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**GENETIC SUSCEPTIBILITY FOR MICROVASCULAR
COMPLICATIONS IN PATIENTS WITH
TYPE 1 DIABETES
PRELIMINARY RESULTS FROM
A CASE-CONTROL STUDY**

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Background - Type 1 Diabetes (T1D)

- US prevalence: 0.5-2 per 1000
- 10% are familial cases
- 40% of patients develop it before 20 years of age
- Much of the burden due to vascular and microvascular complications



Background - T1D complications

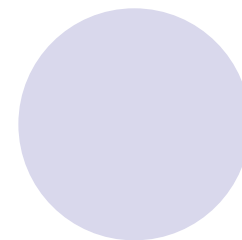
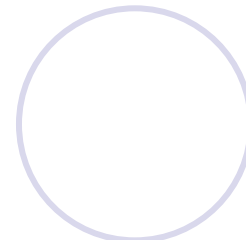
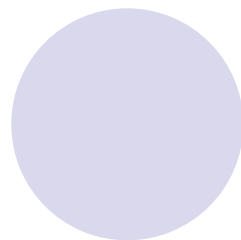
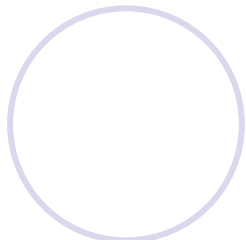
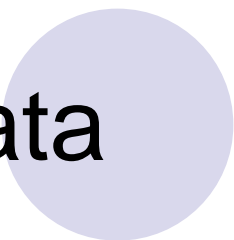
- Microvascular complications are responsible for much of the morbidity T1D and Type 2 (T2D) Diabetes
- **Retinopathy:**
is a major cause of blindness and occurs in up to 50% of T1D patients who have had the disease for 15 or more years
- **Nephropathy:**
present in 30-40 % of patients with diabetes, leading cause of end-stage renal failure
- **Neuropathy:**
leads to 80% of the diabetic foot amputations



Goal

Explore the genetic susceptibility of T1D patients to retinopathy, neuropathy and nephropathy by genetic analysis of the extensive clinical data assembled by the Human Biological Data Interchange (HBDI) and genotyped by the Type 1 Diabetes Genetics Consortium (T1DGC)

Data



(National Institute of Health)

NIH



T1DGC

(T1D Genetics Consortium)



HBDI (Human Biological Data Interchange)

Other T1D subject



Genotyping Project



CIDR



RR1 ILMN



RR1 SQNM



RR2 BROAD

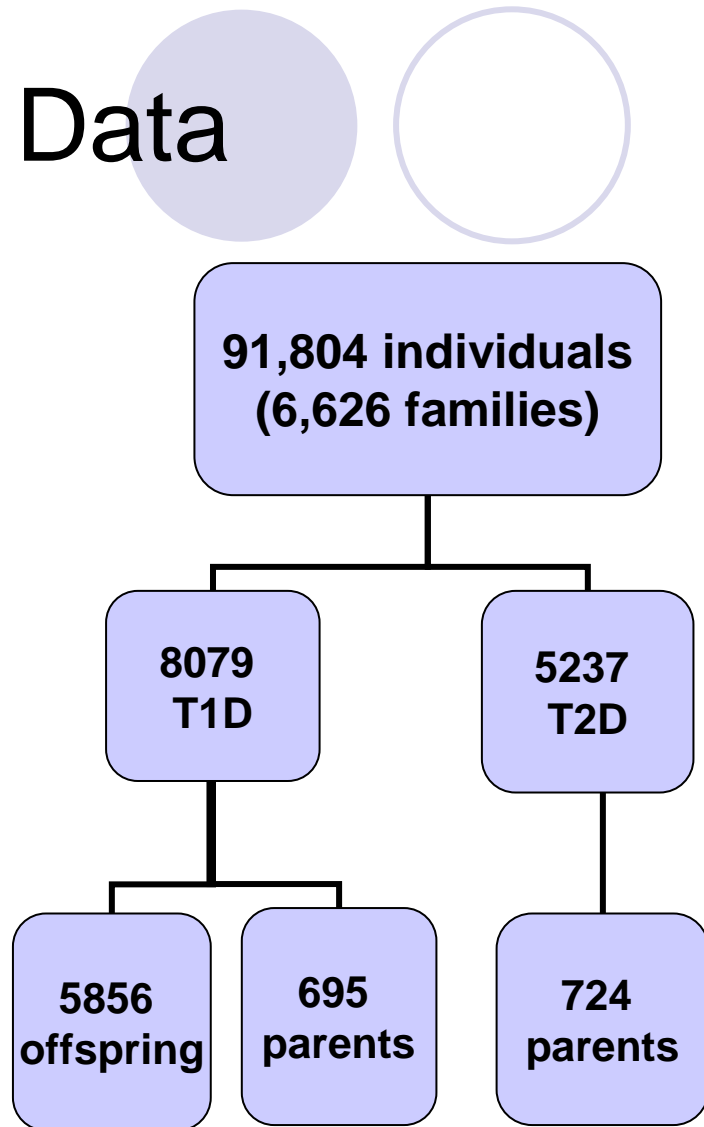


RR2 SANGER



HBDI

Data



- 2532 Caucasian, from 424 nuclear families
- 861 T1D subjects
- 30% had at least one confirmable microvascular complication



Cases - Controls definition

- Cases: T1D probands, diagnosed before age 30, requiring insulin treatment and with retinopathy, neuropathy or nephropathy
- Controls: probands with at least a 20 year history of T1D but without any complications and without 1st degree relatives with complications

Results - Case-Control data

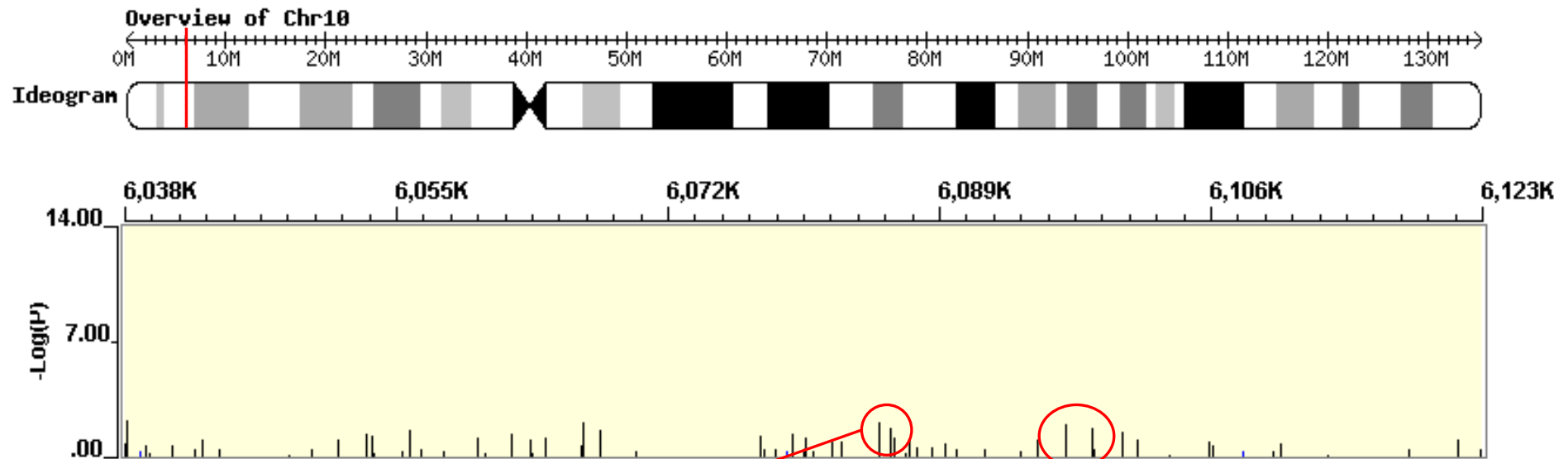
| Subject | Retinopathy | Neuropathy | Nephropathy |
|-----------------|--------------------|-------------------|--------------------|
| Cases | 108 | 29 | 53 |
| Controls | 140 | 140 | 140 |
| Total | 248 | 169 | 193 |

Results - Association

| Project | # SNPs | Retino* (%) | Neuro* (%) | Nephro* (%) |
|---------------|--------|----------------|---------------|----------------|
| CIDR | 5943 | 273 (4.6) | 296 (5.0) | 288 (4.8) |
| RR1 ILMN | 398 | 18 (4.5) | 11 (2.8) | 27 (6.8) |
| RR1 SQNM | 398 | 34 (8.5) | 17 (4.3) | 25 (6.3) |
| RR2 BROAD | 768 | 24 (3.1) | 25 (3.3) | 19 (2.5) |
| RR2 SANGER | 1536 | 82 (5.3) | 72 (4.7) | 76 (5.0) |

* $p < 0.05$

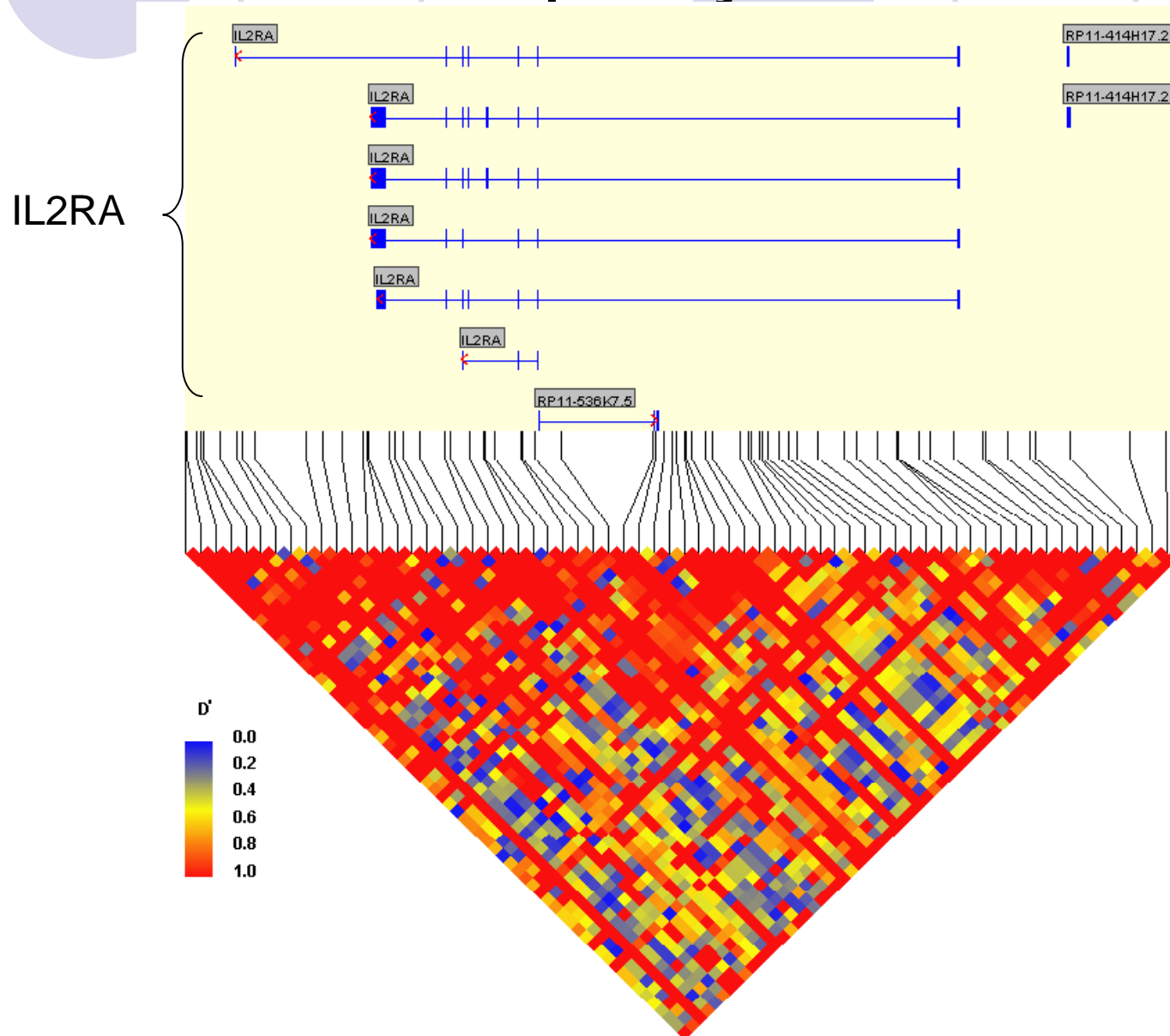
Results – Retinopathy RR1 SQNM



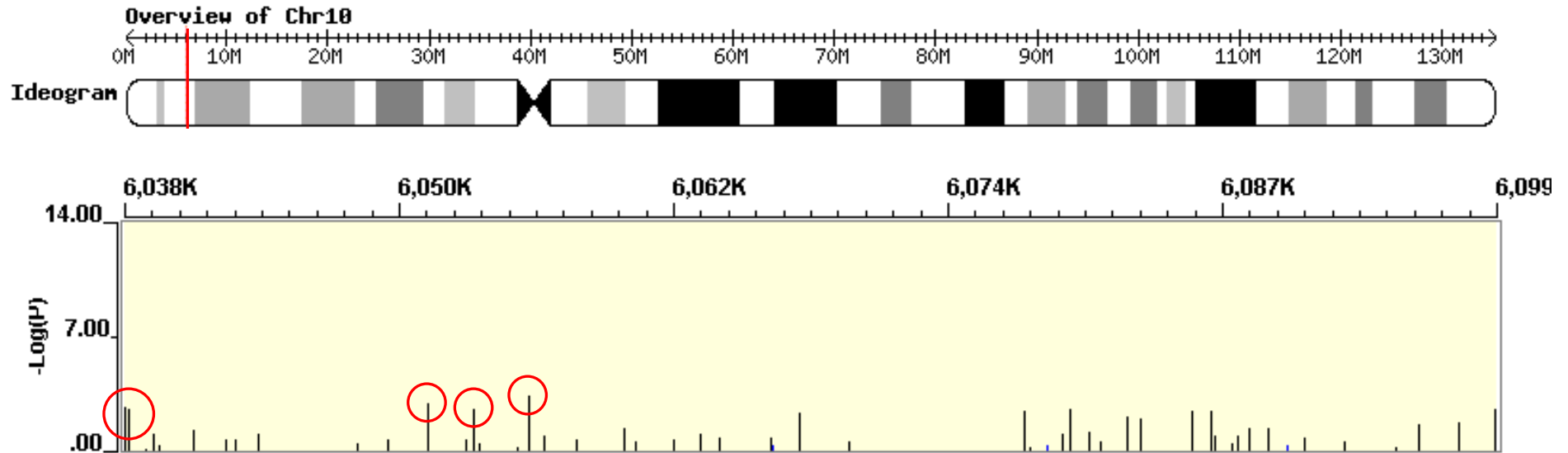
| SNP | p-value | OR |
|------------|----------|--------|
| rs4749926 | 0.01077 | 0.5756 |
| rs10905656 | 0.007185 | 0.5835 |

| SNP | p-value | OR |
|-----------|----------|--------|
| rs2256774 | 0.005849 | 0.5558 |
| rs706779 | 0.00284 | 0.5446 |

Results – Retinopathy RR1 SQNM

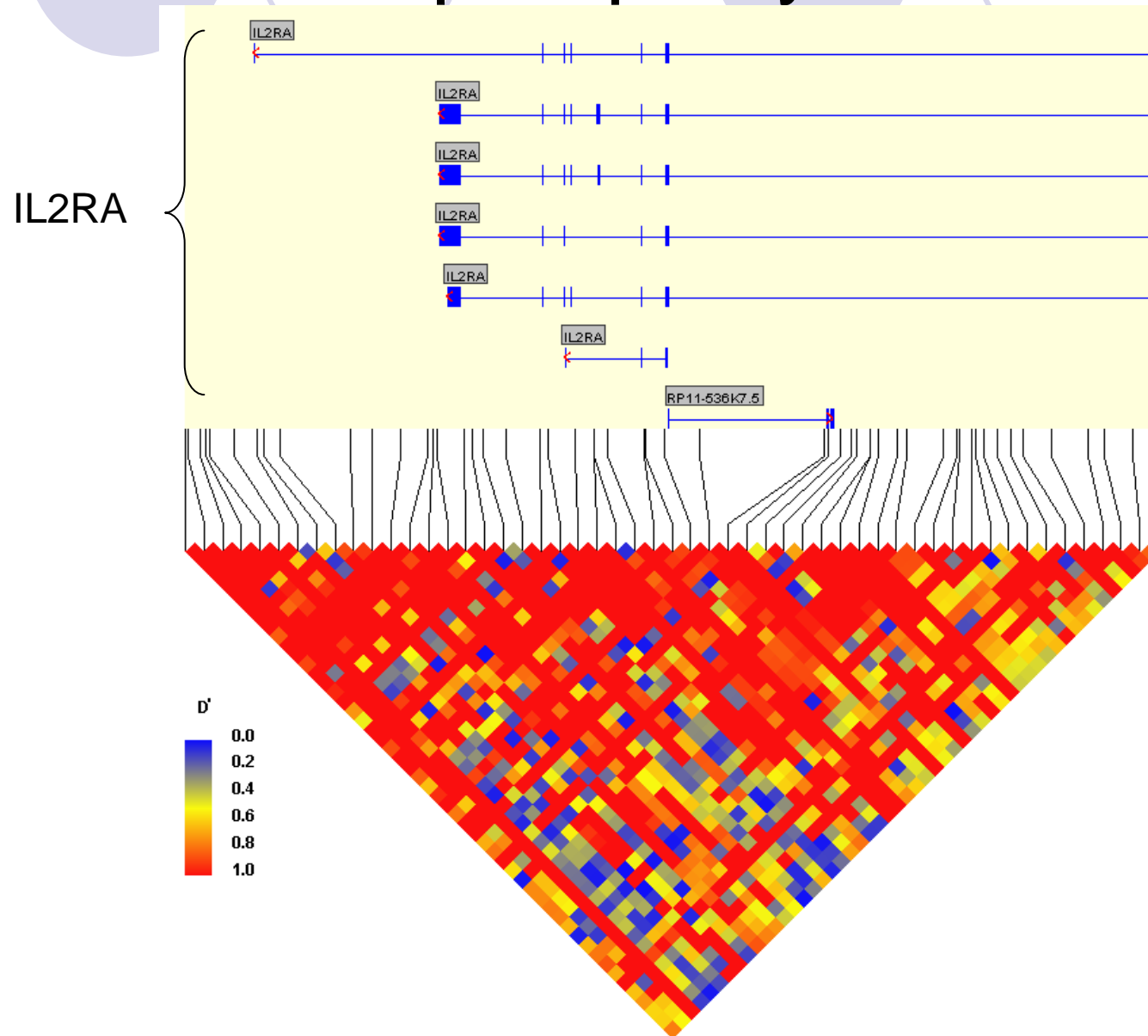


Results – Nephropathy RR1 SQNM

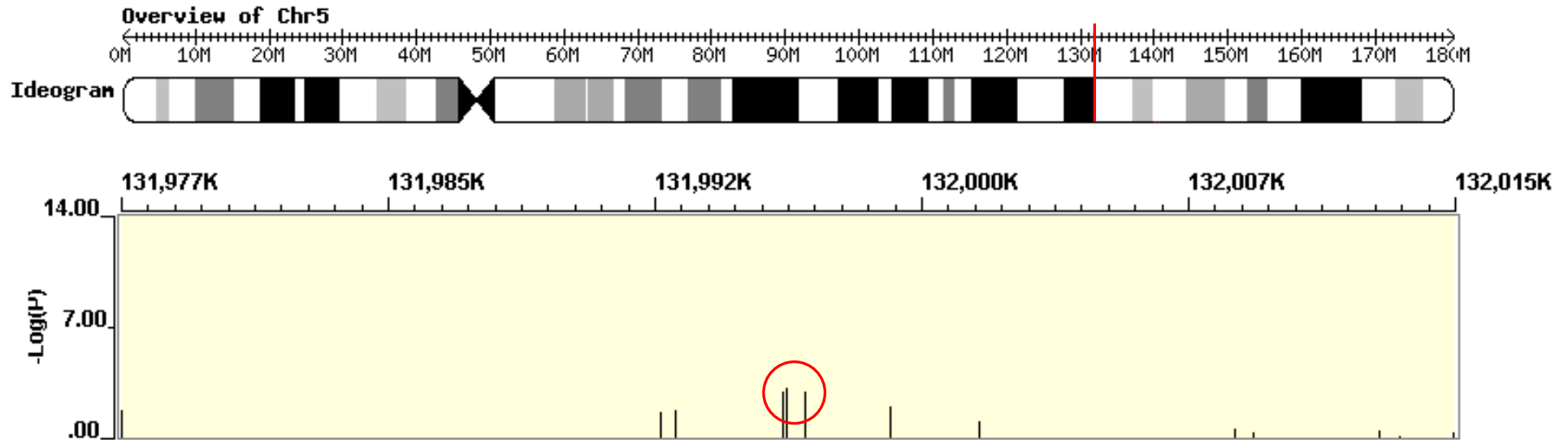


| SNP | p-value | OR |
|------------|-----------|--------|
| rs7898880 | 0.002583 | 0.3447 |
| rs7911500 | 0.003848 | 0.1981 |
| rs12359875 | 0.001439 | 0.3265 |
| rs12722605 | 0.003704 | 0.2617 |
| rs9663421 | 5.138E- 4 | 0.3317 |

Results – Nephropathy RR1 SQNM

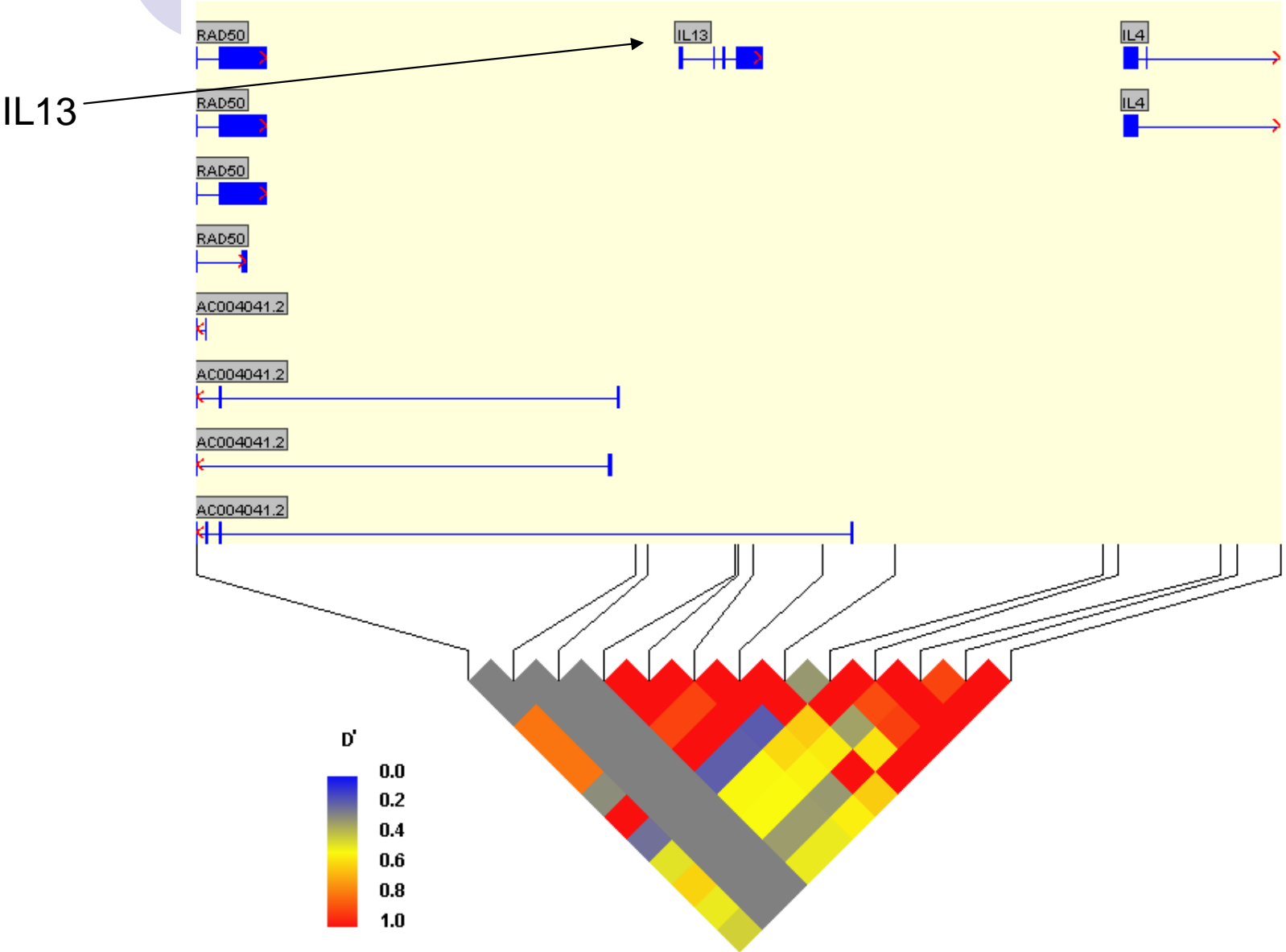


Results – Neuropathy RR1 SQNM

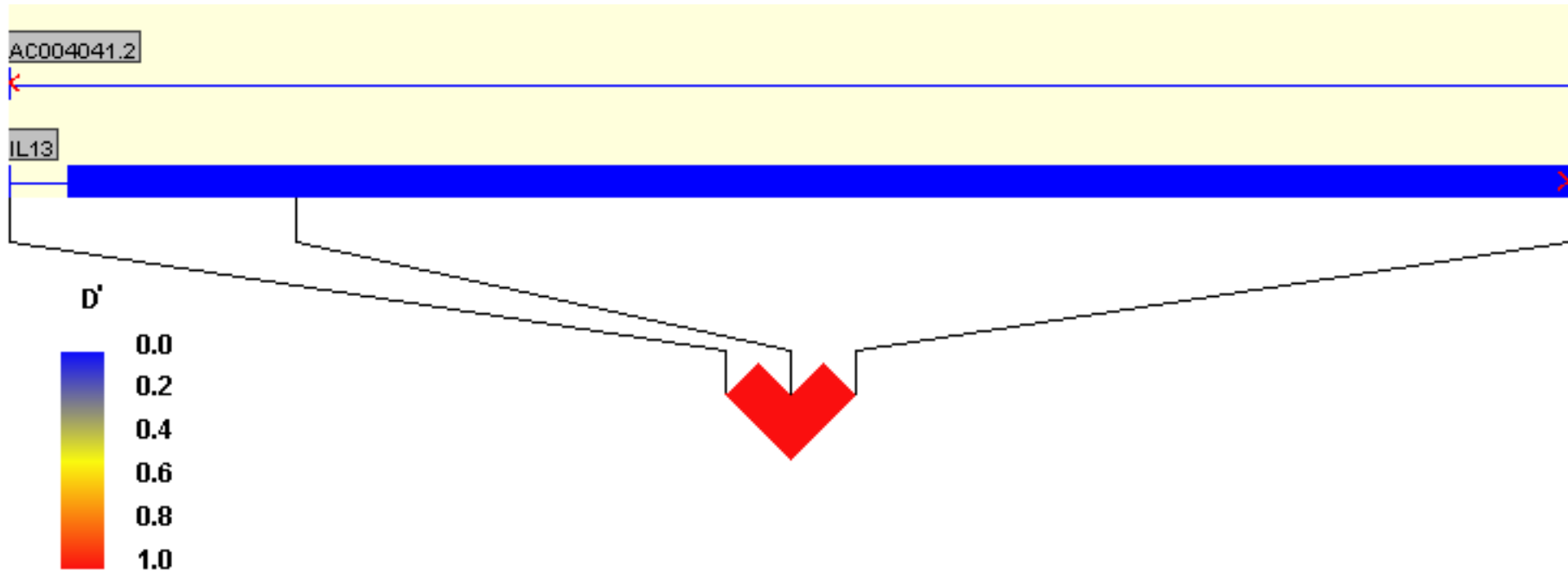


| SNP | p-value | OR |
|-----------|----------|-------|
| rs1295686 | 0.00178 | 2.86 |
| rs20541 | 0.0008 | 3.106 |
| rs848 | 0.001596 | 2.9 |

Results – Neuropathy RR1 SQNM



Results – Neuropathy RR1 SQNM



A decorative graphic at the top of the slide consists of two groups of three circles. The left group has a solid light purple circle on the left and an outlined light purple circle on the right. The right group has a solid light purple circle on the left, an outlined light purple circle in the middle, and a solid light purple circle on the right.

Conclusion

- Preliminary results
- Next steps
 - Fine mapping
 - Family-based association study
 - Linkage analysis