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: Genetic evidence in support of 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 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 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.

On the **gene** page, click the link directing you to additional drug information about *HMGCR*. The 'Drugs' drop-down menu in the Open Targets Platform lists statins targeting *HMGCR* and the accompanying clinical trial info.

Exercise 2: Genetic evidence in support of a successful drug repurposing opportunity

USTEKINUMAB (Stelara) is an approved inhibitor of *IL12B*, the gene encoding 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 Open Targets Genetics.

Using the **gene** page, identify the two most recent studies which implicate *IL12B* in the aetiology of psoriasis and Crohn's disease. Note that there may be more recent studies for these traits which do not implicate *IL12B*. Focus on published studies rather than UK Biobank results (author: *Neale et al.*).

Use the 'Compare overlapping studies' tool to confirm that the two studies implicate *IL12B* through a shared locus. Start by loading one of the studies into the comparison view from its study page, then add the other once in the comparison view using the drop-down. The two studies you should be comparing are **de Lange (2017)** for Crohn's, and **Yin (2015)** for psoriasis. Be aware; the shared locus you see may not have *IL12B* as its top-ranked gene because the gene assignment shown is for the lead variant only, without consideration of the functional effects of its proxies (tag variants).

To get a fuller view of the functional gene assignments at this locus, including all tags, load the **locus view** from the study comparison page. The view will be loaded with the psoriasis and Crohn's studies pre-selected. Amongst the genes implicated by these studies (highlighted red), you will see *IL12B*; select it to further restrict the plot to only evidence which implicates *IL12B*.

Order the locus view table descending on V2G Score to place tag variants which more strongly implicate *IL12B* first. Click through the tag variant links from the table to explore the functional data by which each implicates *IL12B* on the **variant** page. Note that clicking through the lead variant in this instance will not show links to *IL12B*, as each variant page only displays the functional assignments of the selected variant, and the assignment of *IL12B* to this locus is via proxies.

Are the tag variants which implicate *IL12B* at this locus shared or separate? Is *IL12B* the top-ranked gene for each tag variant? Which tag variant more strongly implicates *IL12B*?

Exercise 3 (Back-up): Genetic evidence in support of 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 hepatotoxicity, with regular monitoring of liver function (standard LFT panel) mandated in all recipients. A black box is the highest level of warning which regulatory authorities can require to be placed on a medication.

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

Use the **gene** page to identify liver function traits associated with loci which implicate *ALDH5A1*. Specifically, you are looking for serum alkaline phosphatase levels (ALP, Chambers 2011).

In each case, click through to the **study** page and explore the functional basis by which these loci implicate *ALDH5A1*, using the **variant** page. Pay particular attention to eQTL evidence from GTEx, and the specific tissues in which this functional evidence is seen. You will not be able to use the **locus view** for this gene at present (see NB).

If there is time, consider whether there is directional consistency between the eQTL functional evidence implicating *ALDH5A1* and **SODIUM VALPROATE**'s mode of action. Remember that the effect allele throughout Open Targets Genetics is the ALT allele from Ensembl; the second allele shown in our variant ID. To identify reported effect alleles in studies, you will currently need to refer to the original manuscript - we are in the process of integrating this data into the portal.

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 enabled in an upcoming release.