User's Guide for LnCeVar

- Background of LnCeVar development.
- How to identify Variant-ceRNA events?
- Basic information in LnCeVar.
- Variant associated binding affinity in LnCeVar.
- Functional annotation in LnCeVar.
- Hallmark annotation in LnCeVar.
- Network visualization in LnCeVar.
- Survival analysis in LnCeVar.
- External annotation in LnCeVar.
- Blast in LnCeVar.
- Genome browser in LnCeVar.
- Cluter tool in LnCeVar.

Background of LnCeVar development

Emerging evidence suggests that lncRNAs can function as competing endogenous RNAs (ceRNAs) and dynamically buffer the expression of downstream genes during different physiological and pathological processes. Genomic variations such as single nucleotide polymorphisms (SNPs) and somatic mutations on lncRNAs will alter the miRNA binding sites and further lead to the gain or loss of ceRNA interactions. Furthermore, copy number variations (CNVs) such as amplifications and deletions will generate or delete large amounts of miRNA binding sites and cause ceRNA network disturbances. Identification of these personalized variation-ceRNA events will help us to understand the individual disease pathology and further contribute to precision medicine. To meet this need, we describe a comprehensive database, LnCeVar, which documents personalized variation-ceRNA events of high quality manual curation based on the published literature and high-throughput identification from individual genomics data.

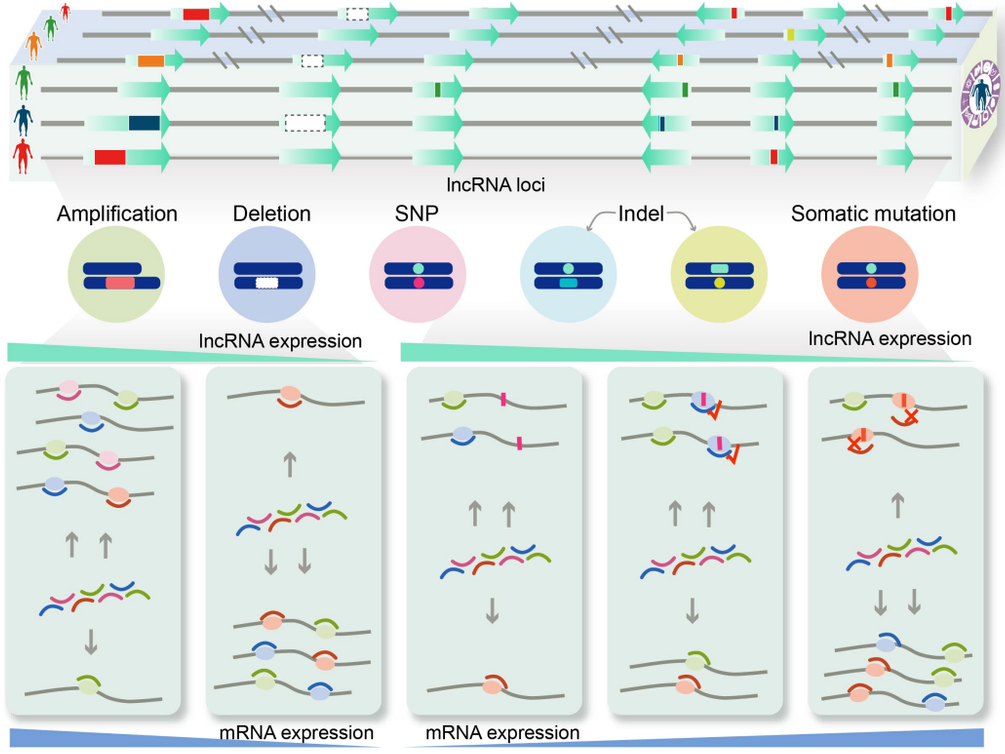

Figure 1-1

LnCeVar curated 119,501 variation-ceRNA events from thousands of samples and cell lines, including: (i) more than 2,000 experimentally supported circulating, drug resistant and prognosis-related lncRNA biomarkers; (ii) 11,418 somatic mutation-ceRNA events from TCGA and COSMIC; (iii) 112,674 CNV-ceRNA events from TCGA; (iv) 67,066 SNP-ceRNA events from the 1000-Genome project. LnCeVar provides a user-friendly searching and browsing interface. In addition, as an important supplement of the database, we have set up several flexible tools that facilitate retrieval and analysis of the data. The LnCeVar-Blast interface is a convenient way for users to search ceRNAs by interesting sequences. LnCeVar-Function performs functional enrichment analysis. LnCeVar-Hallmark identifies dysregulated cancer hallmarks of variation-ceRNA events. LnCeVar-Survival performs COX regression analysis and survival curves for variation-ceRNA events. LnCeVar-Network identifies and creates a visualization of a dysregulated variation-ceRNA network. Collectively, LnCeVar will serve as an important resource for investigating the functions and mechanisms of various genomic variations that disturb ceRNA regulation in human diseases.

How to identify SNP-ceRNA events?

Firstly, we mapped SNPs into lncRNA regions and identified SNPs that show altered binding affinity between reference and alternative alleles. And For each candidate SNP_ceRNA relationship, we established multivariate multiple regression on each SNP_ceRNA unit, and correct population and batch effect. The specific model is displayed in Figure 2-1.

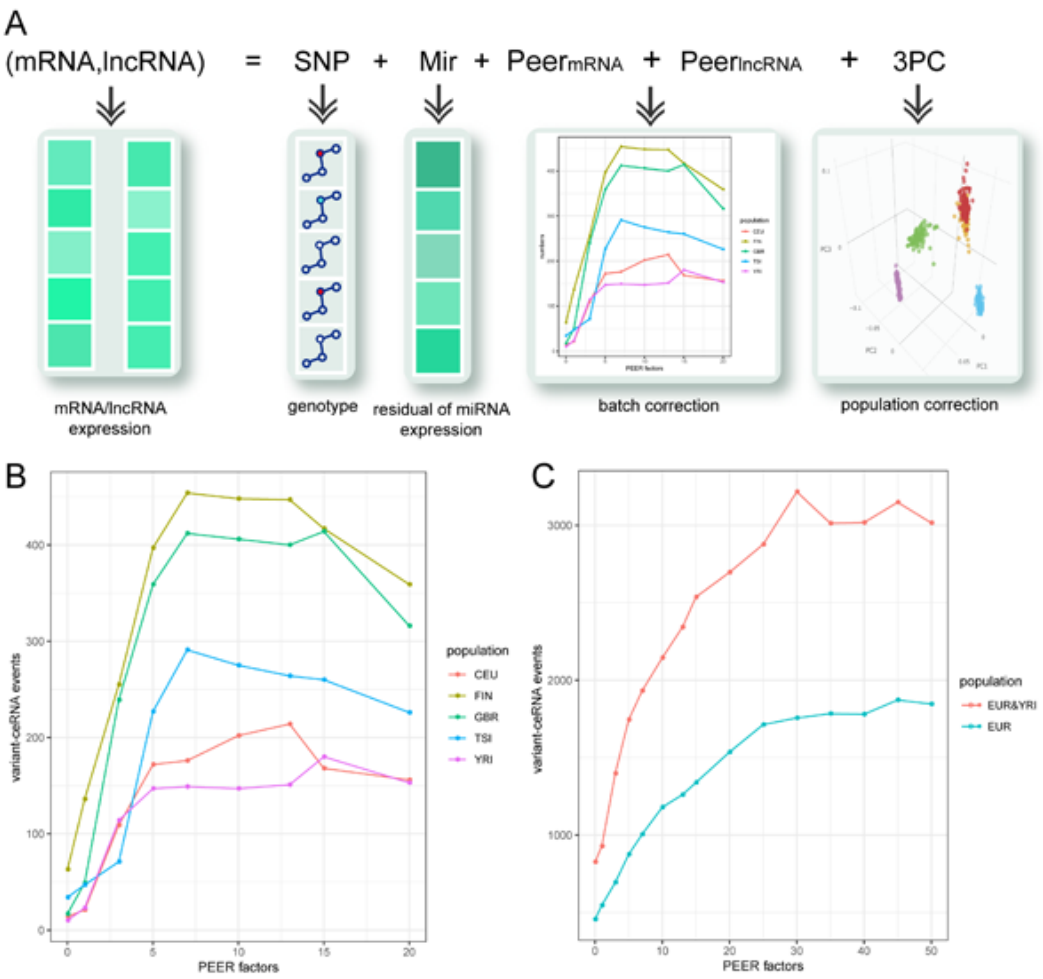

Figure 2-1

How to identify CNV-ceRNA events?

Firstly, we get lncRNA CNV profile using GISTIC 2.0 in TCGA cancer samples. And For each candidate CNV_ceRNA relationship, we established multivariate multiple regression on each CNV_ceRNA unit, and correct batch effect of CNV and expression profile. The specific model is displayed in Figure 2-2.

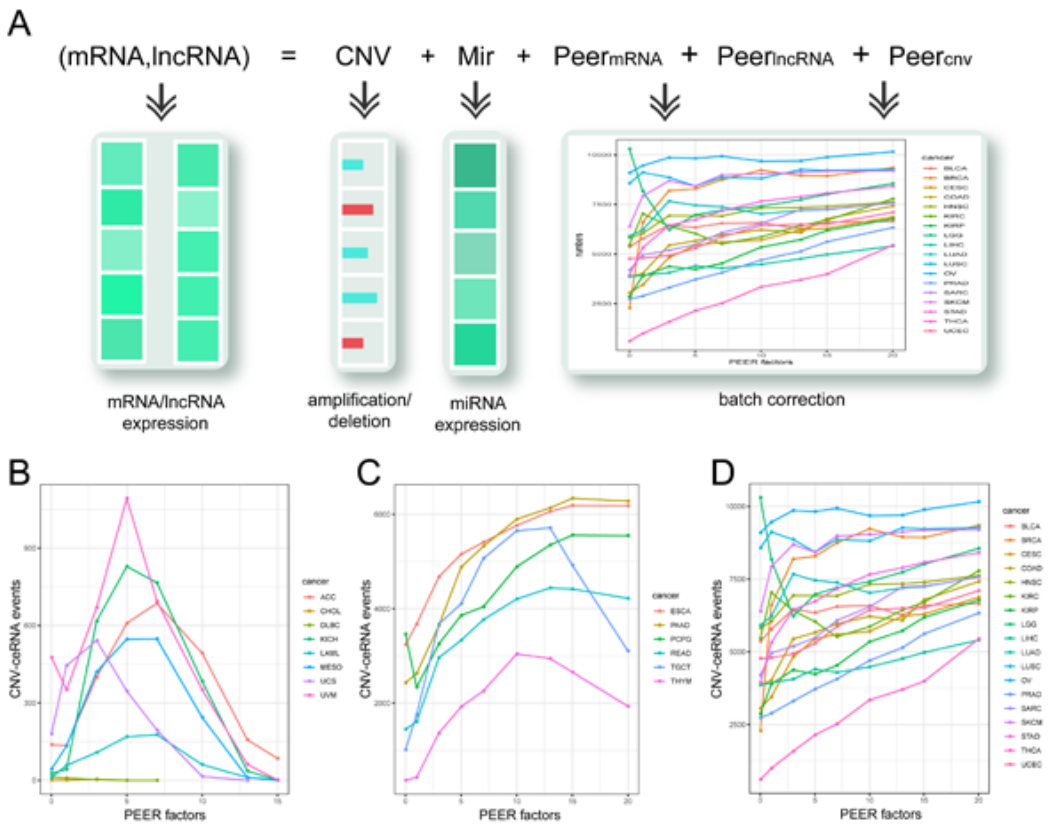

Figure 2-2

How to identify mutation-ceRNA events?

Firstly, we mapped somatic mutations into lncRNAs based on TCGA cancers and COSMIC cell lines. And select mutations effect binding affinity between lncRNAs and miRNAs. Finally, we map the remaining mutations into ceRNA. The specific process is displayed in Figure 2-3.

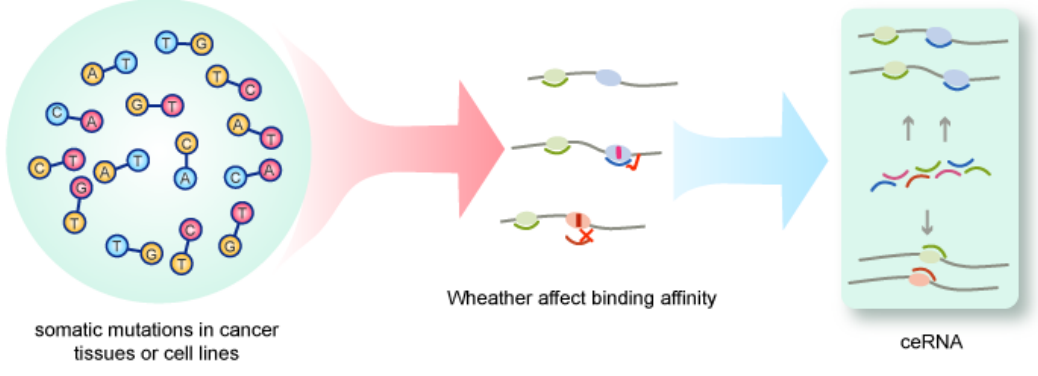

Figure 2-3

Basic information in LnCeVar.

For each variant-ceRNA unit, we provide basic information, which is displayed in Figure 3-1.

Figure 3-1

Variant associated binding affinity in LnCeVar.

For each variant, we provide detailed binding affinity between reference and alternative allele, which is displayed in Figure 4-1.

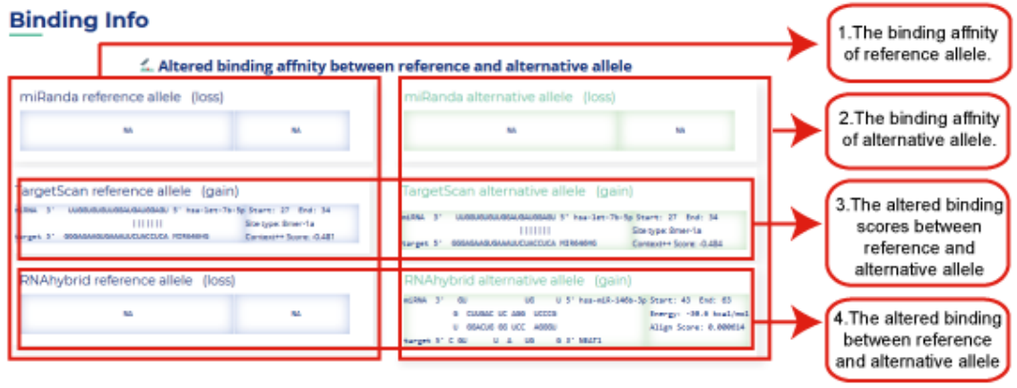

Figure 4-1

Functional annotation in LnCeVar.

For the hit variant-ceRNA, we provide functional annotation analysis in LnCeVar, which is displayed in Figure 5-1.

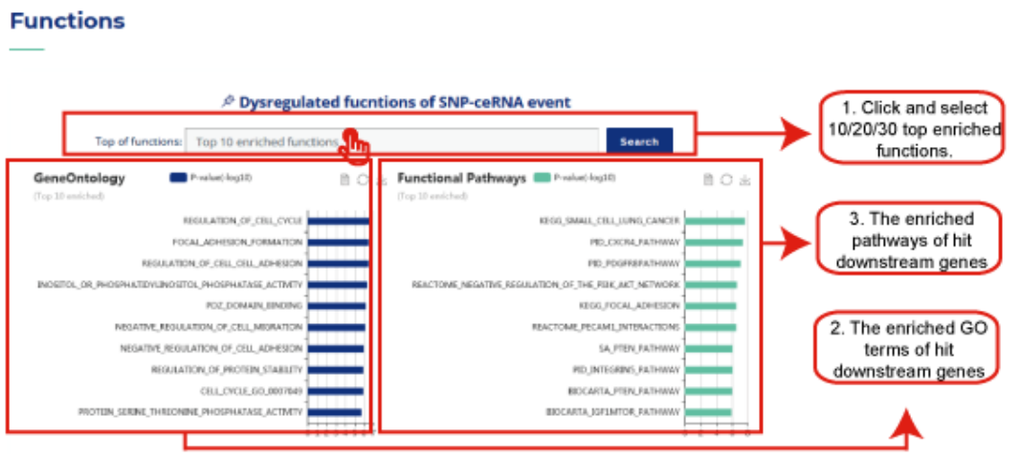

Figure 5-1

Hallmark annotation in LnCeVar.

For the hit variant-ceRNA, we provide hallmark analysis in LnCeVar, which is displayed in Figure 6-1.

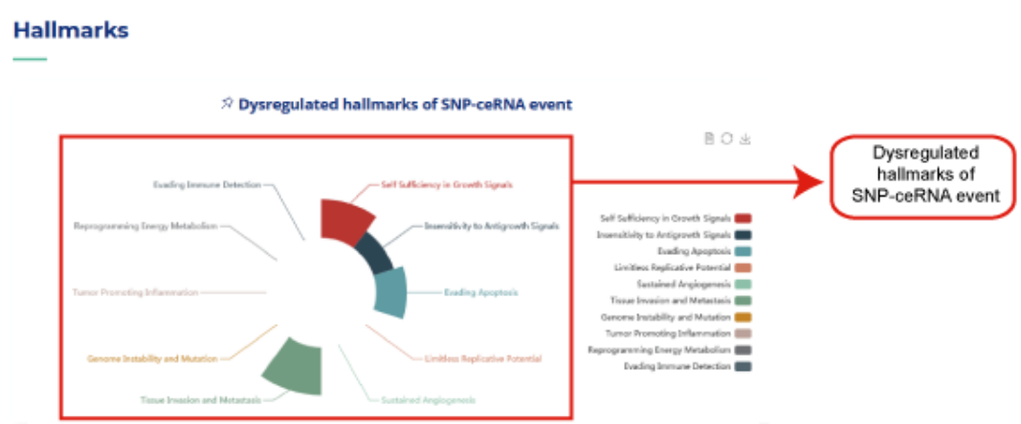

Figure 6-1

Network visualization in LnCeVar.

For the hit variant-ceRNA, it's related network can be displayed using different neighbor numbers, which is displayed in Figure 7-1.

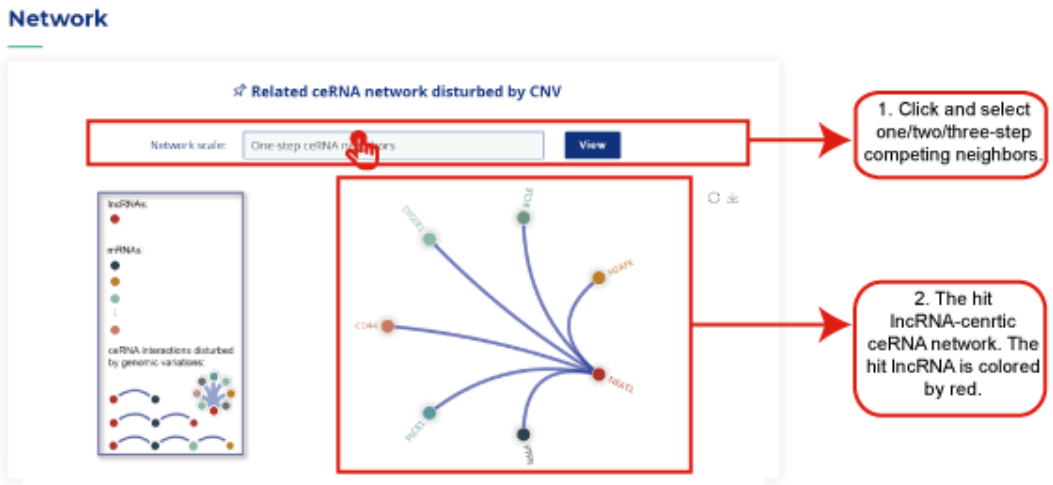

Figure 7-1

Survival analysis in LnCeVar.

For the hit variant-ceRNA, we provide survival analysis service based on ceRNA expression information, which is displayed in Figure 8-1.

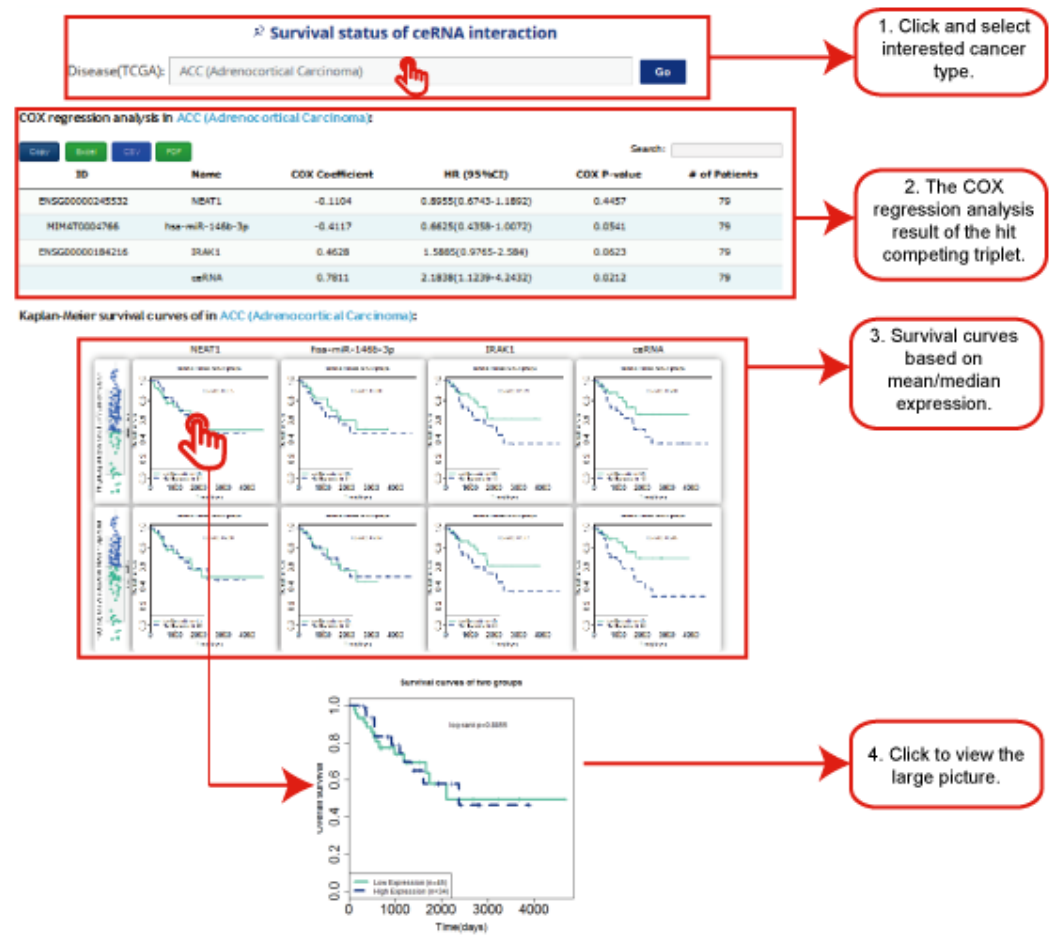

Figure 8-1

External annotation in LnCeVar.

For the hit variant-ceRNA, we provide comprehensive external annotation, which is displayed in Figure 9-1.

Figure 9-1

Blast in LnCeVar.

Users can input sequeces to blast with the LnCeVar database, which is displayed in Figure 10-1.

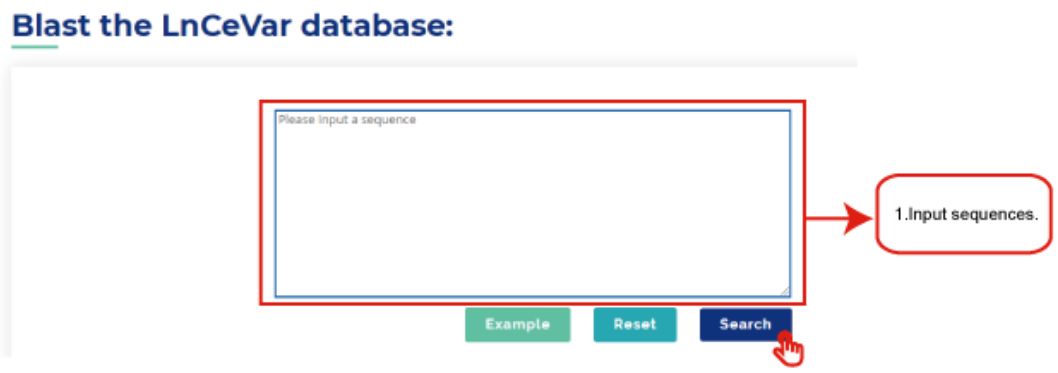

Figure 10-1

Genome browser in LnCeVar.

We provide genome browser in LnCeVar,users can input transcript information to navigate results, which is displayed in Figure 11-1.

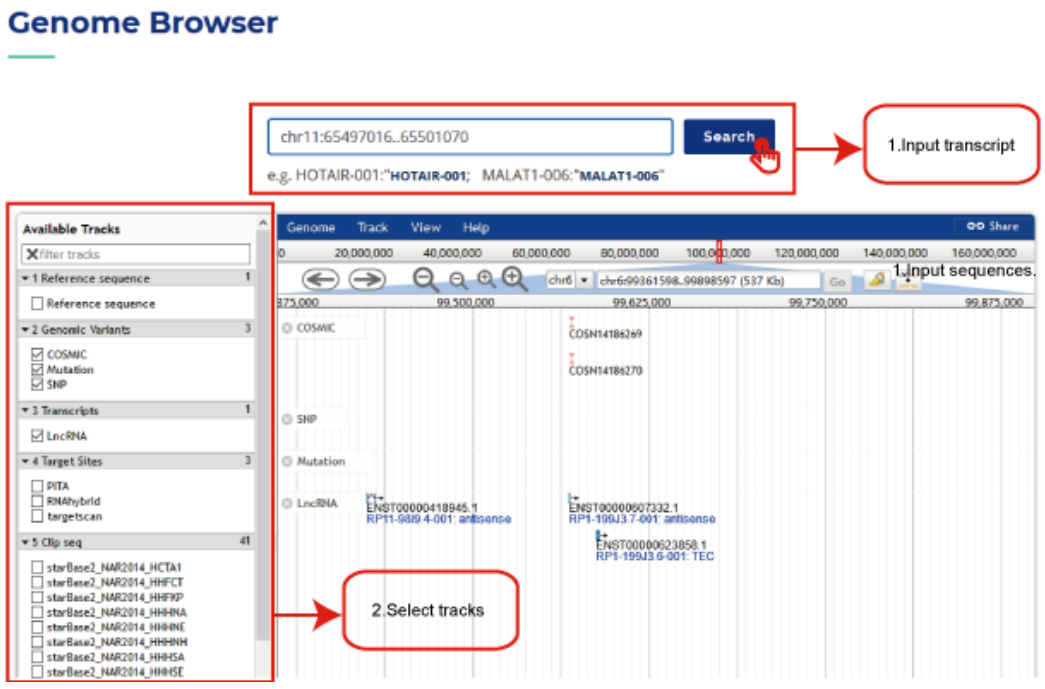

Figure 11-1

Cluter tool in LnCeVar.

We provide cluster tool in LnCeVar,for each hallmark in the certain cancer, its related lncRNAs and the lncRNA-mRNA correlation is clustered and displayed in matrix pattern, users can adjust the cluster results with different manners, and get the functional annotation results in enrichr web server, which is displayed in Figure 12-1.

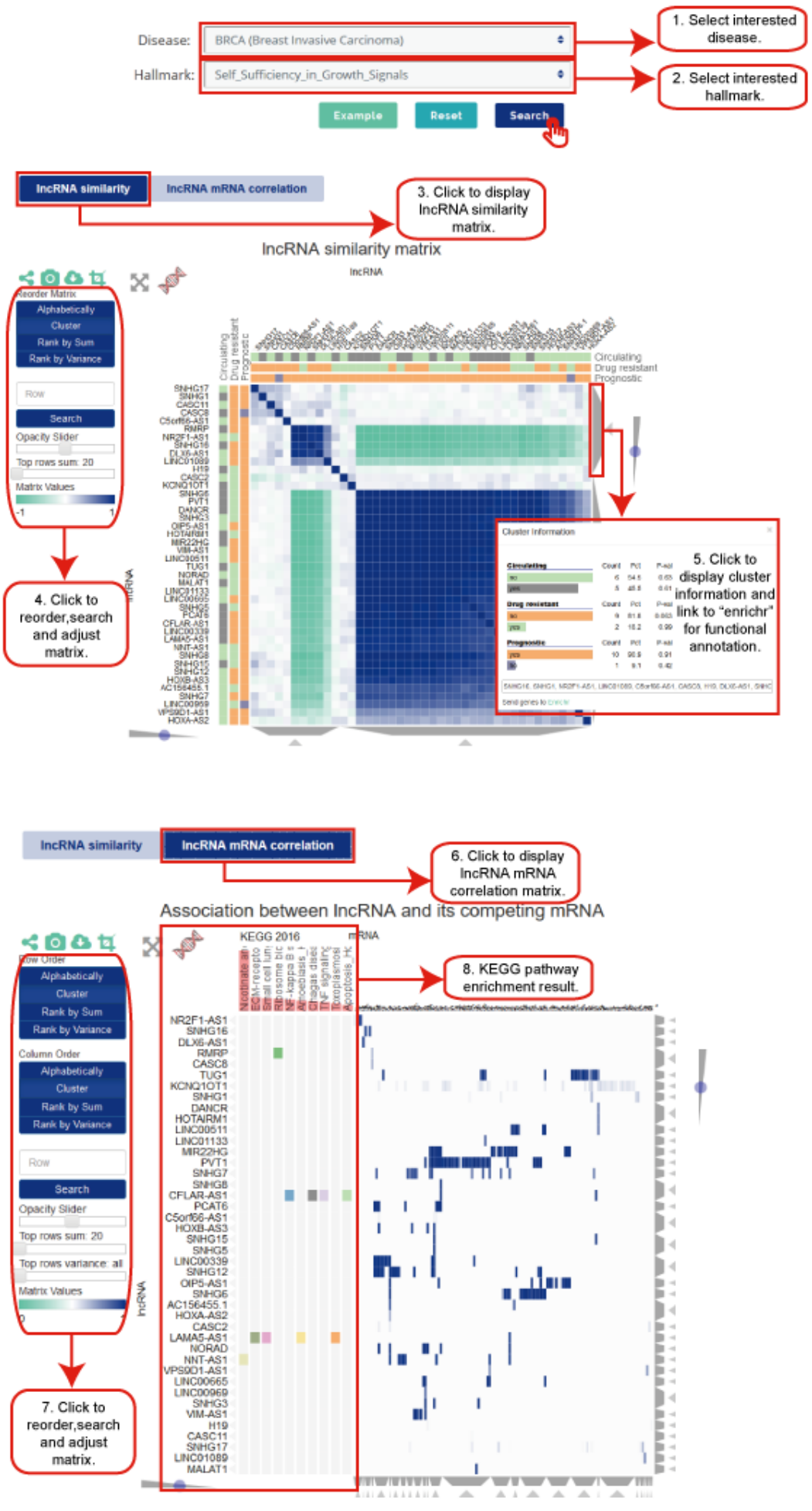

Figure 12-1