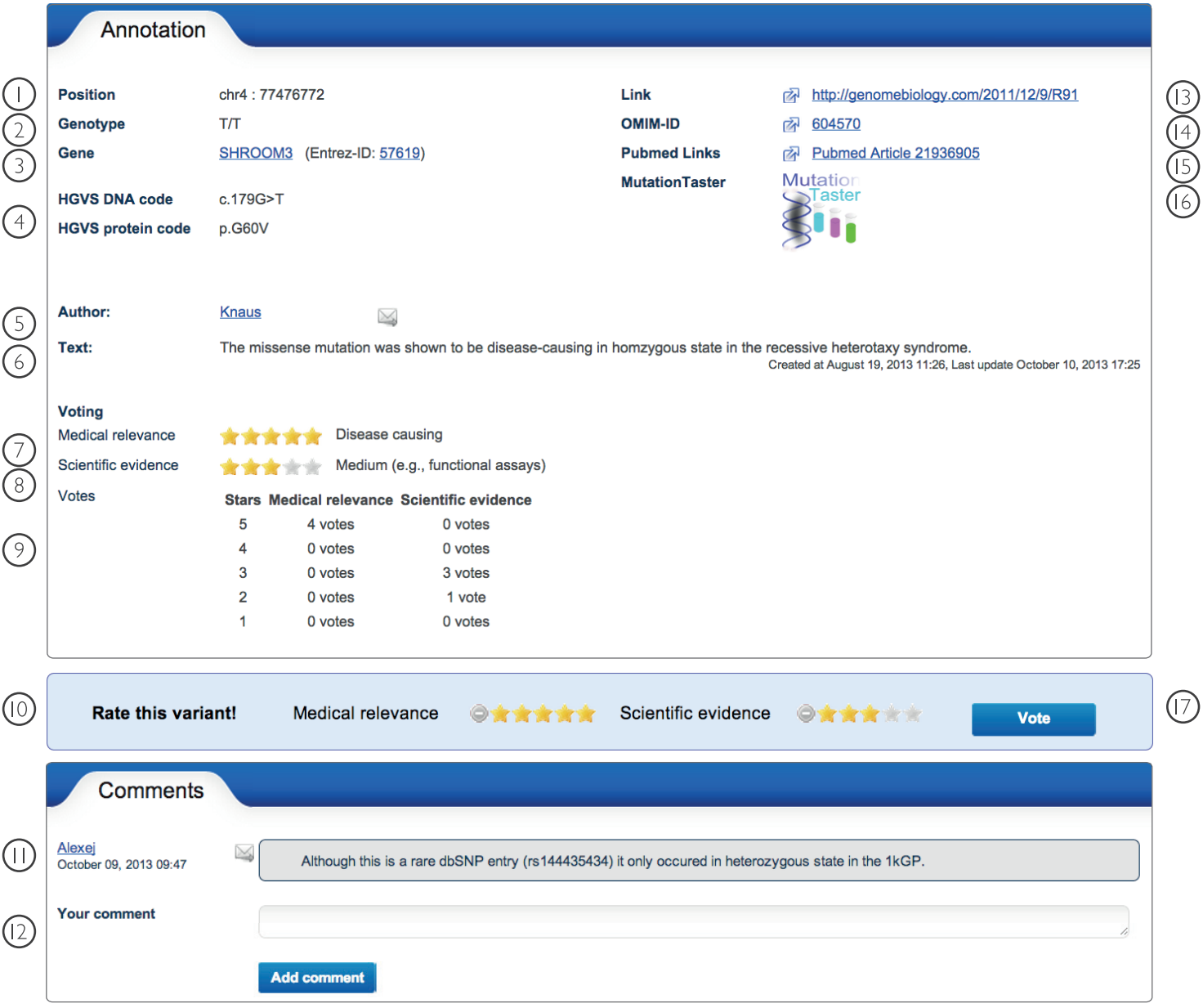
GeneTalk's Variant Specific Annotations

An Annotation in GeneTalk is user-generated content specific genomic position about, for example, a genetic disorder. Users can provide more details such as links to a scientific articles. Other users can rate annotations in the subjects *Medical Relevance* and *Scientific Evidence*. Users can comment annotations to provide additional information or start a discussion.



1 Genomic position
2 Genotype or allele
3 Gene name and Entrez ID
Click to open the gene info
4 HGVS codes for DNA and protein level
5 Author of annotation
6 Annotation Text
7 Majority vote for *Medical Relevance*
8 Majority vote for *Scientific Evidence*
9 Votes (score list)
10 Your votes
11 Comment from a user
Click the mail button to contact the user
12 Add your comment here
13 Link to external source or website
14 OMIM-ID
Click to open a link to http://omim.org
15 Link to publication in Pubmed
Click to open a link to www.ncbi.nlm.nih.gov
16 Link to MutationTaster
Click to evaluate disease-causing potential
17 Click the VOTE button to apply your vote

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How to Find Annotations

There are several ways to find annotations in GeneTalk.

① Open a VCF file in the VCF file viewer (Manage Files → List → 👁). An expert icon 👩‍🔬 , a patient icon 🤒 , or a star rating show that there are annotations for a variant. Just click the stars or the icons to open a list of annotations for this variant.

② Search for a gene (Search Genetalk → Genes) to find all annotations for a gene.

③ Search by genomic position(Search Genetalk → Annotations)

How to Add Annotations

In the VCF Viewer, just click the *Annotate* button to add an annotation. You can choose, whether your annotation is visible just for you, for a selected group of GeneTalk users, or publicly visible.

Votes for Annotations

The votes for *Medical Relevance* and *Scientific Evidence* range from one star (irrelevant/artifact and very low, respectively) to five stars (disease causing and very high, respectively). New annotations must have initial votes for both medical relevance and scientific evidence.

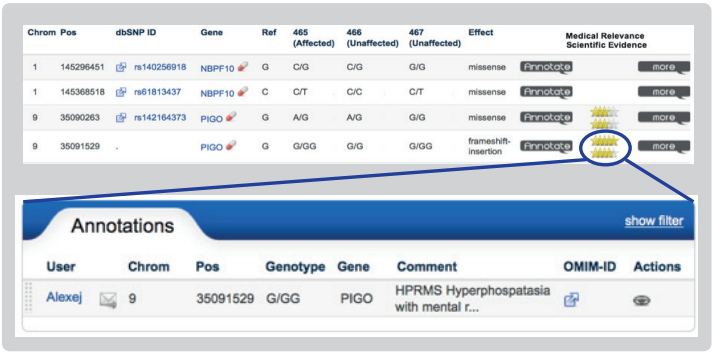
The total votes for an annotation in both subjects are fixed by the majority of the users' votes. Users can revise their vote. A majority vote changes as soon as a new majority of users is found.

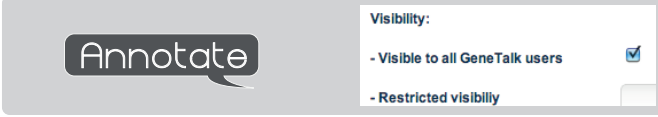
Genetalk's Knowledgebase

GeneTalk combined annotations from publicly available databases to set up its knowledgebase. For example, annotations from ClinVar defined as "disease causing" are initialized in GeneTalk's medical relevance ranking with 5 stars. Sequence variants that were encountered as common artifacts in the 1000 genomes project were classified as medically irrelevant. However, especially for the variants of unknown clinical signifiance, VUCS, we count on the wisdom of the crowd. In a wiki like approach we encourage the GeneTalk user community to contribute their own ranking so that the status of each VUCS will be as up to date as possible.

Filtering Variants Using Annotation Votes

You can set GeneTalk's *annotation filter* to any level of medical relevance and scientific evidence. If, for example, the filter is set to two stars in medical relevance, all sequencing artifacts and irrelevant variants will be removed. As a first approach in diagnostic filtering it might be reasonable to start with a five star rating for medical relevance and at least a two star rating for scientific evidence. Removing variants without annotations will result in a short list of variants with additional information in GeneTalk. This setting can be used to check if there are variants in a data set with known mutations. If a patient cannot be diagnosed using this setting, it is a more elaborated research question and other filtering parameters have to be chosen.



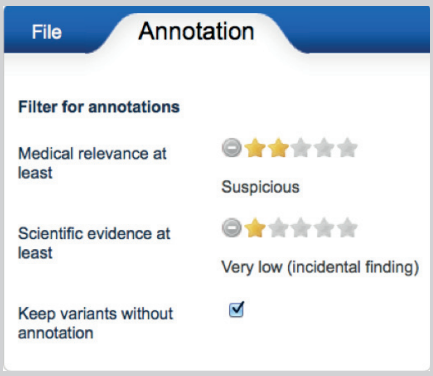


Medical Relevance

- ★☆☆☆☆ Irrelevant or artifact
- ★★☆☆☆ Suspicious
- ★★★☆☆ Disease associated
- ★★★★☆ Disease modifying
- ★★★★★ Disease causing

Scientific Evidence

- ★☆☆☆☆ Very low (e.g. incidental finding)
- ★★☆☆☆ Low (e.g. multiple cases)
- ★★★☆☆ Medium (e.g. functional assays)
- ★★★★☆ High (e.g. animal models)
- ★★★★★ Very high (e.g. therapy studies



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