

Fine-Mapping Causal SNPs in Celiac Disease Using SuRE-SNP

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AIM

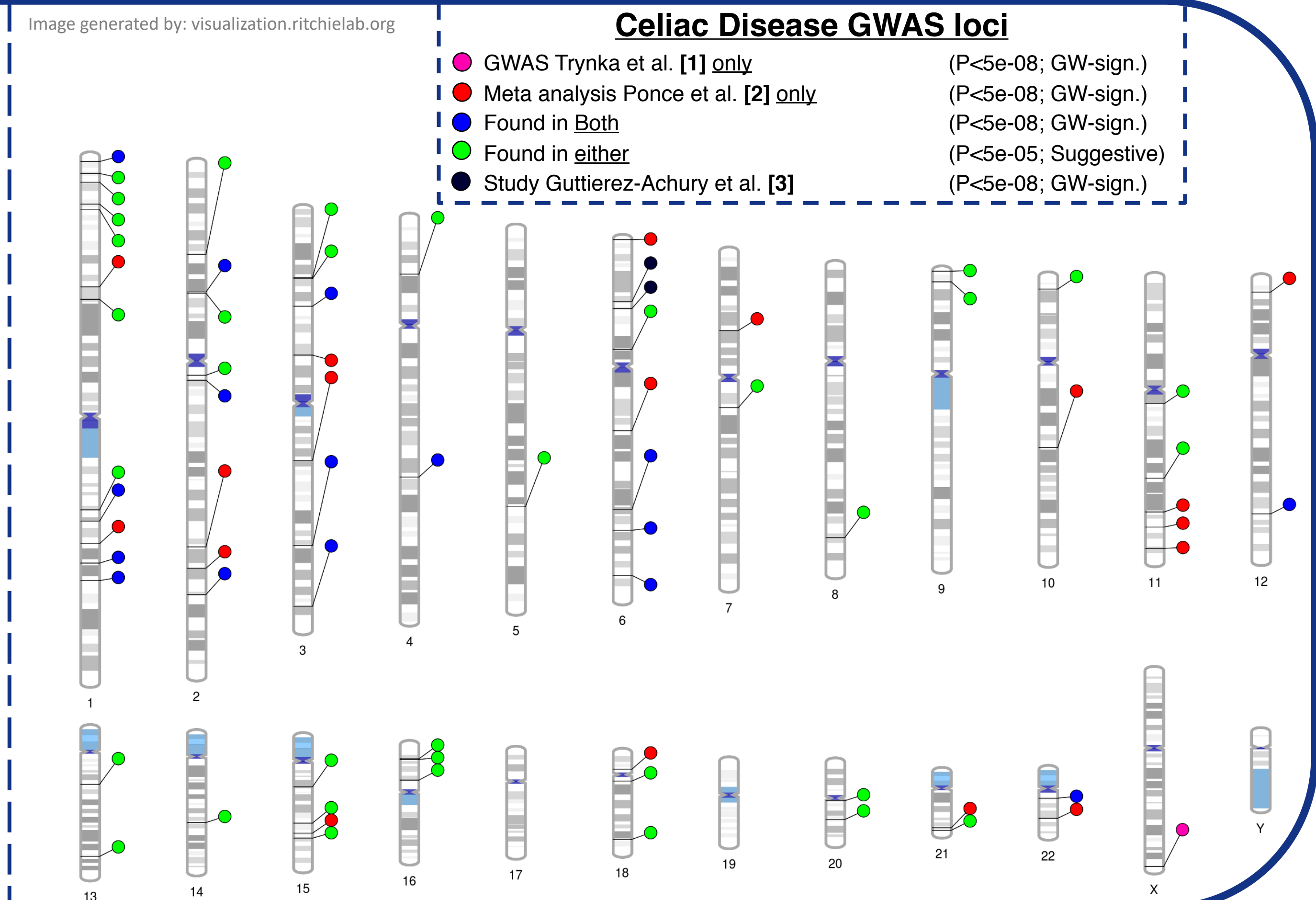
- Identify potential causal SNPs in Celiac Disease (CeD) associated GWAS loci.

BACKGROUND

- 95% of the CeD-associated SNPs are located in non-coding DNA.
- These SNPs probably affect genes through regulatory regions (enhancers).
- Enhancer activity is highly cell-type specific.
- SNP causality is difficult to ascertain due to linkage disequilibrium.

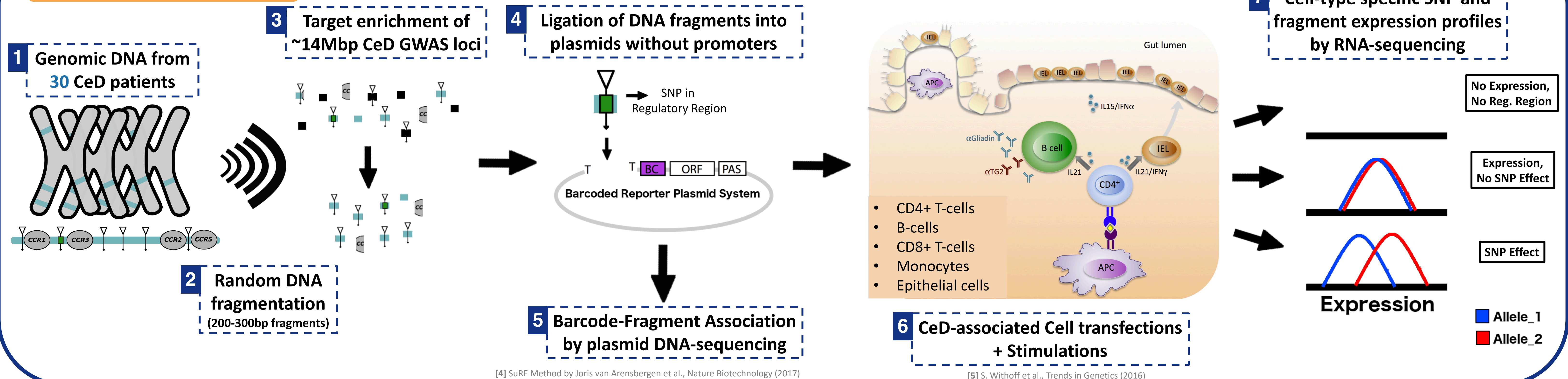
CONCLUSIONS

- The SuRE-SNP biological high throughput approach identifies SNPs that disrupt the transcription of cell-type-specific regulatory regions.
- The SuRE-SNP method allows us to evaluate the accuracy of currently used computational and biological fine-mapping approaches.



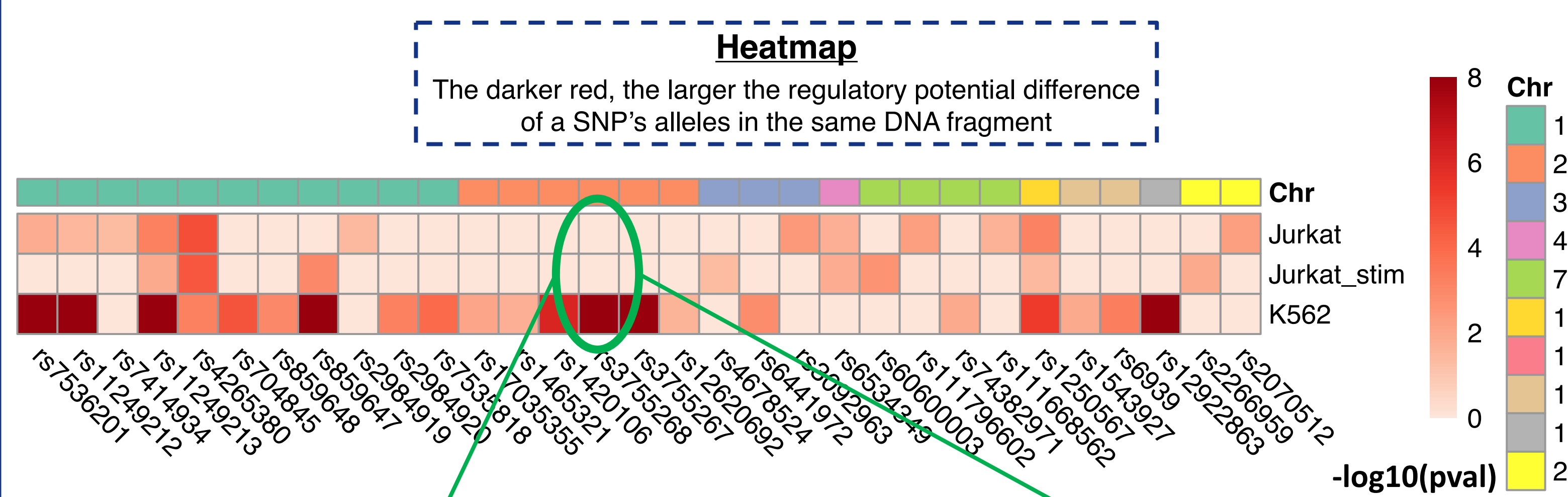
METHODS

Survey of Regulatory Elements & SNPs (SuRE-SNP)

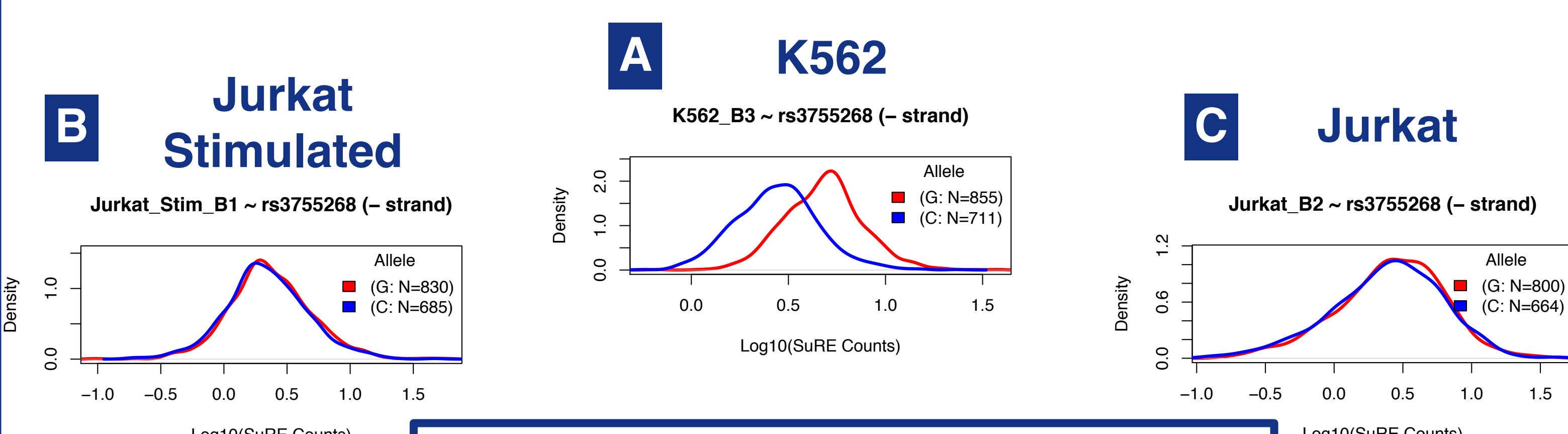


PILOT RESULTS

- Tested 96 CeD-associated SNPs, selected based on public data.
- Amplification by PCR from heterozygous CeD patient DNA.
- SNPs were transfected into K562, Jurkat, and Stimulated Jurkat cells.



Most Significant SNP (rs3755268)

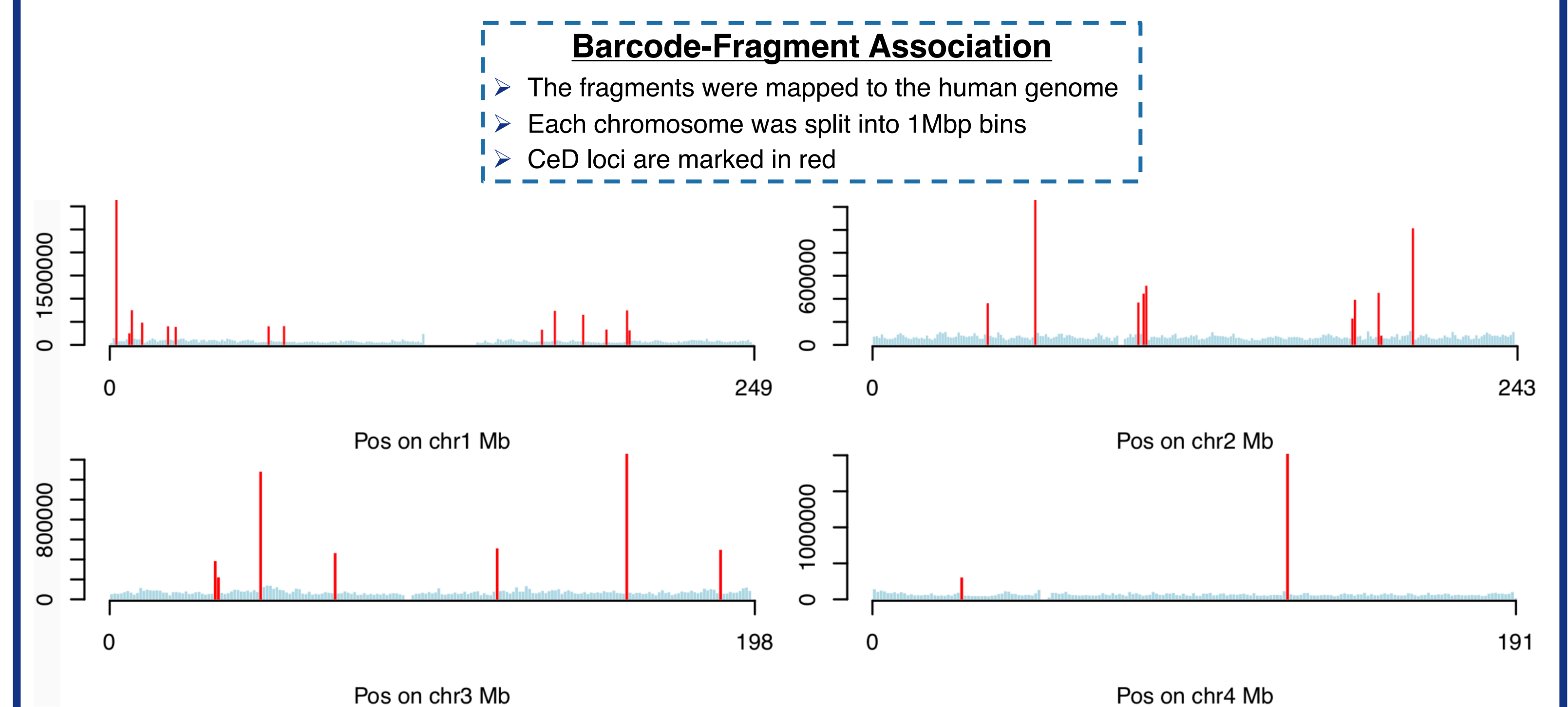


Conclusions

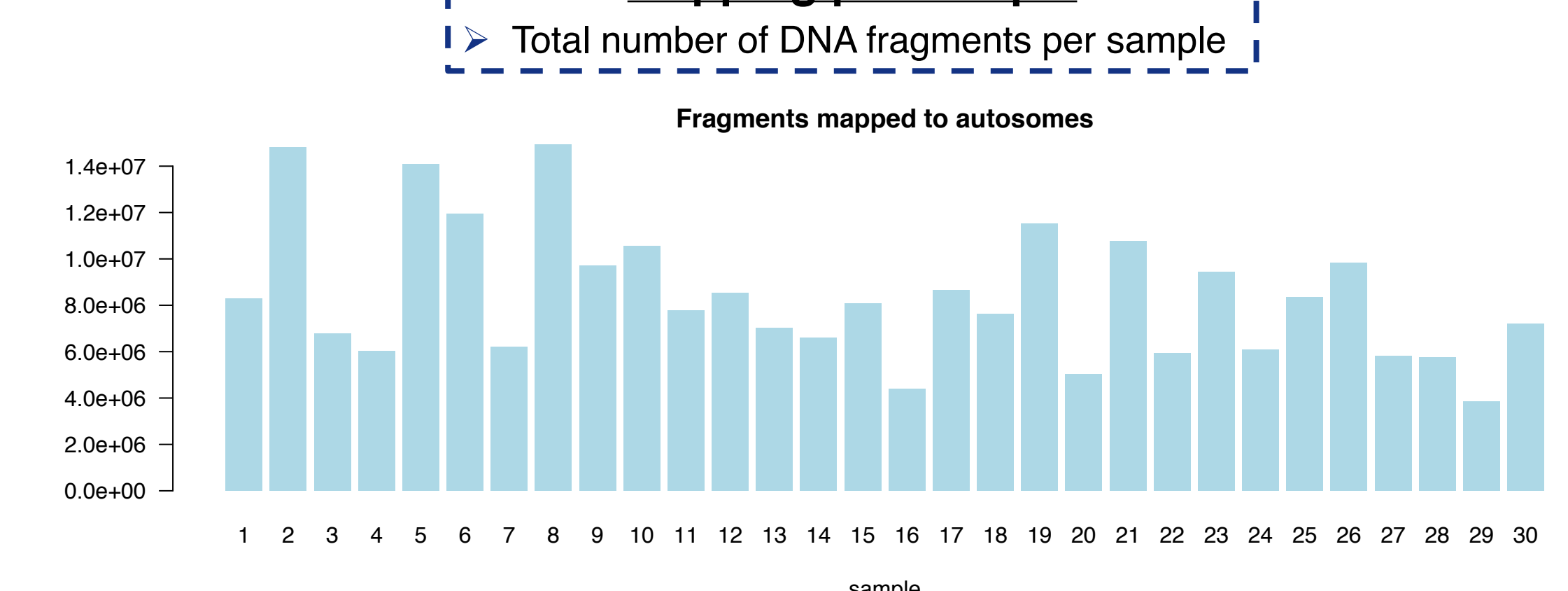
- We can identify regulatory regions
- We can measure how SNPs affect regulatory regions
- We can detect cell-type specific effects

Full SuRE-SNP

- Full CeD loci were selected, including suggestive loci.
- Target enrichment was performed by means of RNA-probes.
- DNA from 30 CeD patients were selected to equally cover all SNP alleles.



Mapping per sample



FUTURE AIM

To identify causal SNPs in CeD loci and prioritize these SNPs for functional follow up

REFERENCES

- [1] Trynka et al. (2011). Dense genotyping identifies and localizes multiple common and rare variant association signals in Celiac Disease, *Nature Genetics*, 43, 1193-1201
 [2] Ponce et al. (unpublished). Celiac Disease meta-analysis, unpublished.
 [3] Gutierrez-Achury et al. (2015). Fine-mapping in the MHC region accounts for 18% additional genetic risk for celiac disease, *Nature Genetics*, 47, 577-578
 [4] Joris van Arensbergen et al. (2017). Genome-wide mapping of autonomous promoter activity in human cells. *Nature Biotechnology*, 35, 145-153
 [5] Sebo Withoff et al. (2016). Understanding Celiac Disease by Genomics. *Trends in Genetics*, Vol. 32, Issue 5, p295-308.

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