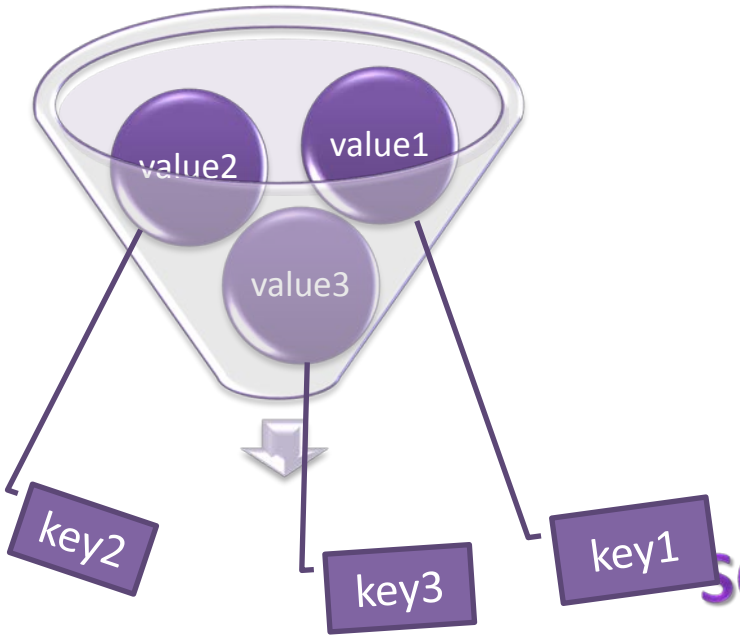
# Methods and Results

## ➢ Statistics and analysis data

- Linux Perl script figure out 20*20 amino acids substitution tables

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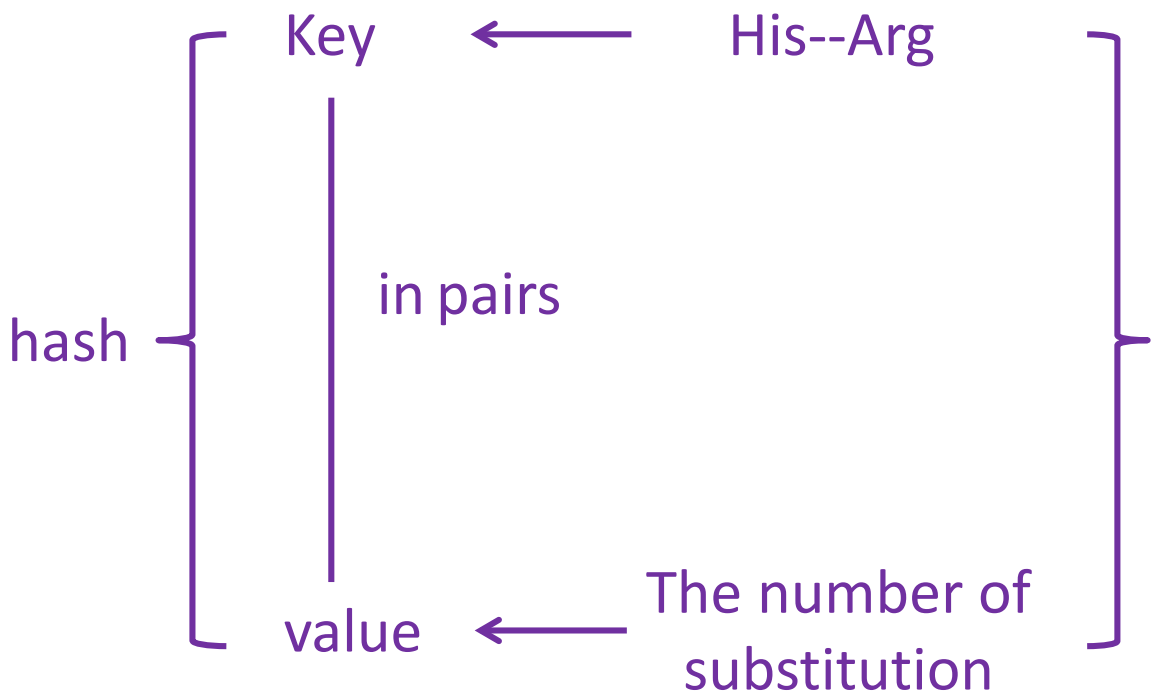
# Methods and Results

## ➢ Statistics and analysis data

| | | | | | | |
|---|---|---|---|---|---|---|
| A1BG | P04217 | VAR_018370 | p.His395Arg | Polymorphism | rs2241788 | - |
| A1CF | Q9NQ94 | VAR_052201 | p.Val555Met | Polymorphism | rs9073 | - |

substitution tables




| | Arg | Met |
|---|---|---|
| His | XX | |
| Val | | XX |

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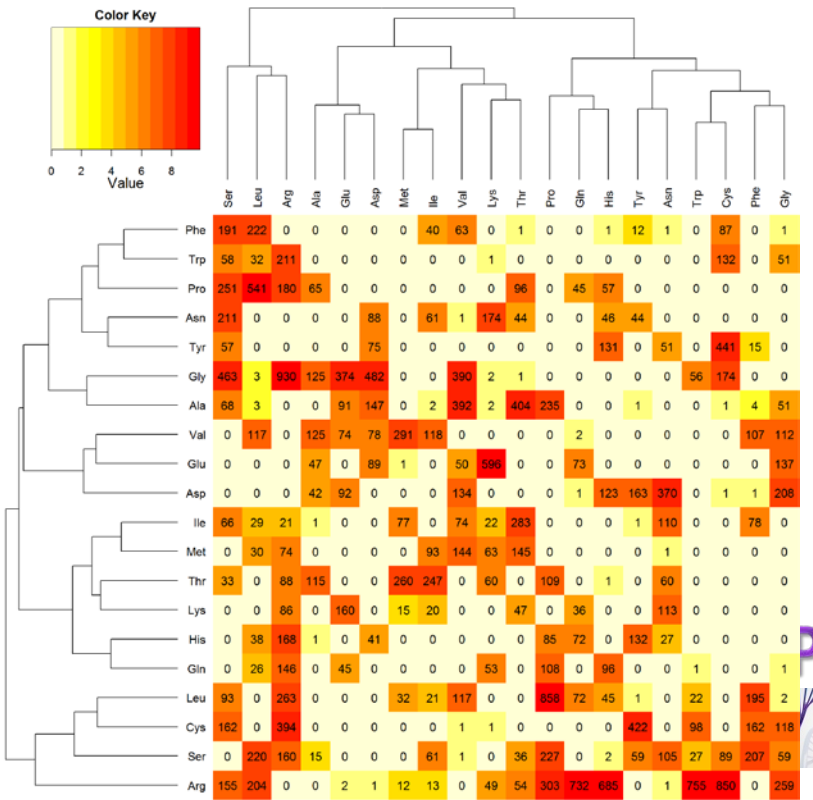
# Methods and Results

## ➢ Draw heatmap

- R draw 20*20 substitution heatmap

| | Ala | Arg | Asp | Asn | Cys | Gln | Glu | Gly | His | Ile | Leu | Lys | Met | Phe | Pro | Ser | Thr | Trp | Tyr | Val |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ala | 0 | 0 | 147 | 0 | 1 | 0 | 91 | 51 | 0 | 2 | 3 | 2 | 0 | 4 | 235 | 68 | 404 | 0 | 1 | 392 |
| Arg | 0 | 0 | 1 | 1 | 850 | 732 | 2 | 259 | 685 | 13 | 204 | 49 | 12 | 0 | 303 | 155 | 54 | 755 | 0 | 0 |
| Asp | 42 | 0 | 0 | 370 | 1 | 1 | 92 | 208 | 123 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 163 | 134 |
| Asn | 0 | 0 | 88 | 0 | 0 | 0 | 0 | 0 | 46 | 61 | 0 | 174 | 0 | 0 | 0 | 211 | 44 | 0 | 44 | 1 |
| Cys | 0 | 394 | 0 | 0 | 0 | 0 | 0 | 118 | 0 | 0 | 0 | 1 | 0 | 162 | 0 | 162 | 0 | 98 | 422 | 1 |
| Gln | 0 | 146 | 0 | 0 | 0 | 0 | 45 | 1 | 96 | 0 | 26 | 53 | 0 | 0 | 108 | 0 | 0 | 1 | 0 | 0 |
| Glu | 47 | 0 | 89 | 0 | 0 | 73 | 0 | 137 | 0 | 0 | 0 | 596 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 50 |
| Gly | 125 | 930 | 482 | 0 | 174 | 0 | 374 | 0 | 0 | 0 | 3 | 2 | 0 | 0 | 0 | 463 | 1 | 56 | 0 | 390 |
| His | 1 | 168 | 41 | 27 | 0 | 72 | 0 | 0 | 0 | 0 | 38 | 0 | 0 | 0 | 85 | 0 | 0 | 0 | 132 | 0 |
| Ile | 1 | 21 | 0 | 110 | 0 | 0 | 0 | 0 | 0 | 0 | 29 | 22 | 77 | 78 | 0 | 66 | 283 | 0 | 1 | 74 |
| Leu | 0 | 263 | 0 | 0 | 0 | 72 | 0 | 2 | 45 | 21 | 0 | 0 | 32 | 195 | 858 | 93 | 0 | 22 | 1 | 117 |
| Lys | 0 | 86 | 0 | 113 | 0 | 36 | 160 | 0 | 0 | 20 | 0 | 0 | 15 | 0 | 0 | 0 | 47 | 0 | 0 | 0 |
| Met | 0 | 74 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 93 | 30 | 63 | 0 | 0 | 0 | 0 | 145 | 0 | 0 | 144 |
| Phe | 0 | 0 | 0 | 1 | 87 | 0 | 0 | 1 | 1 | 40 | 222 | 0 | 0 | 0 | 0 | 191 | 1 | 0 | 12 | 63 |
| Pro | 65 | 180 | 0 | 0 | 0 | 45 | 0 | 0 | 57 | 0 | 541 | 0 | 0 | 0 | 0 | 251 | 96 | 0 | 0 | 0 |
| Ser | 15 | 160 | 0 | 105 | 89 | 0 | 0 | 59 | 2 | 61 | 220 | 0 | 0 | 207 | 227 | 0 | 36 | 27 | 59 | 1 |
| Thr | 115 | 88 | 0 | 60 | 0 | 0 | 0 | 0 | 1 | 247 | 0 | 60 | 260 | 0 | 109 | 33 | 0 | 0 | 0 | 0 |
| Trp | 0 | 211 | 0 | 0 | 132 | 0 | 0 | 51 | 0 | 0 | 32 | 1 | 0 | 0 | 0 | 58 | 0 | 0 | 0 | 0 |
| Tyr | 0 | 0 | 75 | 51 | 441 | 0 | 0 | 0 | 131 | 0 | 0 | 0 | 0 | 15 | 0 | 57 | 0 | 0 | 0 | 0 |
| Val | 125 | 0 | 78 | 0 | 0 | 2 | 74 | 112 | 0 | 118 | 117 | 0 | 291 | 107 | 0 | 0 | 0 | 0 | 0 | 0 |

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# Methods and Results

## ➢ Draw heatmap

- R draw 20*20 substitution heatmap

| | Ala | Arg | Asn | Asp | Cys | Gln | Glu | Gly | His | Ile | Leu | Lys | Met | Phe | Pro | Ser | Thr | Trp | Tyr | Val |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Ala | 0 | 0 | 0 | 609 | 0 | 0 | 762 | 1139 | 0 | 1 | 0 | 0 | 0 | 0 | 1011 | 2418 | 7885 | 0 | 0 | 5937 |
| Arg | 0 | 0 | 0 | 0 | 1624 | 3661 | 0 | 1498 | 3123 | 112 | 684 | 2680 | 151 | 0 | 503 | 1158 | 349 | 1027 | 0 | 0 |
| Asn | 0 | 0 | 0 | 1553 | 0 | 0 | 0 | 0 | 520 | 265 | 0 | 1237 | 0 | 0 | 0 | 3021 | 670 | 0 | 250 | 0 |
| Asp | 445 | 0 | 2671 | 0 | 0 | 0 | 2678 | 1567 | 380 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 311 | 278 |
| Cys | 0 | 703 | 0 | 0 | 0 | 0 | 0 | 230 | 0 | 0 | 0 | 0 | 0 | 307 | 0 | 649 | 0 | 179 | 840 | 0 |
| Gln | 1 | 2046 | 0 | 0 | 0 | 0 | 907 | 0 | 1707 | 0 | 513 | 989 | 0 | 0 | 610 | 0 | 0 | 0 | 0 | 0 |
| Glu | 621 | 0 | 0 | 2714 | 0 | 930 | 0 | 1516 | 0 | 0 | 0 | 2889 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 395 |
| Gly | 1074 | 2160 | 0 | 1747 | 331 | 0 | 1744 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 2970 | 0 | 117 | 0 | 839 |
| His | 0 | 1708 | 547 | 261 | 0 | 1458 | 0 | 0 | 0 | 0 | 333 | 0 | 0 | 0 | 301 | 0 | 0 | 0 | 1393 | 0 |
| Ile | 2 | 100 | 303 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 970 | 110 | 1239 | 379 | 0 | 333 | 1930 | 0 | 0 | 4305 |
| Leu | 0 | 478 | 0 | 0 | 0 | 483 | 0 | 0 | 280 | 1059 | 0 | 0 | 1093 | 2561 | 1734 | 772 | 0 | 111 | 0 | 1752 |
| Lys | 0 | 2290 | 1295 | 0 | 0 | 777 | 1728 | 0 | 0 | 134 | 0 | 0 | 228 | 0 | 0 | 0 | 634 | 0 | 0 | 0 |
| Met | 0 | 173 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1791 | 898 | 186 | 2 | 0 | 1 | 0 | 1322 | 0 | 0 | 1693 |
| Phe | 0 | 0 | 0 | 0 | 235 | 0 | 0 | 0 | 0 | 337 | 1969 | 0 | 0 | 0 | 0 | 747 | 0 | 0 | 434 | 361 |
| Pro | 1027 | 550 | 0 | 0 | 0 | 644 | 0 | 0 | 424 | 1 | 3438 | 0 | 0 | 0 | 0 | 4240 | 1092 | 0 | 0 | 0 |
| Ser | 1526 | 1302 | 3834 | 0 | 856 | 0 | 0 | 1859 | 0 | 501 | 1399 | 0 | 0 | 1276 | 2690 | 0 | 2244 | 71 | 337 | 0 |
| Thr | 4888 | 363 | 766 | 0 | 0 | 0 | 0 | 0 | 0 | 3007 | 0 | 664 | 2083 | 0 | 903 | 2335 | 0 | 0 | 0 | 0 |
| Trp | 0 | 455 | 0 | 0 | 224 | 0 | 0 | 89 | 0 | 0 | 118 | 0 | 0 | 0 | 0 | 66 | 0 | 0 | 0 | 0 |
| Tyr | 0 | 0 | 223 | 170 | 673 | 0 | 0 | 0 | 911 | 0 | 0 | 0 | 0 | 566 | 0 | 242 | 0 | 0 | 0 | 0 |
| Val | 3587 | 0 | 0 | 248 | 0 | 0 | 377 | 679 | 0 | 6097 | 1902 | 0 | 2718 | 429 | 0 | 1 | 0 | 0 | 0 | 0 |

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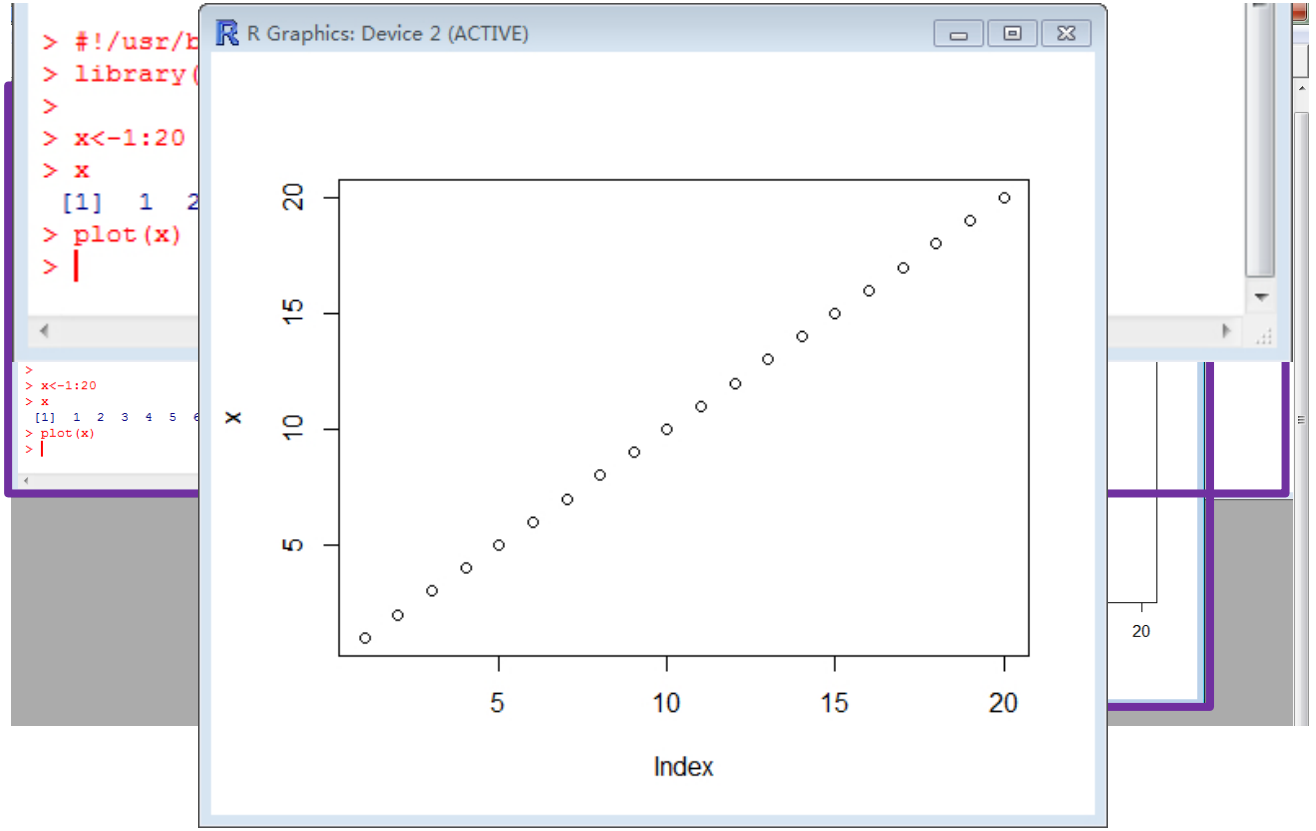
# Methods and Results

## ➢ Draw heatmap

- R introduction

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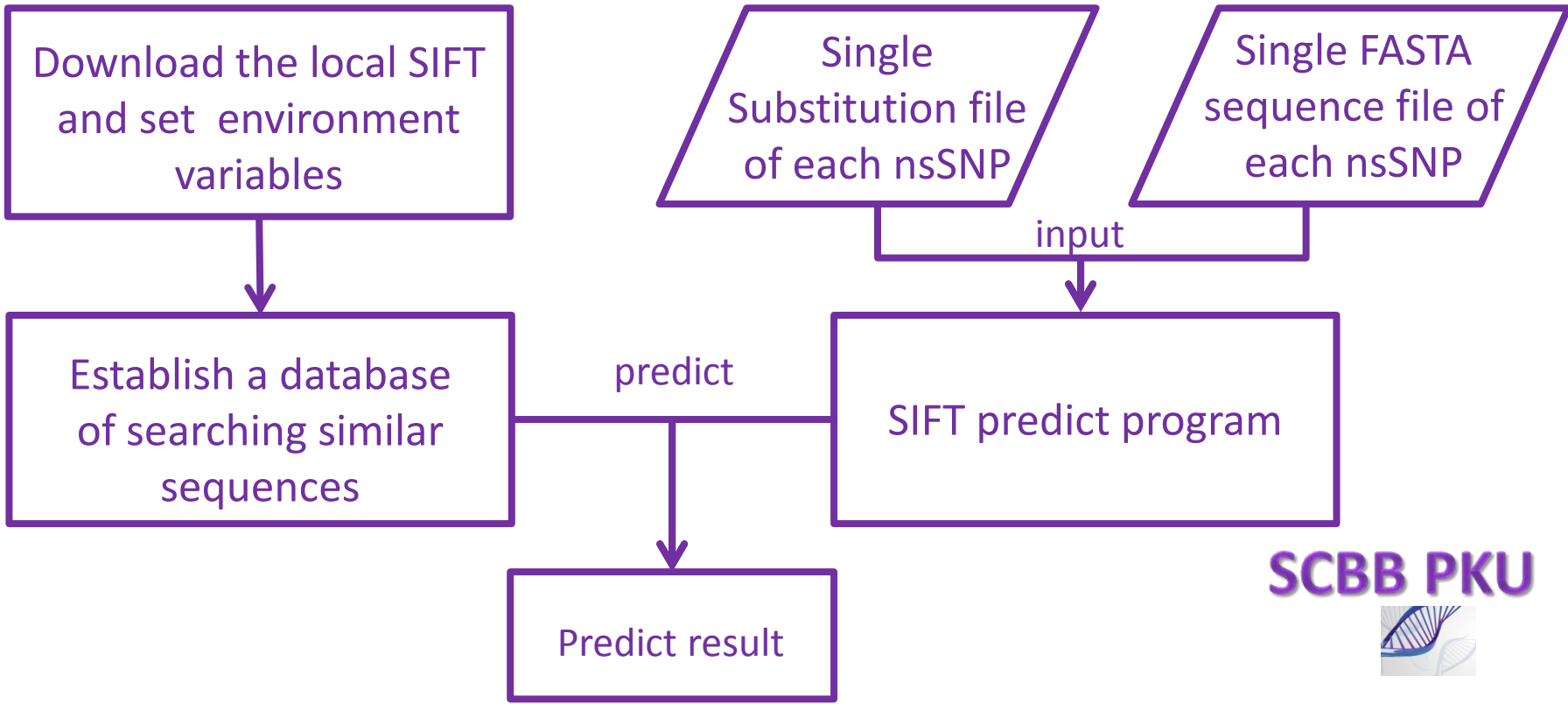
# Methods and Results

## ➢ SIFT prediction

- Local SIFT prediction

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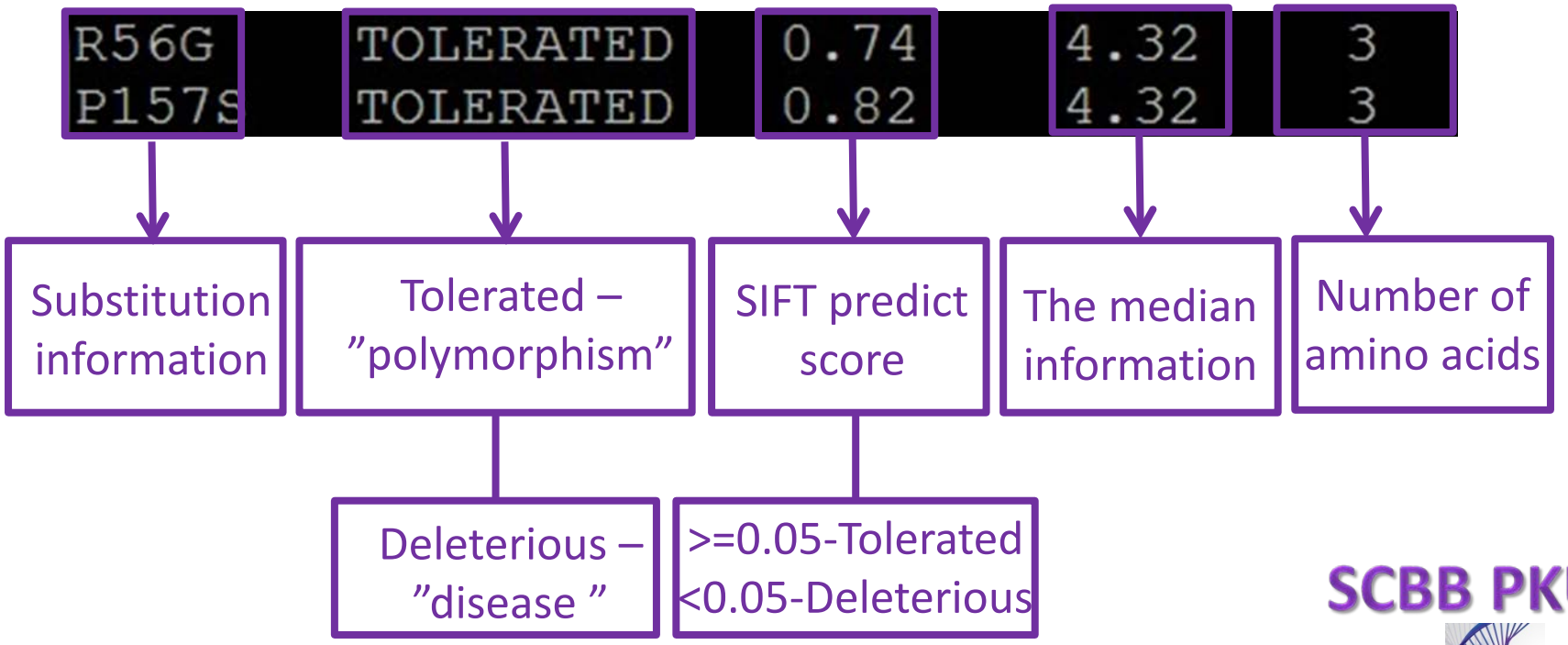
# Methods and Results

## ➢ SIFT prediction

- SIFT predict results

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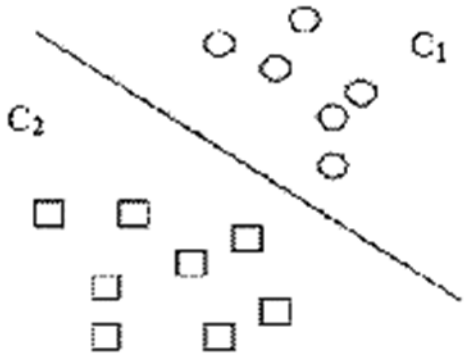
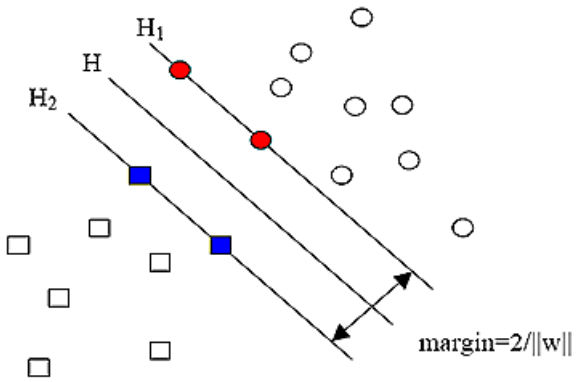
# Methods and Results

## ➢ Libsvm prediction

- SVM introduction

SVM are supervised learning models with associated learning algorithms that analyze data and recognize patterns, used for classification and regression analysis.

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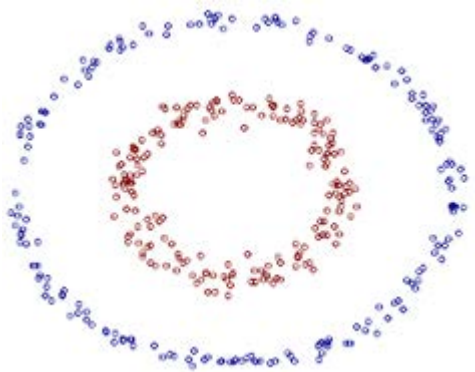
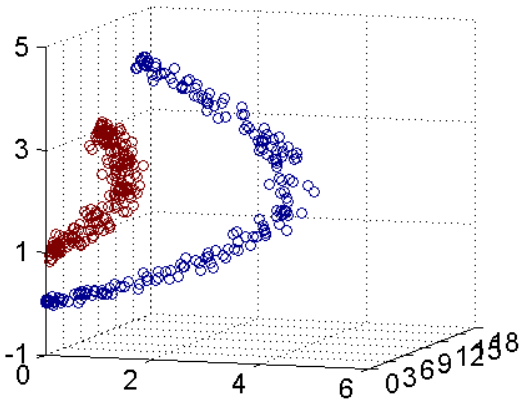
# Methods and Results

## ➢ Libsvm prediction

- SVM introduction

SVMs can efficiently perform a non-linear classification using what is called the kernel trick, implicitly mapping their inputs into high-dimensional feature spaces.



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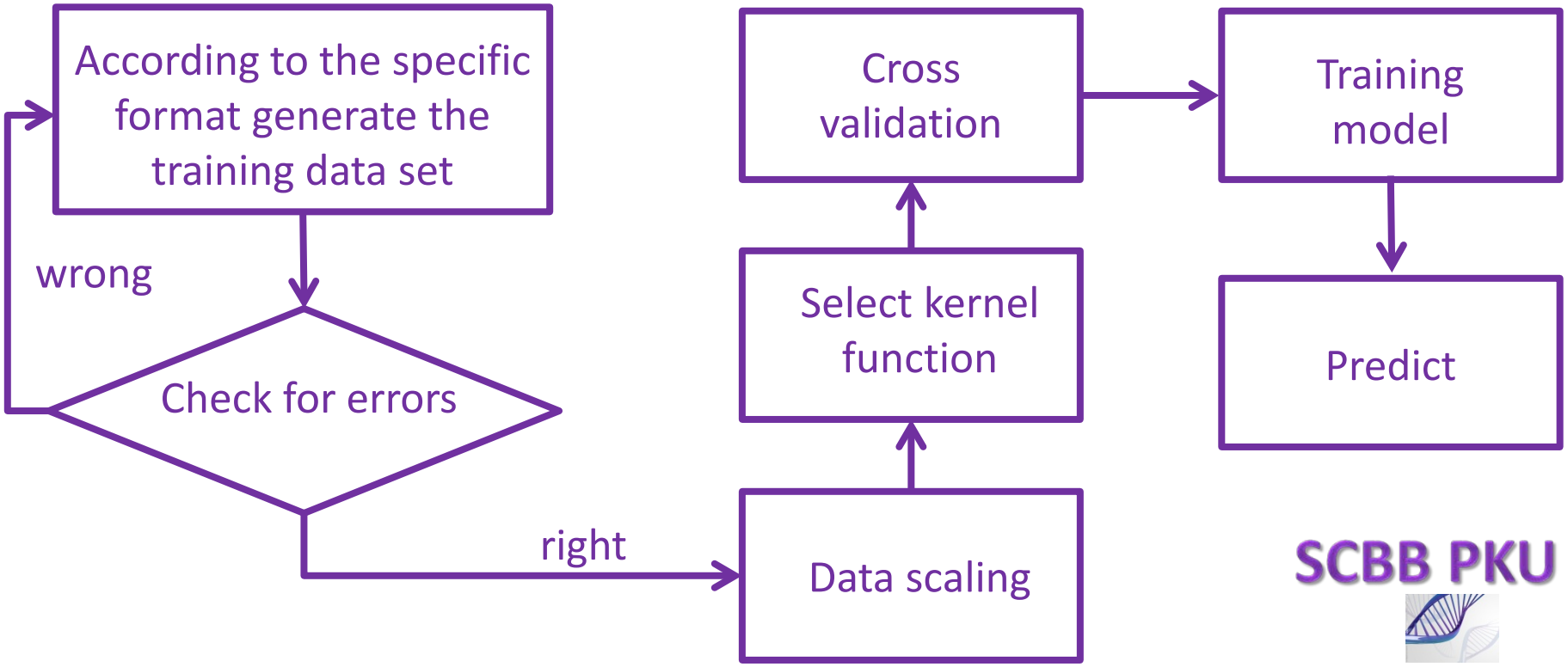
# Methods and Results

## ➢ Libsvm prediction

- Libsvm training and prediction process

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# How to process biological data?

## ➢ Libsvm prediction

- Libsvm training and predicted example

GRANTHAM matrix scores

| | | | | | |
|---|---|---|---|---|---|
| P04217 | H52R | VAR_018369 | Polymorphism | 0 | 29 |
| P04217 | H395R | VAR_018370 | Polymorphism | 0 | 29 |
| Q9NQ94 | V555M | VAR_052201 | Polymorphism | 1 | 21 |
| Q9NQ94 | A558S | VAR_059821 | Polymorphism | 1 | 99 |
| A8K2U0 | G207R | VAR_055463 | Polymorphism | -2 | 125 |
| A8K2U0 | C970Y | VAR_055464 | Polymorphism | -2 | 194 |
| A8K2U0 | T1131M | VAR_055465 | Polymorphism | -1 | 81 |
| A8K2U0 | T1412A | VAR_055466 | Polymorphism | 0 | 58 |
| A8K2U0 | D850E | VAR_059083 | Polymorphism | 2 | 45 |
| A8K2U0 | H1229R | VAR_059084 | Polymorphism | 0 | 29 |
| P01023 | R704H | VAR_000012 | Polymorphism | 0 | 29 |
| P01023 | C972Y | VAR_000013 | Polymorphism | -2 | 194 |
| P01023 | I1000V | VAR_000014 | Polymorphism | 3 | 29 |
| P01023 | N639D | VAR_026820 | Polymorphism | 1 | 23 |
| P01023 | L815Q | VAR_026821 | Polymorphism | -2 | 113 |
| Q9NPC4 | M37V | VAR_014296 | Polymorphism | 1 | 21 |
| Q9NPC4 | G187D | VAR_017508 | Polymorphism | -1 | 94 |
| Q9NPC4 | P251L | VAR_017509 | Polymorphism | -3 | 98 |
| Q9NPC4 | Q163R | VAR_022320 | Polymorphism | 1 | 43 |
| Q9UNA3 | A218D | VAR_022096 | Polymorphism | -2 | 126 |

BLOSUM62 matrix scores

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# How to process biological data?

## ➢ Libsvm prediction

- Libsvm training and predicted example

```
-1 1:0 2:29
-1 1:0 2:29
-1 1:1 2:21
-1 1:1 2:99
-1 1:-2 2:125
-1 1:-2 2:194
-1 1:-1 2:81
-1 1:0 2:58
-1 1:2 2:45
-1 1:0 2:29
-1 1:0 2:29
-1 1:-2 2:194
-1 1:3 2:29
```

Scaling →

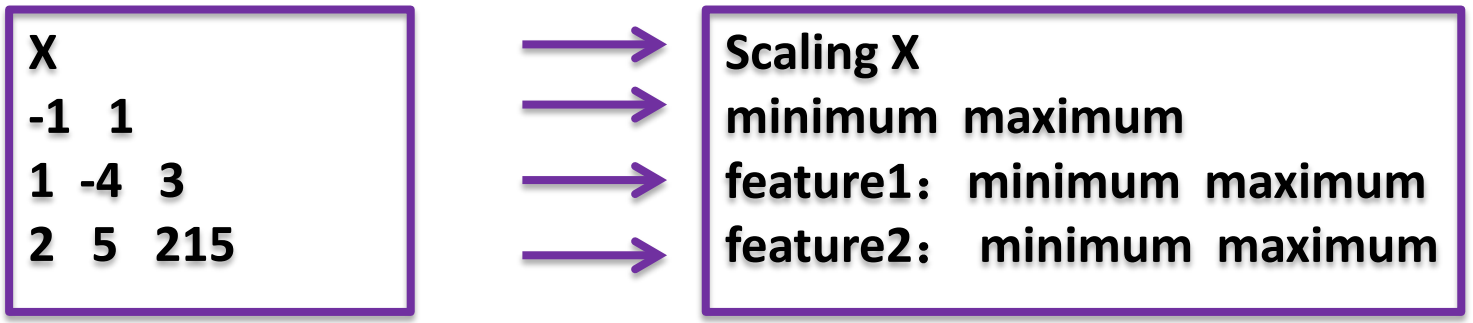
```
-1 1:0.142857 2:-0.771429
-1 1:0.142857 2:-0.771429
-1 1:0.428571 2:-0.847619
-1 1:0.428571 2:-0.104762
-1 1:-0.428571 2:0.142857
-1 1:-0.428571 2:0.8
-1 1:-0.142857 2:-0.27619
-1 1:0.142857 2:-0.495238
-1 1:0.714286 2:-0.619048
-1 1:0.142857 2:-0.771429
-1 1:0.142857 2:-0.771429
-1 1:-0.428571 2:0.8
```

# How to process biological data?

## ➢ Libsvm prediction

- Libsvm training and predicted example

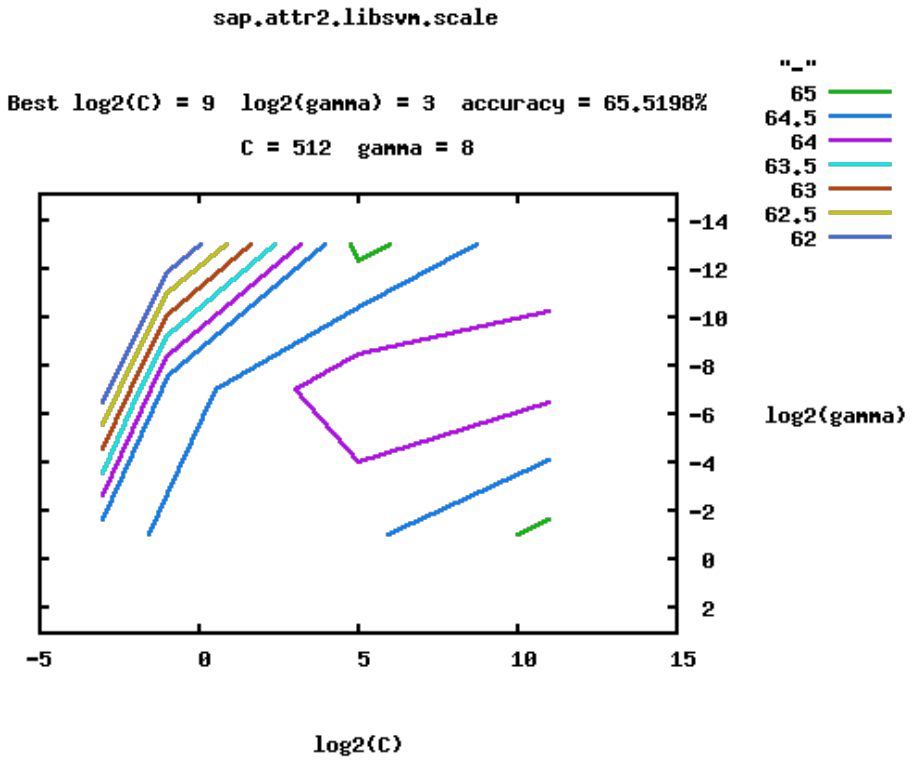
Scaling parameter file



# How to process biological data?

## ➢ Libsvm prediction

- Libsvm training and predicted example-Cross validation result

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# Acknowledge

**Thanks for your attention!**

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