Using Genetics and Functional Genomics to Identify and Prioritize Targets for New Medicines

ASHG Invited Workshop

Thursday, October 18, 2018

7:15 - 8:45 AM

San Diego Convention Center

Room 31, Upper Level

Presented by:

Open Targets Genetics

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

Search for **LDL cholesterol**, and pick **Teslovich *et al*. Nature 2010**.

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

Zoom in on chromosome 5. How many independent associations can you find? In the table, click on the lead variant, **5_74656539_T_C**.

Which genes are functionally implicated by **5_74656539_T_C**? Rank them by their V2G score. What functional evidence supports these links?

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?

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

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, 'Non-cancer illness code, self-reported: high cholesterol'.

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.

Click the **Open Targets Platform** link to direct you to additional information about the gene. Using the 'Drugs' drop-down menu, view drugs targeting *HMGCR* and the accompanying clinical trial info.

Exercise 2: Using *Open Targets Genetics* to demonstrate a successful drug repurposing opportunity

USTEKINUMAB (Stelara) is an approved inhibitor of *IL12B*, which encodes the common β-subunit of interleukin-12 and interleukin-23. It is indicated for **psoriasis** and psoriatic arthritis (Phase IV), and has recently been licensed as a second-line therapy for **Crohn's Disease**. This successful repurposing effort is supported by common population-based genetic evidence, which can be explored using OT Genetics.

We can quickly view information on the targets of **USTEKINUMAB** and the current status of clinical trials using this compound by navigating to the drug page on OT Genetics' sister site, targetvalidation.org: https://www.targetvalidation.org/summary?drug=CHEMBL1201835

Using OT Genetics, identify the most up-to-date studies which provide evidence for a role of *IL12B* in Crohn's Disease and psoriasis. Use the **gene** page to do this most quickly.

Having identified these studies, explore whether they implicate *IL12B* in Crohn's and psoriasis via the same signal, or distinct loci. The 'Compare to Related Studies' view accessed from the study page has been designed for rapid look-up and assessment of overlapping loci between studies. Take a look at the documentation here to help you compare reported loci between the two studies of interest.

Load the **Locus View** from within the study comparison to explore the tag variants through which the disease-associated lead variants implicate IL12B, and the functional evidence for the assignment of IL12B to these loci. Are the tag variants shared or separate? Is IL12B the top-ranked gene for each tag variant? Which tag variant more strongly implicates IL12B?

Exercise 3: Using *Open Targets Genetics* to highlight known adverse effects of a black-boxed drug

SODIUM VALPROATE is an anti-epileptic inhibitor of succinate semialdehyde dehydrogenase (*ALDH5A1*), which is also licensed for Bipolar Disorder. It carries a black-boxed warning for severe (potentially fatal) hepatotoxicity, with regular monitoring of LFTs mandated in all recipients.

Common genetic evidence supports the observation of hepatotoxicity as an adverse effect. Investigate this evidence base using OT Genetics:

1) Identify hepatic traits associated with loci which implicate *ALDH5A1*, and their lead variant. You will find the **gene** and **study** pages most helpful.

2) Investigate the functional evidence linking the main liver function-associated loci to *ALDH5A1*, paying particular attention to expression data. Using the **variant** page, establish whether the effect of liver function-associated variants on the expression of *ALDH5A1* is consistent with the mode of action of **SODIUM VALPROATE** and its adverse effects.

3) Note the tissues in which the eQTL effect of the liver function-associated variant is seen.

N.B. The Locus View is temporarily disabled for the full HLA region (including the megabase flanking *ALDH5A1*) due to the complexities of effectively displaying this locus. This will be updated in an upcoming release.