QIAGEN

Ingenuity® Variant Analysis™ Quick-Start Guide

For accessing and using Ingenuity Variant Analysis

Sample to Insight

Ingenuity® Variant Analysis™ is a web-based application that combines analytical tools and integrated genomics content with user panel, exome, or genome data to rapidly identify and prioritize compelling causal variants using published biological evidence. This Quick-Start Guide summarizes how to access the online application, upload data files, perform and share analyses.

Before using Variant Analysis, visit **https://www.qiagenbioinformatics.com/products/ingenuity-variant-analysis/** where you can access pre-recorded webinars, reference materials and profiles of featured researchers who have used the product. Tutorials are available at **http://ingenuity.force.com/variants/VariantTutorials**.

The "Help" function in Variant Analysis is a comprehensive, keyword-searchable resource, designed for quickly finding necessary information and instructions. Click "Help" at the top of the Variant Analysis application or visit **http://ingenuity.force.com/variants/VariantTutorials**.

Access Variant Analysis

Anyone with a valid email address* can register for a trial account by going to the secure site **https://www.qiagenbioinformatics.com/products/ingenuity-variant-analysis/** and clicking "Request a trial".

After registering, log into Variant Analysis at **https://variants.ingenuity.com/va/**, where you will find published datasets to explore and instructional videos to get started.

You can reset your username or password at **https://apps.ingenuity.com/isa/account/forgotpassword** or contact Customer Support at **http://www.ingenuity.com/customer-support** or +1 (650) 381-5111.

*Company or institute email address

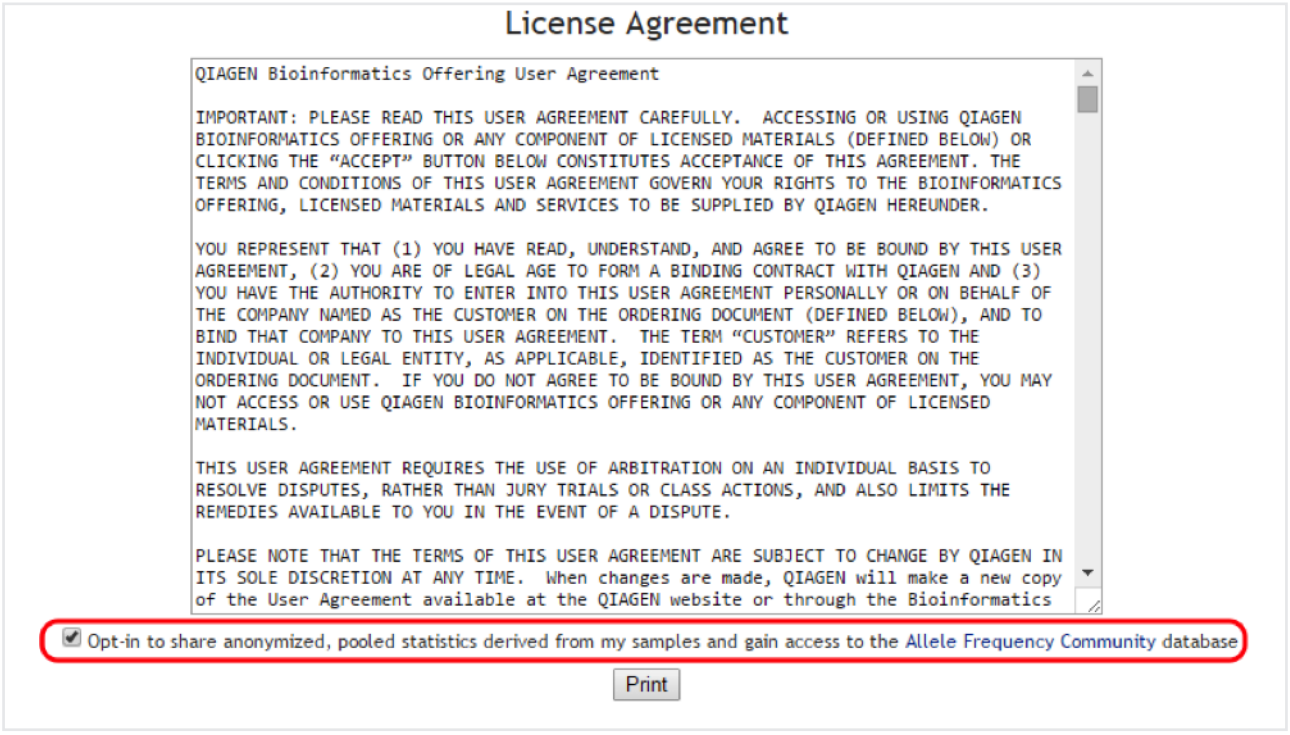
Uploading data files to Variant Analysis

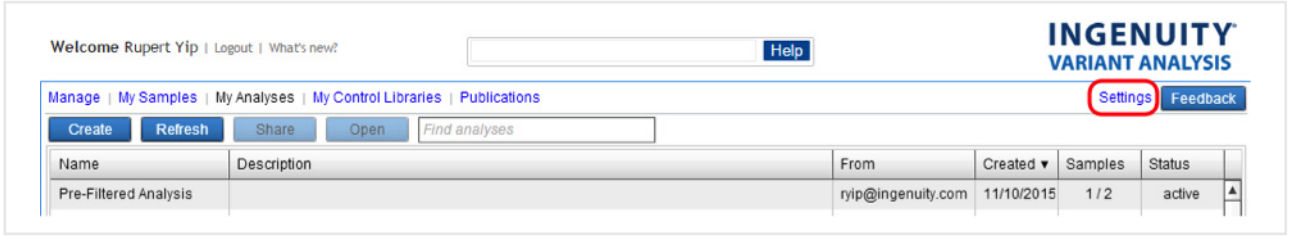
Variant Analysis is a web-based application delivered via the Ingenuity secure private cloud environment. User data to be analyzed must be uploaded by clicking "My Samples" in the top navigation bar.

Variant Analysis supports called variant files from human whole genome, whole exome, or targeted gene panel files that are in one of the following formats:

- Variant Call Format (VCF)
- Genome Variation Format (GVF)
- Complete Genomics files (Var, MasterVar, High confidence junction, etc.).

More information about file format requirements and uploading data can be found in Variant Analysis Help under "Upload your sample". Samples can be annotated in Variant Analysis with pedigrees, clinical features, and sample pairings, with an individual subject ID. To learn how, see "Annotating your samples" in Help.





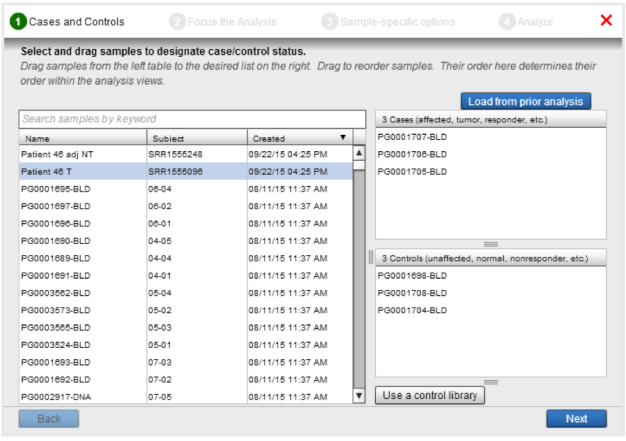
Creating an analysis

Start by selecting the samples to analyze together. Variant Analysis will merge the variants into a single analysis and annotate all variants using available content from the Ingenuity Knowledge Base.

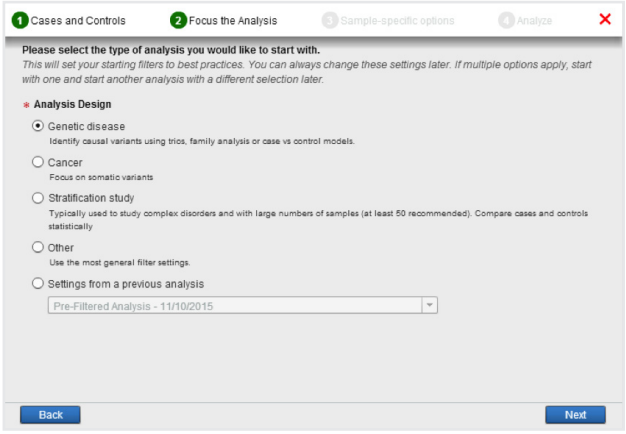
1. Click the "My Sample" tab in the top navigation bar, and then select the sample(s) you wish to include in your analysis.

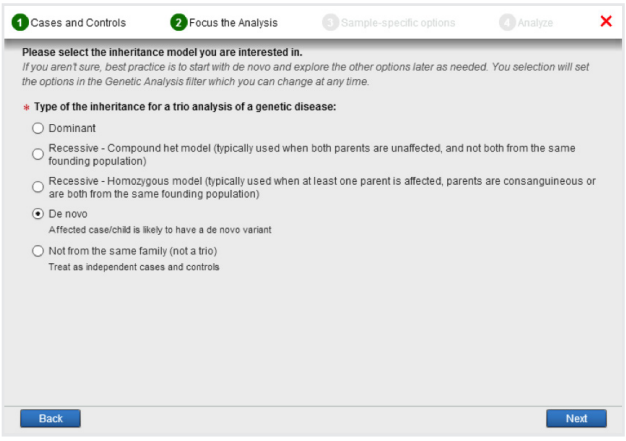
2. Click the Analyze button to begin the Analysis build wizard 

3. Confirm your case and control samples are properly grouped otherwise you can click and drag samples from one window to the other. When you are satisfied with your analysis design, click the Next button on the lower right to proceed.

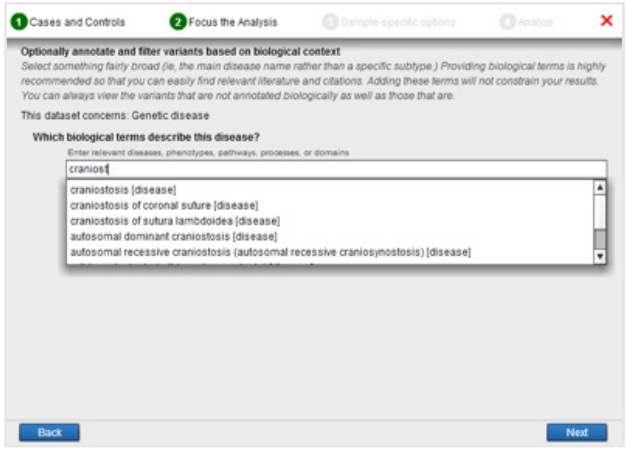


4. Select your desired Analysis Design. Note that you can always alter your analysis settings even after the analysis has completed. Click Next in the bottom right to proceed.

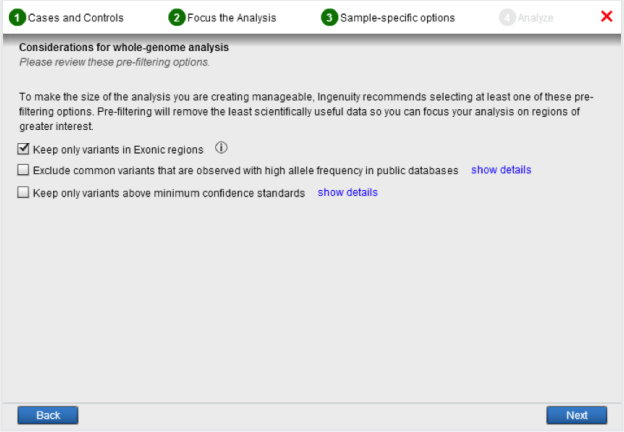




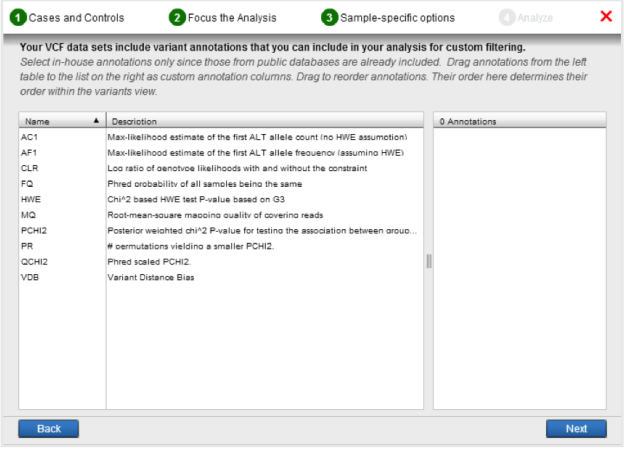
5. If your analysis consists of a trio of samples the Wizard will assume you would like to perform a trio analysis and will offer mode of inheritance analysis options. If your analysis is not a trio, the wizard will proceed straight to the Biological Context window where you can optionally specify any relevant biological term(s) to help narrow down the list of variants likely contributing to disease or phenotype. Variant Analysis will use this information to automatically focus initial results to a short list of relevant variants. The terms used in the analysis can be changed at any time.



6. This next Wizard window will only appear if you are analyzing genomes. You may choose to analyze only the exonic regions or entire regions of you genome(s). Note that due to compute resource requirements, Variant Analysis has a default upper limit of 299 genomes that are allowed full genome analysis. To perform full genome analysis of greater than 299 genomes, please contact Customer Support.

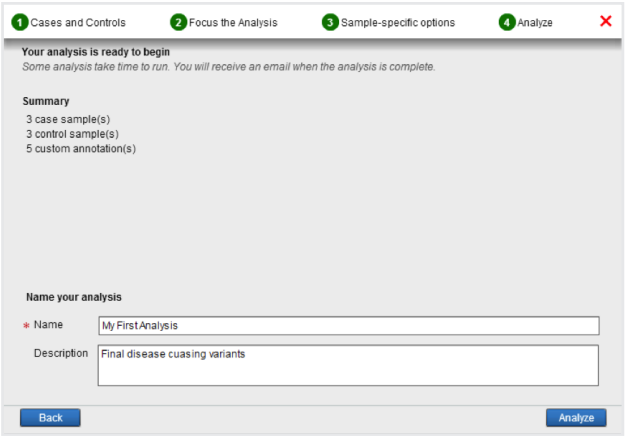


7. If your VCF file contains annotations, you can optionally click and drag up to 5 annotations to be part of your analysis.

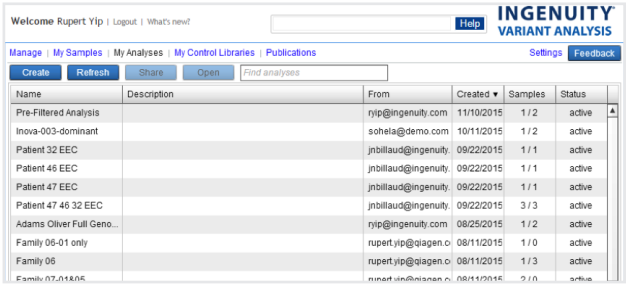


8. Finally, provide a name for your analysis and optionally a description. Click Analyze to begin your analysis.

For more details, see "Creating an Analysis in Variant Analysis" in Help.

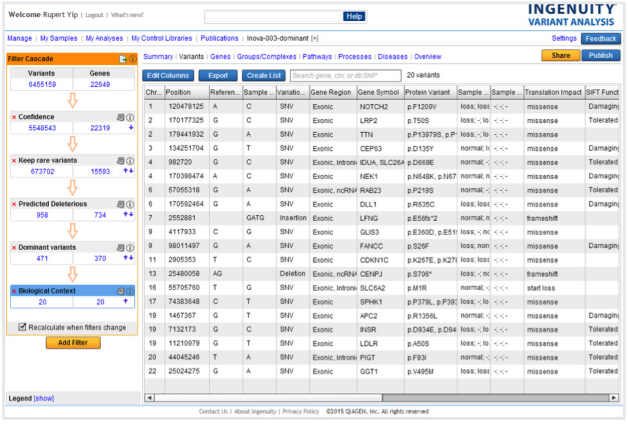


Explore analysis and review results



Variant Analysis uses the QIAGEN Knowledge Base to link variants in an analyzed dataset to biologically relevant information. Easy to use filters enable rapid identification of variants likely to be causal in the analyzed experiment.

1. Open the analysis under the "My Analyses" tab. The resulting analysis screen displays a series of customizable filters called the "Filter Cascade" and a table of annotated data on the right. Each filter displays 2 numbers. The number to the left indicates the number of variants that remain in the dataset after applying the respective filter and all filters above it. The number to the right indicates the number of distinct genes within which those variants are observed in the analysis.



Variant Analysis Filter Type	Function
Biological Context	Identifies variants with compelling links to disease progression or drug response by specifying relevant biological or clinical terms, including diseases, symptoms, genes, domains, processes, and pathways.
Genetic Analysis	Identifies variants consistent with a particular heritance pattern, or represented in a certain percentage of case or control individuals in a study.
Common Variants	Keep or exclude variants using allele frequencies in healthy control populations' data.
Predicted Deleterious	Quickly identifies variants in the analyzed dataset with predicted or observed evidence suggesting that they disrupted gene function or expression or are known to be involved in disease.
Cancer Driver	Finds variants within an analyzed dataset with predicted or established association to tumorigenesis or metastasis.
Custom Annotation	Generates filters based on variant, region, or gene annotations imported into Ingenuity Variant Analysis.
Pharmacogenetics	Identifies variants inferred or observed to impact drug response, metabolism, or toxicity based on literature evidence.
Physical Location	Identifies variants on a particular chromosome or within a particular region of a chromosome.
Statistical Association	Excludes or includes variants based on a basic association test that compares allele frequencies between case and control samples.
Confidence Filter	Enables the user to filter out variants of potentially low quality.
User-defined Variants	Enables the user to save and reuse variant sets across analyses.

For more details, see sections corresponding to each filter type in Help.

2. To change the settings of each filter by clicking the "Edit" icon. The following table provides a description of the function performed by each filter type.

3. Remove a filter entirely by clicking "Delete".

4. Move a filter up or down in the Filter Cascade using the up and down arrows.

5. Add an additional filter by clicking "Add filter" under the filter cascade.

Sharing an Analysis

Datasets and analyses can be shared with colleagues and collaborators. Recipients that do not already have one, can set up a free, secure account when they receive the shared results.

1. Click the "My Analysis" tab in the top navigation bar

2. Select 1 or more analysis to share and click "Share"

3. In the resulting dialog box, enter the email address(es) of recipients and click "Share"

4. Recipients will receive an automated email informing them there are analysis results awaiting them in their Variant Analysis account. If the recipients don't have an existing Variant Analysis account, the system will automatically create an account and place the shared analysis therein.

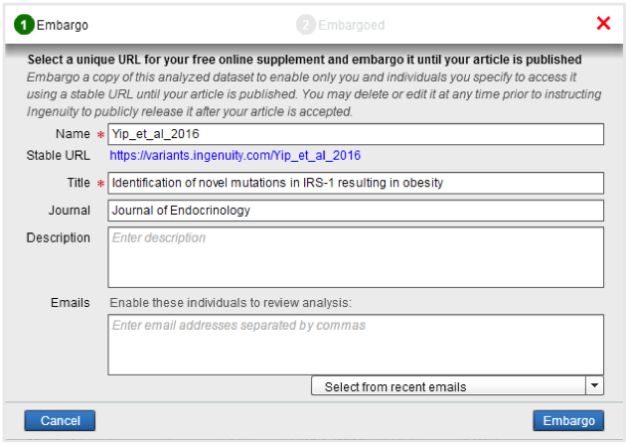
For more details, see "Sharing in Variant Analysis" in Help.

Publishing in Variant Analysis

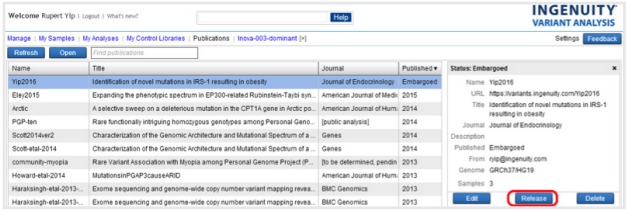
1. Click "Publish" in the upper right corner of the analysis to generate an online copy of the analysis to be included as a supplement for any journal article through a stable URL.

2. If the supplement is to be included in an accepted publication, update the supplement title, add the target journal, and click "Release" in the publication status box.

Releasing a dataset gives Ingenuity permission to make the data public and perpetually available via the URL.



The URL can be embargoed so that only specified individuals can access the analysis.



For more details, see "Publishing in Variant Analysis" in Help.

Inova Genomes

Inova is a not-for-profit healthcare system based in Northern Virginia that has sequenced over 7000 genomes that are well phenotyped, broadly consented, spanning several disease areas, and ethnically diverse. Variant Analysis users may purchase access to these samples. To learn more, or obtain a quote go to: **https://www.qiagenbioinformatics.com/products/inova-genomes/**.

Allele Frequency Community

You may participate in the research crowdsourcing initiative, the Allele Frequency Community (AFC) through Ingenuity Variant Analysis. The AFC is a collection of user-contributed, diverse human NGS samples used to generate summarized statistics. Allele frequencies from the anonymized, pool data provides critical context for sequence interpretation in the biomedical community. To learn more about the AFC and the founders go to: www.allelefrequencycommunity.org. To access and opt-in to the allele frequency community simply click the "opt-in" option upon first login or click the "Settings" link in the upper right of the Ingenuity Variant Analysis application to opt-in to the AFC.

FAQ

Variant Analysis Filter Type	Function
Are data secure in Variant Analysis?	Ingenuity Systems has passed a Health Insurance Portability and Accountability Act (HIPAA) audit, confirming that Ingenuity's data center and Ingenuity Variant Analysis are in compliance with relevant Federal Regulations of the US. Thus, Ingenuity securely serves clients such as clinical researchers, molecular pathologists and medical geneticists with strict controls for patient security. For more details, see the Ingenuity privacy policy at www.ingenuity.com/privacy-policy.
What file formats are supported for upload to Variant Analysis?	Variant Analysis currently supports Variant Call Format (VCF), Genome Variation Format (GVF), and Complete Genomics' files (Var, VarMaster, High confidence junction, etc.). For more details, see "Variant Analysis file format" in Help.
Can multiple samples be analyzed together?	Yes. Any number of cases and optional controls can be analyzed together
How can large datasets (i.e., more than 10 samples) be uploaded?	Large datasets can be securely uploaded via the High-volume uploader link, available within the upload window.
What species are accepted for analysis in Variant Analysis?	Variant Analysis accepts variants aligned and called relative to a human reference genome (Hg18, Hg19, and Hg20) . For more details, see "Creating an Analysis in Variant Analysis" in Help.
How many samples can be included in a single analysis?	There is no limit to the number of cases or controls that can be analyzed. To accommodate large studies, the graphical icons that indicate function, genotype, copy number, call quality, etc., will shrink to colored vertical lines that indicate loss, normal, or gain function. This way, quick comparison of frequency and impact of variants between case and control samples is still possible.
Can RNA-Seq data be integrated with DNA re-sequencing data?	Yes. Use the Custom Annotation Filter to create filters based on RNA-Seq data imported into Variant Analysis. For more details, see "Custom Annotation" in Help.
Can variant sets be saved for reuse across analyses?	Yes. Click "Create list" above the variant table, give the list a name, and click "Save". For more details, see "User Defined Variants" in Help.
Is it possible to define terminology for describing variants?	Terminology in Variant Analysis is aligned to current standards, including HGVS. For more details, see "Glossary for Variant Analysis" in Help.
Can analyses from Variant Analysis be shared?	Yes. Variant Analysis is licensed on a per-sample basis. One advantage of this cost structure is that sharing samples and analysis results with colleagues and collaborators in the same group is free of charge. For more details, see "Sharing in Variant Analysis" in Help.
Can the Ingenuity Variant Analysis software be cited in a scientific article?	Yes. For more details, see "Citing Ingenuity Variant Analysis" in Help.

For further support with technical difficulties please contact
Ingenuity Customer Support:
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www.ingenuity.com

Ingenuity Variant Analysis is intended for molecular biology applications. This product is not intended for the diagnosis, prevention, or treatment of a disease.

For up-to-date licensing information and product-specific disclaimers, see the respective Ingenuity product site. Further information can be requested from support-ingenuity@qiagen.com or by contacting your local account manager.

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