Type 1 Diabetes Risk Is Influenced by Both Immune Cell and Pancreatic Islet Regulatory Variation

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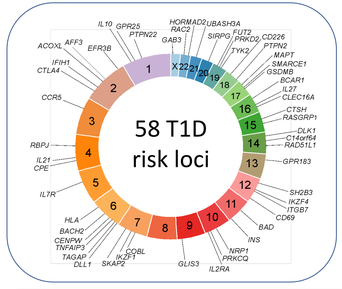
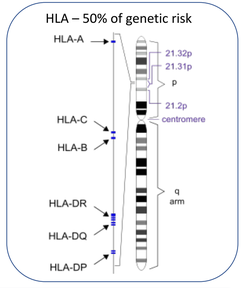
1. Background

Many genomic loci influence T1D risk, but causal mechanisms at most loci are unknown





Previous studies identified enrichment of T1D variants in immune enhancers

- Most T1D risk variants lie in non-coding genomic regions, and probably have regulatory effects.
- Epigenomic maps from human cells can provide information about mechanisms of disease loci.
- A previous genetic fine-mapping study found that T1D variants are enriched predominantly in immune-related enhancers.

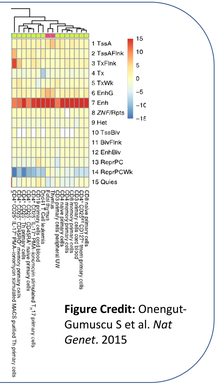
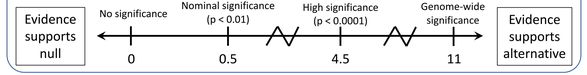


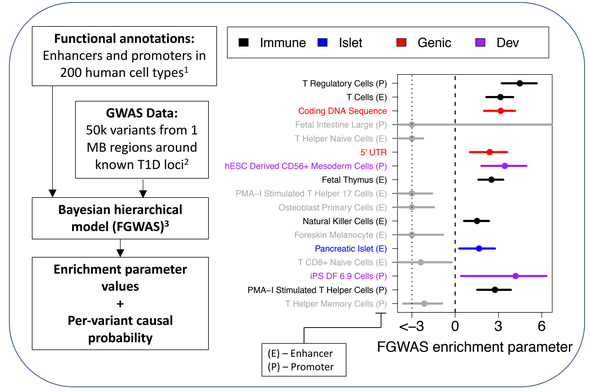
Figure Credit: Onengut-Gumuscu S et al. *Nat Genet*. 2015

Statistics: Log Bayes Factor Scale (Log BF)

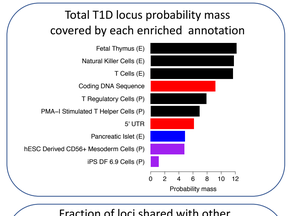


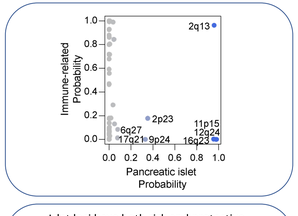
2. Modeling T1D risk using epigenome data

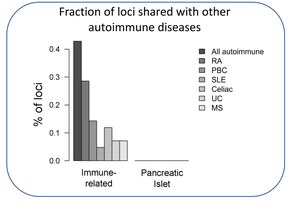
Statistical modeling reveals that regulatory sites in immune cells and pancreatic islets are enriched for T1D risk variants



Variants in pancreatic islet enhancer regions represent a distinct subset of T1D loci







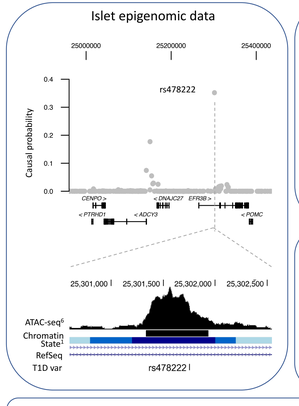
Islet loci have both risk and protective effects on T2D risk

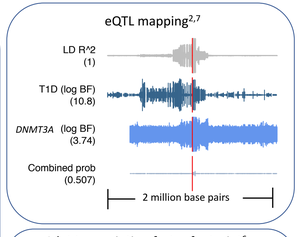
Locus	T1D Effect*	T2D Effect*
EFR3B	Protective[2]	None
GLIS3	Risk[2,4]	Risk[5]
BCAR1	Risk[2,4]	Protective[5]

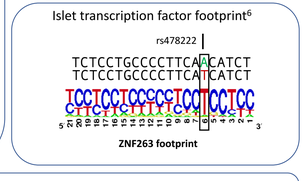
* Oriented to HG19 reference allele

3. Candidate T1D variants affect islet regulation

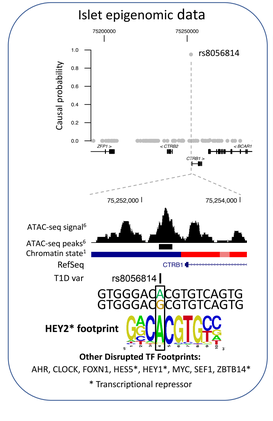
EFR3B Locus: Candidate variant overlaps islet accessible chromatin and affects islet *DNMT3A* expression

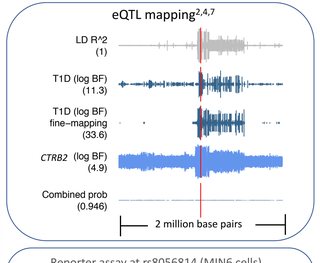


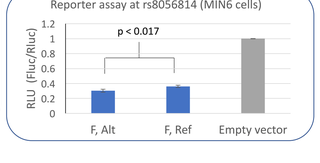




BCAR1 Locus: Candidate variant overlaps islet accessible chromatin and alters islet regulatory activity and *CTRB2* expression

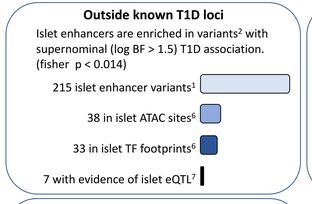


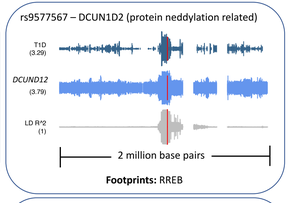


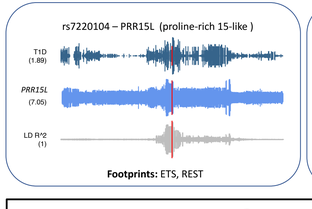


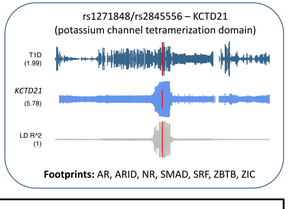
4. Islet regulatory variants broadly influence T1D

Variants with nominal T1D association are enriched in pancreatic islet enhancers









Summary

1. Statistical models demonstrate variants in both immune cell and pancreatic islet regulatory elements are enriched for T1D risk
2. T1D loci can be partitioned into immune- and islet-related groups with distinct properties based on epigenomic annotations
3. Evidence that pancreatic islet regulatory mechanisms underlie T1D risk at known loci, including *EFR3B* and *BCAR1*, in addition to several novel loci.

References

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2. Bradfield JP et al. *PLoS Genet*. 2011
3. Pickrell JK. *Am J Hum Genet*. 2014
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6. Unpublished data
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