Fine-mapping variants and genes that contribute to celiac disease

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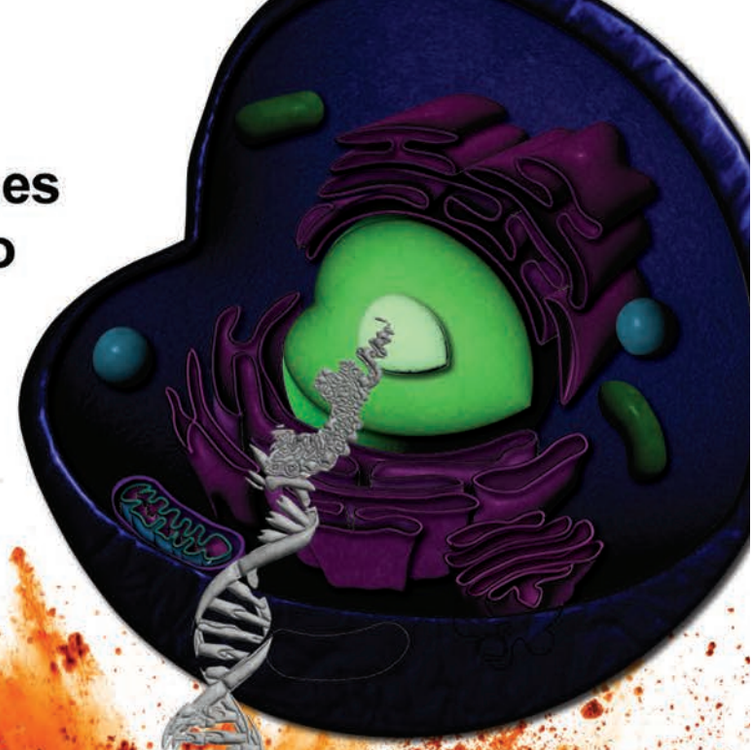

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university of groningen

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Propositions

1. Fine-mapping should be done in disease-relevant cell types in their tissue- and disease-specific context (this thesis).

2. Variants and genes collectively contribute to a disease phenotype; hence it is more accurate not to refer to variants and genes as causal but as contributing to a complex trait or disease (this thesis).

3. Fine-mapping aims to increase the functional understanding of 1) cells in their disease-specific state, 2) genetic and epigenetic regulatory elements, 3) contributing variants, and 4) contributing coding and non-coding genes, in the context of a trait or disease (this thesis).

4. Representative experimental models are essential to validate fine-mapped variants and genes to establish causality in the correct disease-specific cell states (this thesis).

5. Non-coding RNAs possibly play a role in maintaining CD8+ IEL cell homeostasis, as evidenced by downregulation of many non-coding RNAs upon cytokine and TCR stimulation (this thesis).

6. The regulatory elements containing the celiac disease associated variants rs2888524 and rs71327063 show allele-specific expression in epithelial cells as measured in the SuRE-SNP MPRA method, and therefore likely contribute to celiac disease (this thesis).

7. Nearly all of the 22 celiac-associated genes that were prioritized in CD8+ IELs, play a role in initial activation, signaling, and transcription factor events in CD8+ IELs, suggesting that the impact of these genes in celiac disease pathogenesis may be relatively strong due to a downstream cascade effect (this thesis).

8. According to the polygenic model, many combinations of variants can lead to the same disease phenotype, this implies that the same disease can manifest in different individuals when, through a different combination of variants, the same disease-associated biological processes are sufficiently dysregulated (this thesis).

9. While reviews are an effective method to relay concepts and ideas, they are an inefficient and old-fashioned method of collecting and visualizing the currently available highly complex genetic and epigenetic data.

10. Saturated GWASs, like the height meta-analysis with >12k associated variants, are nothing short of a fine-mapping nightmare.

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