## How to evaluate driver roles of candidate disease genes?

| Project tes            | it                        | Organism: huma        | an 👻            |                   |         |
|------------------------|---------------------------|-----------------------|-----------------|-------------------|---------|
| Altered                | gene sets Network         | Functional gene set   | s Chec          | k and submit      | Results |
| Submit                 | gene/protein groups that  | you want to character | ize             | to a list of IDec |         |
| Upload                 | a local file:             |                       | BCL11A          |                   |         |
| Brows                  | No file selected.         |                       | BRCA2           |                   |         |
| If file is             | already there: List files |                       | CSF3R<br>CSMD3  |                   |         |
|                        |                           |                       | DSP             |                   |         |
| As an example, w       | e investigat              | e roles               | IDH1            |                   |         |
|                        |                           |                       | INHBE<br>ITCB2  |                   |         |
| of point mutations in  | i one somat               | .IC                   | LDHA            |                   |         |
| genome of alightasta   | oma multifo               | rme                   | MAPK10          | 0                 |         |
| Scholle of ghobidste   |                           | -                     | MAPK9           |                   |         |
| We start by pasting    | the whole li              | st of                 | MKL1            |                   |         |
| 21 mutations in the    | first tob "Alt            | arad                  | MN1             |                   |         |
| 34 mutations in the    | Institad All              | ered                  | NRAP            |                   |         |
| gene sets". Although   | , each gene               | is /                  | PCDH2           | D                 |         |
| going to be analyzed   | separately                |                       | PDZD2<br>PRKD2  |                   |         |
| (cubmitting the list y | ,<br>Yould just s         |                       | PTEN            |                   |         |
| (submitting the list v | voulu just se             | ave                   | SLC2A2<br>STK36 |                   |         |
| time). Note that you   | can also su               | bmit                  | SYNE1<br>TAS1R1 |                   |         |
| them as a text file, e | .g. <u>this one</u>       | and                   | TBK1<br>TGFBR2  |                   |         |
| select mutations for   | particular c              | ancer                 | TMBIM4<br>TNK2  | ł                 |         |
| genome (column 3).     | Second, we                | will                  | VAV1            |                   |         |
| select a network in t  | he next tab               | (see                  |                 |                   |         |
| details in tutorial "H | ow to begin               | ?").                  |                 |                   |         |



| ect test  | Organis                             | m: human      | •               |         |                  |     |
|-----------|-------------------------------------|---------------|-----------------|---------|------------------|-----|
| tered gei | ne sets Network Functional          | gene sets Che | eck and submit  | Results | Help             |     |
|           |                                     |               |                 | O       |                  | [?] |
| elect col | lection(s) of functional gene sets. | Search        | :               | Past    | e a list of IDs: |     |
| Incude    | Source                              | 🔶 No. of ger  | nes 🔶 No. of gr | oups 🔶  |                  |     |
|           | BioCarta                            | 1259          | 219             |         |                  |     |
|           | CPW_collection                      | 1529          | 42              |         |                  |     |
|           | GO biological process               | 6032          | 825             |         |                  |     |
|           | GO collular compartment             | 5115          | 233             |         |                  |     |
|           | GO molecular function               | 5190          | 396             |         |                  |     |
|           | KEGG pathways, all                  | 4851          | 236             |         |                  |     |
|           | KEGG pathways, basic                | 1878          | 133             |         |                  |     |
|           | KEGG pathways, disease              | 44            | 35              |         |                  |     |
|           | KEGG pathways, signaling            | 3069          | 68              |         |                  |     |

Following scenario 2, we investigate how the genes relate to known pathways. For cancer applications one can utilize the group of 42 database- and publicationbased cancer pathways "CPW\_collection". Similarly to scenario 1, we use checkbox "Analyze AGS genes / proteins individually" at the next tab.



This gives many more findings than scenario 1 which is mostly due to using many more sets of much better characterized genes. However this approach requires a control analysis: how many such findings would be made for a randomly picked gene set of size 34?



Thus, stronger evidence was accumulated in the both scenarios for MALX9 and NTRK1 and a few other genes scored high against multiple cancer pathways (e.g. TNK2, TGFBR2). See <u>another analysis</u> of the same mutation list using other parameters.

However a full-scale statistical framework should be implemented for a systematic analysis of multiple cancer genes and genomes. Examples can be found in Merid et al., 2014 and might require additional information from the same samples (methylation, copy number events etc.). Required software in R and/or perl can be downloaded from https://www.evinet.org

| Search:AOC 3Incude & SourceNo. of genesNo. of groupsBCL11ABIoCarta1259219DSPCPW_collection152942DH1GO biological process6032825ITG82GO cellular compartment5115233MAPK10GO molecular function5190396MKL1KEGG pathways, all4851236MIH1KEGG pathways, disease74435PCDH20KEGG pathways, signaling306968PRK0 CMetaCyc pathways2933486SLC2 A2Reactome pathways4075430SYNE             | Select colle | ction(s) | of functional  | gene sets. |                |                    | )<br>Pas    | te a list of           | IDs:  |
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"Functional gene sets". The FGS menu on the left is not used.

There are two major modes in the analysis that can be run separately or in parallel. We can evaluate connections between a given candidate gene and a group of genes that together are likely to be implicated in the disease. Such a group can be either:

- 1) a set of altered genes discovered experimentally (typically the whole set of mutations, genetic variants, or differentially methylated or expressed genes), or
- 2) a curated gene set with well characterized functional role in the disease.

|                  | Organism: human  | •   |   |  |         |   |  |   |             |
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| nks<br>SS        | FGS<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA | <ul> <li>         #genes<br/>FGS     </li> <li>         A         67         A         B</li></ul>  | #links<br>FGS<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975 | #linksA<br>14<br>16<br>7<br>9<br>2<br>17<br>11<br>9      | GS2FGS  | S ♦ Score ♦       19.66       57.69       26.00       10.14       9.50       38.96       22.82       15.80                  | Search: FDR<br>FDR<br>2.091255E-04<br>2.972822E-12<br>1.100783E-05<br>1.786068E-02<br>2.409463E-02<br>2.572950E-08<br>4.665679E-05<br>1.265433E-03<br>Previou    | Shared<br>genes   | Show<br>net |
| nks<br>≥s        | FGS<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA | <ul> <li>         #genes<br/>FGS     </li> <li>         A         67         A         A         A         A         A         B         &lt;</li></ul>   | #links<br>FGS<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975 | #linksA<br>14<br>16<br>7<br>9<br>2<br>17<br>11<br>9      | GS 2FGS | S ♦ Score ♦<br>19.66<br>57.69<br>26.00<br>10.14<br>9.50<br>38.96<br>22.82<br>15.80  | Search: FDR<br>FDR<br>2.091255E-04<br>2.972822E-12<br>1.100783E-05<br>1.786068E-02<br>2.409463E-02<br>2.572950E-08<br>4.665679E-05<br>1.265433E-03<br>Previou    | Shared genes       ●         0       0         0       0         0       0         0       0         0       0         0       0         0       0         0       0         0       0         0       0         0       0         0       1  | Show net    |
| nks<br>≩S        | FGS<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>Send us email     | <ul> <li>         #genes<br/>FGS     </li> <li>         67      </li> <li>         67      </li> <li>         67     </li> <li>         67     </li> <li>         67     </li> <li>         67     </li> <li>         67     </li> <li>         67      </li> <li>         67      </li> <li>         67      </li> <li>         67      </li> <li>         67     </li> <li>         67      </li> <li>         67     </li> <li>         67</li></ul>   | #links<br>FGS<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975<br>11975 | #linksA<br>14<br>16<br>7<br>9<br>2<br>17<br>11<br>9      | GS2FGS  | S ♦ Score ♦<br>19.66<br>57.69<br>26.00<br>10.14<br>9.50<br>38.96<br>22.82<br>15.80  | Search: FDR<br>FDR<br>2.091255E-04<br>2.972822E-12<br>1.100783E-05<br>1.786068E-02<br>2.409463E-02<br>2.572950E-08<br>4.665679E-05<br>1.265433E-03<br>Previou    | Shared genes         0 <tr< td=""><td>Show net</td></tr<> | Show net    |
| nks<br>§S        | FGS<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>KEGG_05214_GLIOMA<br>Send us email     | <ul> <li>         #genes<br/>FGS     </li> <li>         A         67         A         A         A         A         A         A         A         B         A         B         <p< td=""><td>#links<br/>FGS</td><td>#linksA<br/>14<br/>16<br/>7<br/>9<br/>2<br/>17<br/>11<br/>9<br/>9</td><td>GS2FGS</td><td>S Score S<br/>19.66<br/>57.69<br/>26.00<br/>10.14<br/>9.50<br/>38.96<br/>22.82<br/>15.80</td><td>Search:<br/>FDR<br/>2.091255E-04<br/>2.972822E-12<br/>1.100783E-05<br/>1.786068E-02<br/>2.409463E-02<br/>2.572950E-08<br/>4.665679E-05<br/>1.265433E-03<br/>Previou</td><td>Shared<br/>genes<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0<br/>0</td><td>Show net</td></p<></li></ul> | #links<br>FGS   | #linksA<br>14<br>16<br>7<br>9<br>2<br>17<br>11<br>9<br>9 | GS2FGS  | S Score S<br>19.66<br>57.69<br>26.00<br>10.14<br>9.50<br>38.96<br>22.82<br>15.80  | Search:<br>FDR<br>2.091255E-04<br>2.972822E-12<br>1.100783E-05<br>1.786068E-02<br>2.409463E-02<br>2.572950E-08<br>4.665679E-05<br>1.265433E-03<br>Previou        | Shared<br>genes<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0<br>0  | Show net    |

