test

January 24, 2025

1 I

[2]:
```
setwd('../data/TP_DATA_PROG/')
```

1.1 a: Genetic linkage analysis - lodscore method

1.1.1 a.1

[3]:
```
install.packages('paramlink')
library(paramlink)
```

```
Updating HTML index of packages in '.Library'

Making 'packages.html' …
 done


PLEASE NOTE:
Paramlink has been superseded by the `ped suite` packages
(https://magnusdv.github.io/pedsuite/).
It is maintained for legacy purposes only, and should not be used in new
projects.
```

1.1.2 a.2

[ ]:
```
cols<-c('Family_number','Individual_number','Father_number','Mother_number',␣
 ↪'Sex',␣
 ↪'Disease_status','marker1_1','marker1_2','marker2_1','marker2_2','marker3_1','marker3_2','m

fam<-read.table('I.a.Paramlink/fam.txt')
colnames(fam)<-cols
fam[1:5,1:10]
```

A data.frame: 5 × 10

	Family_number <int>	Individual_number <int>	Father_number <int>	Mother_number <int>	Sex <int>
1	1	1	0	0	1
2	1	2	0	0	2
3	1	21	0	0	2
4	1	5	1	2	1
5	1	4	1	2	1

Q1: genotype of the first marker of the individual of id 5

[ ]:
```
for (row in 1:nrow(fam)){
  if (fam[row,'Individual_number']==5){
    cat(fam[row,]$marker1_1,fam[row,]$marker1_2)
  }
}
```

```
9 1
```

The genotype of the individual 5 is 9/1

1.1.3 a.3

[ ]:
```
x=linkdat(fam)
```

```
Family ID: 1.
47 individuals.
22 affected, 25 non-affected.
10 nuclear subfamilies.
13 markers.
```

Q2:

[7]:
```
## count the number of families in family number of fam
fam$Family_number
```

1. 1 2. 1 3. 1 4. 1 5. 1 6. 1 7. 1 8. 1 9. 1 10. 1 11. 1 12. 1 13. 1 14. 1 15. 1 16. 1 17. 1 18. 1 19. 1 20. 1 21. 1 22. 1 23. 1 24. 1 25. 1 26. 1 27. 1 28. 1 29. 1 30. 1 31. 1 32. 1 33. 1 34. 1 35. 1 36. 1 37. 1 38. 1 39. 1 40. 1 41. 1 42. 1 43. 1 44. 1 45. 1 46. 1 47. 1

There is 1 family in the dataset

[ ]:
```
affected_indiv<-c()
unaffected_indiv<-c()

for (i in 1:nrow(fam)){
  if (fam[i,'Disease_status']==1){
    affected_indiv<-c(affected_indiv,fam[i,'Individual_number'])
  } else {
    unaffected_indiv<-c(unaffected_indiv,fam[i,'Individual_number'])
```

```
  }
}

paste0('affected indiv:',length(affected_indiv))
paste0('unaffected indiv:',length(unaffected_indiv))
```

'affected indiv:25'

'unaffected indiv:22'

There is:

- 25 affected
- 22 unaffected

13 markers are analyzed

Q3:

[ ]:
```
x
```

	ID	FID	MID	SEX	AFF	V1	V2	V3	V4	V5
1	1	0	0	1	2	-/-	-/-	-/-	-/-	-/-
2	2	0	0	2	1	-/-	-/-	-/-	-/-	-/-
3	21	0	0	2	1	-/-	-/-	-/-	-/-	-/-
4	5	1	2	1	2	9/1	5/10	4/2	2/3	3/2
5	4	1	2	1	1	-/-	-/-	-/-	-/-	-/-
6	3	1	2	1	2	-/-	-/-	-/-	-/-	-/-
7	6	0	0	2	1	-/-	-/-	-/-	-/-	-/-
8	36	0	0	2	1	3/9	6/8	4/4	6/5	1/2
9	26	5	21	1	2	9/2	5/6	4/2	2/3	3/2
10	25	5	21	2	1	1/2	10/6	2/2	3/3	2/2
11	23	5	21	2	2	9/2	5/5	4/4	2/4	3/3
12	30	0	0	1	1	-/-	-/-	-/-	-/-	-/-
13	22	5	21	2	2	9/2	5/5	4/4	2/4	3/3
14	27	0	0	1	1	1/1	2/9	3/4	3/4	3/3
15	24	5	21	2	2	9/2	5/6	4/2	2/3	3/2
16	32	0	0	1	1	2/2	9/3	4/4	2/5	3/4
17	44	26	36	2	2	9/3	5/6	4/4	2/6	3/1
18	43	26	36	2	2	9/9	5/8	4/4	2/5	3/2
19	42	26	36	2	1	-/-	-/-	-/-	-/-	-/-
20	41	26	36	1	2	9/9	5/8	4/4	2/5	3/2
21	40	26	36	2	1	3/2	6/6	4/2	6/3	1/2
22	39	26	36	1	1	3/2	6/6	4/2	6/3	1/2
23	38	26	36	1	2	9/3	5/6	4/4	2/6	3/1
24	37	26	36	2	1	3/2	6/6	4/2	6/3	1/2
25	31	30	23	1	1	2/9	5/9	4/4	4/3	3/3
26	29	27	22	1	1	1/2	9/5	4/4	4/4	3/3
27	28	27	22	2	2	9/1	5/2	4/3	2/3	3/3

```
28 35  32  24   1   2 9/2  5/3 4/4 2/5 3/4
29 34  32  24   1   2 9/2  5/9 4/4 2/2 3/3
30 33  32  24   2   2 9/2  5/3 4/4 2/5 3/4
31 14   0   0   1   1 1/2 3/10 4/4 4/4 3/3
32  7   3   6   2   2 9/1  5/6 4/6 2/4 3/2
33  8   3   6   1   1 -/-  -/- -/- -/- -/-
34  9   3   6   2   1 1/4  6/6 6/4 4/6 2/2
35 10   3   6   1   1 -/-  -/- -/- -/- -/-
36 11   3   6   1   1 -/-  -/- -/- -/- -/-
37 12   3   6   1   1 1/4  6/6 6/4 4/6 2/2
38 13   3   6   2   2 9/1  5/6 4/6 2/4 3/2
39 18   0   0   1   1 5/1  9/5 2/7 6/6 2/2
40 15  14   7   2   2 9/2 5/10 4/4 2/4 3/3
41 16  14   7   2   1 1/1  6/3 6/4 4/4 2/3
42 17  14   7   1   2 -/-  -/- -/- -/- -/-
43 19  18  15   1   2 9/5  5/9 4/2 2/6 3/2
44 20  18  15   2   2 9/1  5/9 4/2 2/6 3/2
45 47   0   0   1   1 -/-  -/- -/- -/- -/-
46 46  47  13   2   1 1/8  6/8 6/3 4/5 2/2
47 45  47  13   2   2 9/8  5/5 4/4 2/7 3/3

Only first 5 markers are shown. Use option 'markers=' to print specified markers.
```

They have taken each 2 markers and transformed them into one column of format `allele1/allele2` $\iff$ representing the genotype

Q4

[ ]:
```
summary(x)
```

```
Pedigree:
---------
47 individuals
11 founders, 36 nonfounders; bit size = 61
10 nuclear subfamilies
22 affected by disease, 25 unaffected, 0 with unknown affection status

Marker data:
------------
13 markers in total
13 individuals with no available genotypes: 1, 2, 21, 4, 3, 6, 30, 42, 8, 10,
11, 17, 47
0 % missing alleles (excluding ungenotyped individuals)

Chromosome distribution of markers:
 chromosome unknown: 13 markers

Allele number distribution:
 3 alleles: 1 marker
```

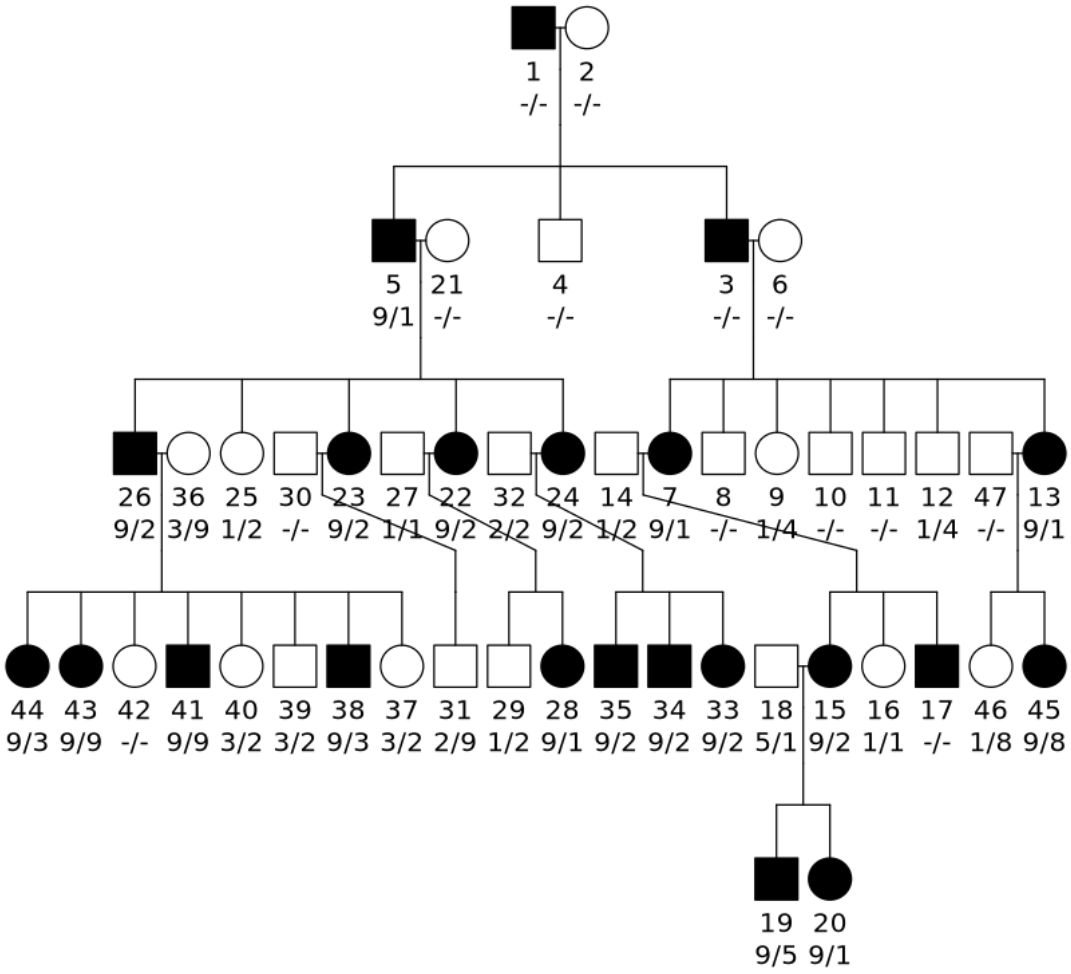
```
 4 alleles: 4 markers
 5 alleles: 2 markers
 6 alleles: 2 markers
 7 alleles: 4 markers

Model parameters:
-----------------
No model parameters set
```

There is:

- 11 founder individuals
- 13 with unknown genotypes
- 4 markers with 7 alleles

1.1.4 a.4

[ ]:
```
plot(x, marker=1)
```



Q5: For indiv 15,16 and 17 repsectively:

- 9/2
- 1/1
- missing (-/-)

1.1.5 a.5

Here `Dd` and `DD` are the at-risk genotypes, since it's autosomal dominant and `d` is the deleterious allele (so dominant allele)

[12]:
```
xdom=setModel(x, model=1, penetrances = c(0.00001,1,1), dfreq=0.00001)
```

Here we have $Phenocopy = P(affected/DD) = 0.00001$

1.1.6 a.6

[13]:
```
lod_values=lod(xdom, theta=c(0,0.05,0.1,0.15,0.2,0.25,0.3,0.4,0.5))
```

[ ]:
```
lod_values
```

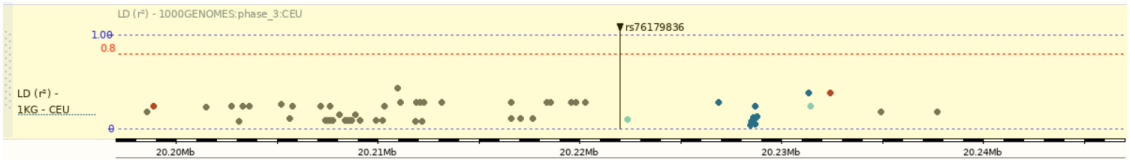
```
                 M1        M2        M3        M4         M5        M6
theta=0:     7.673800  7.247411  4.762693  8.171219  6.0050443  4.969872
theta=0.05:  7.035453  6.653626  4.309984  7.511664  5.4606032  4.555357
theta=0.1:   6.365581  6.030791  3.848484  6.819437  4.8898188  4.121439
theta=0.15:  5.661047  5.376151  3.371107  6.091242  4.2903721  3.666446
theta=0.2:   4.918254  4.686580  2.871736  5.323255  3.6599709  3.188760
theta=0.25:  4.133297  3.958642  2.346428  4.511135  2.9968532  2.687328
theta=0.3:   3.302875  3.189035  1.795610  3.650405  2.3012371  2.162844
theta=0.4:   1.528959  1.530367  0.682811  1.782355  0.8643605  1.069246
theta=0.5:   0.000000  0.000000  0.000000  0.000000  0.0000000  0.000000
                 M7         M8         M9        M10        M11       M12
theta=0:     5.7141323  5.2550744  4.2537353  3.5643218  0.2874061  1.061945
theta=0.05:  5.1742276  4.7499732  3.8555848  3.2523734  3.5708778  4.285454
theta=0.1:   4.6083512  4.2271963  3.4424404  2.9319108  3.4368453  4.088351
theta=0.15:  4.0141596  3.6832892  3.0136955  2.6029704  3.1568696  3.741883
theta=0.2:   3.3894121  3.1151478  2.5688442  2.2654917  2.8032430  3.318095
theta=0.25:  2.7327781  2.5213329  2.1077616  1.9191995  2.3982856  2.839221
theta=0.3:   2.0462455  1.9051123  1.6317013  1.5634218  1.9533074  2.316724
theta=0.4:   0.6694062  0.6923811  0.6734622  0.8170073  0.9867355  1.184283
theta=0.5:   0.0000000  0.0000000  0.0000000  0.0000000  0.0000000  0.000000
                M13
theta=0:    -32.1732679
theta=0.05:   2.1590621
theta=0.1:    2.3859584
theta=0.15:   2.3427504
theta=0.2:    2.1757203
theta=0.25:   1.9301442
theta=0.3:    1.6262113
theta=0.4:    0.8847441
theta=0.5:    0.0000000
```

Q6 We can the same pattern for markers M1 to M10: max lod score is obtained for theta=0 and its value in each of these markers is higher than 3 -> reject the null hypothesis -> conclusion is this gene is very close to each of these genetic markers. And if the disease gene is close to them all it means that the first 10 markers are in cluster, they are very close.

For marker 11 and 12 the max lod score is obtained for same theta value = 0.05 and the value is higher than 3 so we can reject the null hypothesis and conclude that the probable location of the disease locus is around 0.05 cM from these markers.

For the marker 13, there is no theta value for which the lod-score is higher than 3, but for theta=0

the lod-sore = -32 < -2 so the null hypothesis is not rejected, hence we can exclude that the disease gene is close to this marker.



Q7 The recombination rate is between 0 and 0.5 so the confidence interval for the recombination rate will be in this range. Here theta max is 0 because it is for theta = 0 that we have the maximum of the lod score. It means that the lower bound of the confidence interval will be equal to 0 and the intersection is the upper bound. We approximate it.

Confidence interval for Marker 1 is ranging between $[0, 0.07]$

1.1.7 a.7

[27]:
```
lod(xdom, marker=c(5,7,8,12), theta='max')
```

```
              M5        M7        M8         M12
LOD:    6.005044  5.714132  5.255074  4.28823977
t_max:  0.000000  0.000000  0.000000  0.04508497
```

Q8 Interpretation of the results:

For markers M_5, M_7 and M_8, θ_{max} is 0 which means that the markers is very close to the disease gene.

For marker M_{12}, θ_{max} is 0.045 with a lod score of $0.045 > 3$, which is -

Q9

[26]:
```
## as.matrix(lod_values)
for (i in 1:ncol(lod_values)){
    max_lod=max(lod_values[,i])
    cat('max lod value for marker',i,'is',max_lod,'\n')
}
```

```
max lod value for marker 1 is 7.6738
max lod value for marker 2 is 7.247411
max lod value for marker 3 is 4.762693
max lod value for marker 4 is 8.171219
max lod value for marker 5 is 6.005044
max lod value for marker 6 is 4.969872
max lod value for marker 7 is 5.714132
max lod value for marker 8 is 5.255074
max lod value for marker 9 is 4.253735
max lod value for marker 10 is 3.564322
max lod value for marker 11 is 3.570878
```

```
max lod value for marker 12 is 4.285454
max lod value for marker 13 is 2.385958
```

Q10 Markers 1-10 all have the same pattern of lod scores relative to θ values: The highest lod score is at θ_0 and the lowest at $\theta_{0.5}(=0)$, with lod scores > 3, which means that the markers are at very close proximity to the disease gene.

1.1.8 a.8

[43]:
```
## -- before when they were equifrequent
as.data.frame(lod_values[,"M5"])
```

A data.frame: 9 × 1

	lod_values[, "M5"] <dbl>
0	6.0050443
0.05	5.4606032
0.1	4.8898188
0.15	4.2903721
0.2	3.6599709
0.25	2.9968532
0.3	2.3012371
0.4	0.8643605
0.5	0.0000000

[30]:
```
## -- after modifying allele frequencies
xdom5=modifyMarker(xdom,marker = 5, afreq = c(0.1, 0.1, 0.1, 0.7))
lod(xdom5, marker=5, theta=c(0, 0.05, 0.1, 0.15, 0.2, 0.25, 0.3, 0.4, 0.5))
```

```
                  M5
theta=0:     6.1601384
theta=0.05:  5.6089781
theta=0.1:   5.0311016
theta=0.15:  4.4242603
theta=0.2:   3.7862270
theta=0.25:  3.1152044
theta=0.3:   2.4110015
theta=0.4:   0.9454197
theta=0.5:   0.0000000
```

Q11 Results have been modified slightly in each, overall the same pattern (decreasing when increasing theta values) with only a small increase of lod values of when we changed the frequencies, and then reaching 0 when $\theta = 0.5$

why? –

1.1.9 a.9

```
[ ]: xrec=setModel(x, model=2, penetrances=c(0.00001,0.00001, 1), dfreq=0.00001)
lod(xrec)
```

```
                 M1         M2         M3         M4         M5         M6
theta=0:  -11.52737  -20.34523  0.8394887  -20.80169  -11.46918  -16.24291
                 M7         M8         M9        M10        M11        M12
theta=0:  -6.483199  -3.089972   1.408298  -14.51178  -16.13149  -8.403986
                M13
theta=0:  -3.274896
```

Q12 Markers $M_1, M_2, M_4, M_5, M_6, M_7, M_8, M_{10}, M_{11}, M_{12}, M_{13}$ have a negative value < -2 for θ_{max}, which means that the markers are far from the disease gene.

Except for M_3 and M_9 which have a positive value however ranging between $-2 < lodscore < 3$ hence nothing can be concluded

In this section we have changed the mode of inheritance from autosomal dominant to autosomal recessive, we can clearly see the differences in the results as in here we haven't concluded any marker that is in close proximity to the desiease gene, this is because the mode of inheritance changes the at risk genotypes which in return affect the calculation of the lod score

This is the imortance of the disease model's influence, it's crucial to be near the true model.

The lod score is parametric because it's affected by genetic mode of the diseaese and the alellic frequencies

1.2 b: Familial association analysis - TDT

```
!./fbat.exe
```

```
*********************************************************
*                                                       *
*     *********  * * *          *       *********     *
*     *          *     *       * *          *         *
*     *******    *  * *       *   *         *         *
*     *          *     *     * *** *        *         *
*     *          *     *    *       *       *         *
*     *          * * *     *         *      *         *
*                                                       *
*          Xin Xu  C1999-2009       v2.0.4(beta1)      *
*          Program for Population Genetics             *
*          Harvard School of Public Health             *
*                                                       *
*********************************************************

>> log resfbat
logging to file "resfbat" is on
>> load fbat.ped
read in: 6 markers from 651 pedigrees (652 nuclear families,2011 persons)
```

Q13 There are:

- 652 nuclear families
- 2011 persons i.e. $\frac{2011}{652} \approx 3$ individuals per family

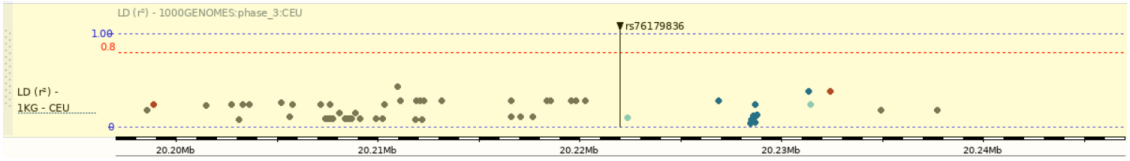
- 6 markers

```
>> fbat
trait affection; offset 0.000; model additive; test bi-allelic; minsize 10; min_freq 0.000; p
```

Marker	Allele	afreq	fam#	S-E(S)	Var(S)	Z	P
SNP2	1	0.636	409	3.500	138.750	0.297	0.766365
SNP2	2	0.364	409	-3.500	138.750	-0.297	0.766365
SNP3	1	0.370	402	2.000	140.500	0.169	0.866009
SNP3	2	0.630	402	-2.000	140.500	-0.169	0.866009
SNP4	1	0.403	425	5.000	148.500	0.410	0.681582
SNP4	2	0.597	425	-5.000	148.500	-0.410	0.681582
SNP5	1	0.626	393	-4.500	136.750	-0.385	0.700377
SNP5	2	0.374	393	4.500	136.750	0.385	0.700377
SNP6	1	0.212	283	-52.000	91.000	-5.451	5.01e-008
SNP6	2	0.788	283	52.000	91.000	5.451	5.01e-008

Q14 An informative family is a family where there exists at least one parent that is heterozygous (make sure)

All SNPs are present in the results, i.e., they have at least 10 informative families (lowest one is 283), hence no, there are no markers for which the number of informative families is insufficient



Q15

Q16 According to the results coming from `fbat`, SNP6 is in association with the disease, it's actually the only one in the table with a p-value less tahn 0.05, thus there is a significant association. It's either that SNP6 is the disease gene or is in linkage disequilibrium with the disease gene.
Allele 2 is the at-risk allele that is more transmited from a heterozygous parent to a diseasee child, since the $S - E(S) > 0$

From Ensembl plot, r^2 is below threshold for all nearby markers, meaning that none of the markers are in linkage disequilibrium with the SNP of interest (SNP6) `rs76179836`, so we can conclude that it is the causal variant

2 II. Study of a multifactorial disease: rheumatoid arthritis

2.1 a. Genetic linkage analysis–affected sib-pairsmethod