Open Targets Genetics

Integrating evidence from genome-wide associations and functional genomics to identify and prioritise drug targets

genetics.opentargets.org

ESHG Invited Workshop

Saturday, 15 June 2019

10:30 – 12:00 hrs

Swedish Exhibition and Congress Centre

Room H2

Gothenburg, Sweden

Exercise 1: Using *Open Targets Genetics* to retrospectively demonstrate the role of genetics supporting an existing drug

In Open Targets Genetics, search for **LDL cholesterol**, and pick **Willer CJ (2013) *Nat Genet***.
https://genetics.opentargets.org/study/GCST002222

How many loci are independently associated with LDL cholesterol at genome-wide significance in this study (p-value < 5e-8)?
There are 123 loci with genome-wide significance.

In the Manhattan-like plot, zoom in on chromosome 5. How many independent associations can you find? In the table, click on the lead variant, **5_75329662_C_A**.
There are 4 independent associations on chromosome 5.
https://genetics.opentargets.org/variant/5_75329662_C_A

Which genes are functionally implicated by **5_75329662_C_A**? Rank them by their V2G score. What functional evidence supports these links?

The genes functionally implicated by **5_75329662_C_A**, ranked from highest to lowest V2G score, are *HMGCR, COL4A3BP, ANKDD1B, GCNT4, POC5, AC008897.2, AC008897.3, ANKRD31, POLK, AC010245.2, AC010245.1, AC116337.3, AC010501.1, FAM169A*. There is supporting evidence available from Distance to TSS, eQTLs, PCHi-C, and Ensembl VEP.

Click on the GTEx tab to view tissue and direction of effect. In which tissue is there GTEx evidence for *HMGCR*? What is the direction of effect?

There is GTEx evidence in Blood (eQTLGen) for *HMGCR*. The beta is positive, suggesting that an increase in gene expression with respect to the alternative allele is associated with elevated LDL cholesterol.

Scroll down to the PheWAS plot. You can see that **'high cholesterol | Non-cancer illness code, self-reported'** is the most significantly-associated trait in UK Biobank. What other traits are associated with this variant at phenome-wide significance? Observe the direction of effect by the triangles pointing upward or downward.

There are several related UK Biobank traits associated with this variant including Disorders of lipoid metabolism (SAIGE_272) and Hyperlipidemia (SAIGE_272_1) as well as treatment/medication for simvastatin and atorvastatin.

Now, let's look closer at the *HMGCR* locus. In the table below the PheWAS plot, click on the 'Locus' icon for the UK Biobank study with the most significant association, **'high cholesterol | Non-cancer illness code, self-reported'**.
https://genetics.opentargets.org/locus?chromosome=5&end=76329662&selectedIndexVariants=5_75329662_C_A&start=74329662

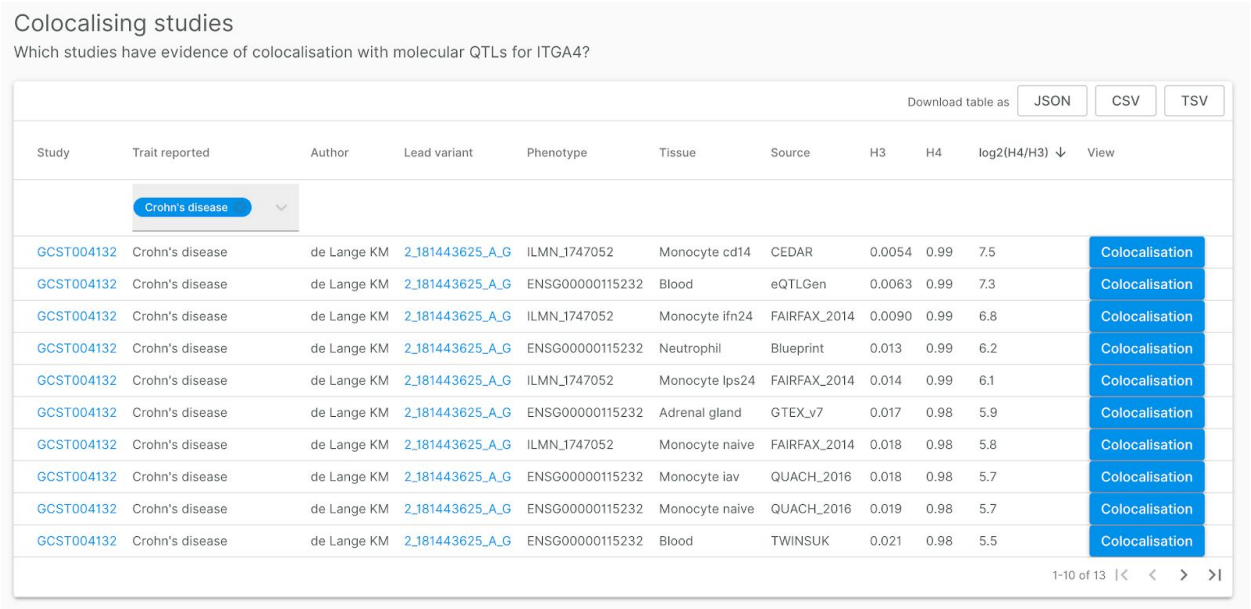
Use the drop-down to toggle between LD and fine mapping at this locus. The table below the figure displays the variants tagging this lead variant and the genes functionally implicated by these tag variants.

To learn more about *HMGCR*, including ongoing or approved drug clinical trials, and a list of other studies associated with this gene, click on *HMGCR* in the table.
https://genetics.opentargets.org/gene/ENSG00000113161

The link, '**Is there known drug data?**', directs you to the **Open Targets Platform** (targetvalidation.org) where you can view additional information about the gene. Using the 'Drugs' drop-down menu, view drugs targeting *HMGCR* and the accompanying clinical trial info. There are multiple statins in Phase IV with antagonist activity to treat lipid-related disorders.
https://www.targetvalidation.org/target/ENSG00000113161?view=sec:known_drug

Exercise 2: Using *Open Targets Genetics* to identify diseases and molecular QTLs that colocalise with a disease-associated signal

VEDOLIZUMAB is an approved, Phase IV completed drug targeting *ITGA4* to treat Crohn's disease. Find this genetic association on the *ITGA4* **Gene page** by searching for Crohn's disease in the 'Colocalising studies' table.
https://genetics.opentargets.org/gene/ENSG00000115232



Colocalising studies

Which studies have evidence of colocalisation with molecular QTLs for ITGA4?

Download table as JSON CSV TSV

Study	Trait reported	Author	Lead variant	Phenotype	Tissue	Source	H3	H4	log2(H4/H3) ↓	View
	Crohn's disease									
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ILMN_1747052	Monocyte cd14	CEDAR	0.0054	0.99	7.5	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Blood	eQTLGen	0.0063	0.99	7.3	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ILMN_1747052	Monocyte ifn24	FAIRFAX_2014	0.0090	0.99	6.8	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Neutrophil	Blueprint	0.013	0.99	6.2	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ILMN_1747052	Monocyte lps24	FAIRFAX_2014	0.014	0.99	6.1	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Adrenal gland	GTEX_v7	0.017	0.98	5.9	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ILMN_1747052	Monocyte naive	FAIRFAX_2014	0.018	0.98	5.8	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Monocyte iav	QUACH_2016	0.018	0.98	5.7	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Monocyte naive	QUACH_2016	0.019	0.98	5.7	Colocalisation
GCST004132	Crohn's disease	de Lange KM	2_181443625_A_G	ENSG00000115232	Blood	TWINSUK	0.021	0.98	5.5	Colocalisation

1-10 of 13

There is genetic evidence of association between variant 2_181443625_A_G at the *ITGA4* locus and Crohn's disease from ***de Lange et al. 2017, Nat Genet***. Click on one of the **Colocalisation** buttons in the table, all of which lead to the colocalisation page for the de Lange study and 2_181443625_A_G.

https://genetics.opentargets.org/study-locus/GCST004132/2_181443625_A_G

What molecular traits (e.g. eQTL, pQTL) colocalise with this Crohn's Disease signal? In which tissues?

QTL Colocalisation

Which molecular traits colocalise with **Crohn's disease (de Lange KM, 2017)** at this locus?

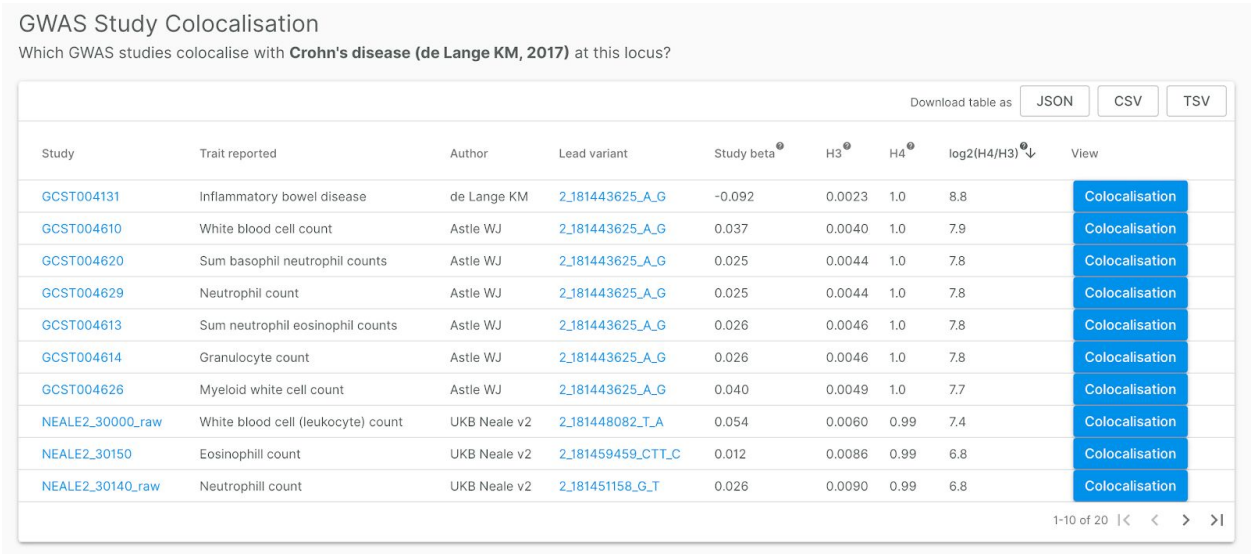
Heatmap | Table

Download table as JSON CSV TSV

Gene	Molecular trait ↑	Source	Adrenal gland	Blood	Monocyte	Monocyte cd14	Monocyte iav	Monocyte ifn24	Monocyte lps	Monocyte lps24	Monocyte naive	Neutrophil
ITGA4	ENSG00000115232	GTEX_v7	●	●								
ITGA4	ENSG00000115232	Blueprint			●							●
ITGA4	ENSG00000115232	eQTLGen		●								
ITGA4	ENSG00000115232	QUACH_2016					●		●		●	
ITGA4	ENSG00000115232	TWINSUK		●								
ITPRID2	ENSG00000138434	eQTLGen		●								
CERKL	ENSG00000188452	QUACH_2016					•				●	
CERKL	ENSG00000188452	GTEX_v7	●	●								
CERKL	ENSG00000188452	TWINSUK		•								
ITGA4	ILMN_1747052	FAIRFAX_2014						●		●	●	

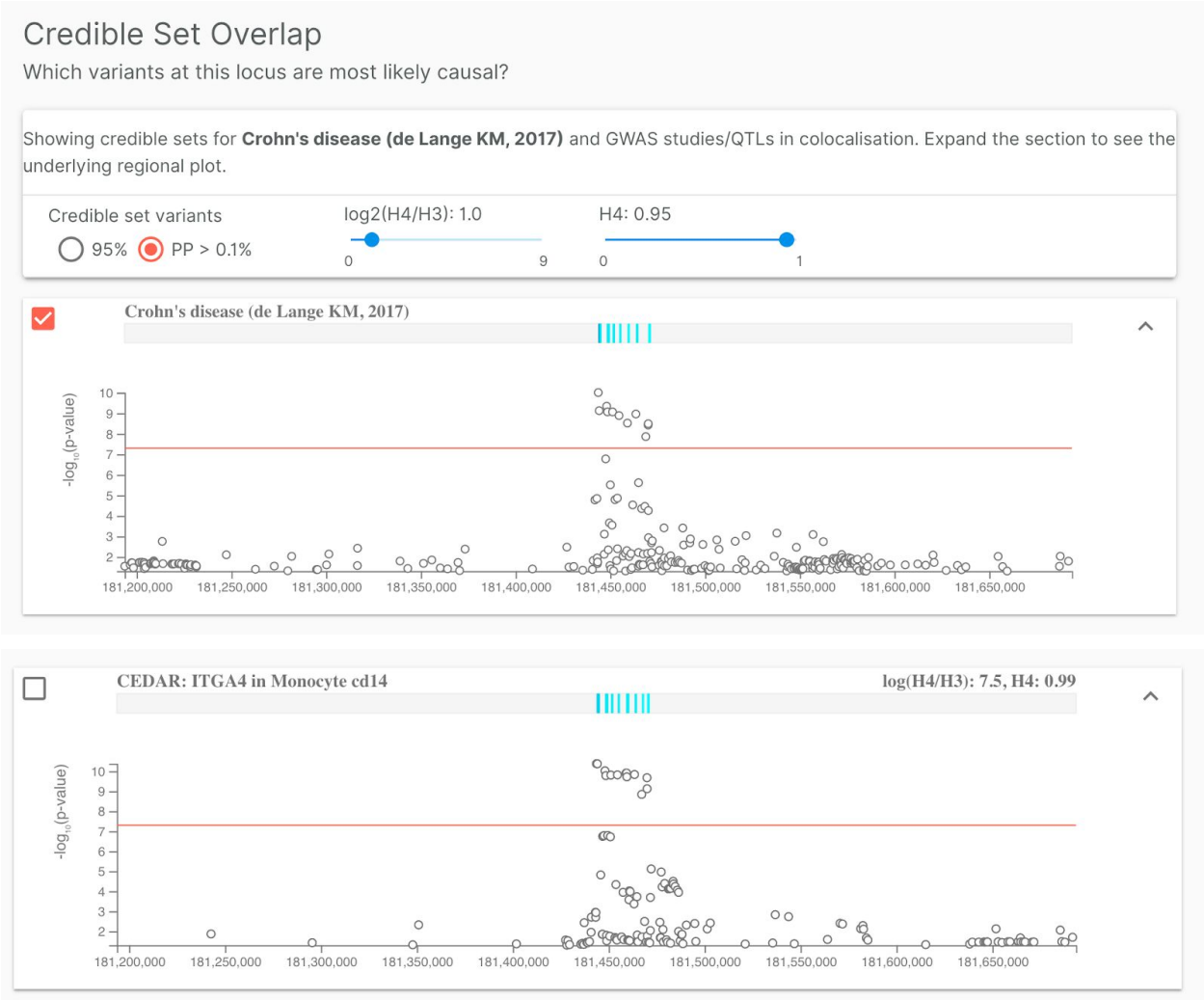
1-10 of 12 |< < > >|

What other GWAS traits colocalise with Crohn's Disease at this locus? By what evidence?



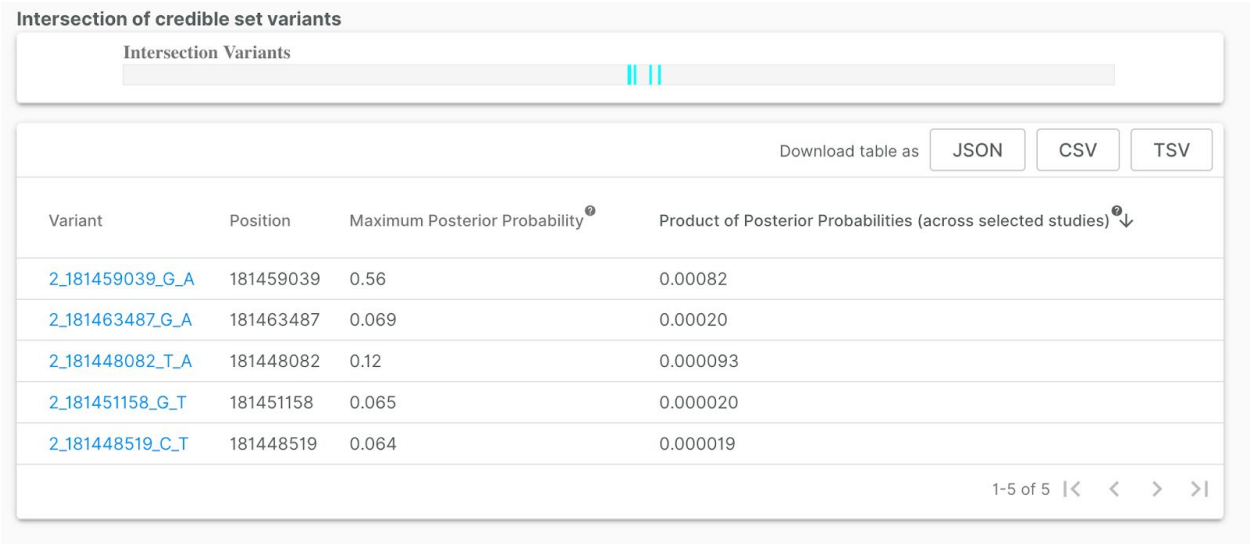
Scroll to the **Credible Set Overlap** section towards the bottom of the Colocalisation page. This visualisation shows the overlap between fine mapping credible sets that colocalise with Crohn's disease (de Lange KM, 2017) at this locus.

You can use the drop-down on each track to view a basic regional plot of the summary statistics. Do the Crohn’s disease and ITG4A (CEDAR Monocyte CD14) signals look the same in the regional plots?



We assume that GWAS signals that colocalise are more likely to share a common causal variant. Based on this, we can use information coming from different GWAS signals in order to refine the credible set. To the left of each credible set track there is a checkbox. Selecting multiple tracks shows the intersection of variants across tracks in the **Intersection of credible set variants** table at the bottom of the page.

Can you identify the set of likely causal variants at this locus based on the Crohn's disease and ITG4A Monocyte signals?



You can use the “TSV” to download these prioritised variants for further analysis.