12/15/2021

Annotation guidelines eMIND

This is the annotation guideline document for annotation of eMIND dataset for protein variation impacts related to protein level properties, in AD/ADRDs

- Biological Process
- Protein Activity/function
- Protein Interaction: includes complex formation
- Protein Aggregation
- Protein Abundance: abundance of a gene product or proteoform (e.g., increase levels of Abeta 42)
- Protein Modification: refers to post-translational modifications
- Protein Processing: common protein processing in AD/ADRDs includes TREM2 shedding, abeta processing (Abeta42/Abeta40) ratio, protein cleavage in general
- Protein Structure: amino acid changes affect the 3D structure of all or a protein region. Also to annotate impact on property of a region, motif, etc
- Protein localization: includes variants that impact cell localization, trafficking to compartment, level of secretion, or surface expression

Some background on specific proteins

Amyloid beta processing

For a review on Amyloid beta processing “Making the final cut: pathogenic amyloid-β peptide generation by γ-secretase” Source:doi: 10.15698/cst2018.11.162. Particularly, Figure 1.

APP is first cleaved by beta-secretase in its ectodomain close to the extracellular/luminal membrane border thereby generating a C-terminal APP fragment (C99). Consecutive cleavages of C99 by gamma-secretase releases the APP intracellular domain (AICD) into the cytosol and 37-43 amino acid amyloid beta (Abeta) species into the extracellular space or lumen of secretory pathway organelles. Longer Abeta forms, e.g., Abeta42, are highly aggregation prone. An alternative cleavage of APP by alpha-secretase in the Abeta domain prevents the formation of Abeta.

For annotation purposes:

- Levels of secretion of Abeta forms, although this reflects the processing we will annotate as impact on protein abundance (of proteoform) and indicate target proteoform in notes

- Ratio between proteoforms should be annotated to protein processing

TREM2 processing

Recent studies suggest that sTREM2 can be generated by either alternative splicing or proteolytic cleavage of the full-length TREM2 protein. The longest TREM2 transcript consists of five exons, with exon 4 encoding a transmembrane domain. This isoform is anchored to the cell membrane and shed by ADAM10 and/or ADAM17, leading to the production of a soluble TREM2 and a C-terminal fragment. This can be further cleaved by gamma-secretase to generate a TREM2 intracellular domain (ICD). The shortest TREM2 transcript encodes a soluble form of TREM2 due to the lack of exon 4 which encodes the transmembrane domain of the receptor. Source: https://doi.org/10.3389/fnagi.2019.00328

For annotation purposes:

- Shedding of TREM2 refers to cleavage, annotate as impact in processing
- Soluble TREM2 annotate as impact on localization

APOE Alleles (source:DOI: 10.5772/59809)

For annotation purposes we will treat APOE4 allele similar to a variant and annotate APOE4 as protein mutation but indicate in note “AD Allele”. The APOE alleles differ in their interaction with Abeta, and APOE4 has been associated with AD risk (source:DOI: 10.1007/s12264-013-1422-z)

Annotation task

Find sentences with variants and impact, and annotate relevant entities (see below) and the impact relation. In addition, indicate the disease context for these. We only care about AD/ADRDs.

Annotation tool: TeamTat (https://www.teamtat.org/)

Entities: gene, disease, mutation, impact, sentence

Name	Color	Sample
Gene	Pick Color	sample annotated text in a sentence
ProteinMutation	Pick Color	sample annotated text in a sentence
Disease	Pick Color	sample annotated text in a sentence
DNAMutation	Pick Color	sample annotated text in a sentence
impact_protein_abundance	Pick Color	sample annotated text in a sentence
impact_protein_aggregation	Pick Color	sample annotated text in a sentence
impact_protein_function_activity	Pick Color	sample annotated text in a sentence
impact_protein_interaction	Pick Color	sample annotated text in a sentence
impact_protein_localization	Pick Color	sample annotated text in a sentence
impact_protein_process	Pick Color	sample annotated text in a sentence
impact_protein_ptm	Pick Color	sample annotated text in a sentence
impact_Protein_processing	Pick Color	sample annotated text in a sentence
impact_protein_structure	Pick Color	sample annotated text in a sentence
sentence	Pick Color	sample annotated text in a sentence
impact_other	Pick Color	sample annotated text in a sentence

Relation:
Has_impact to relate the mutation and its impact(s).

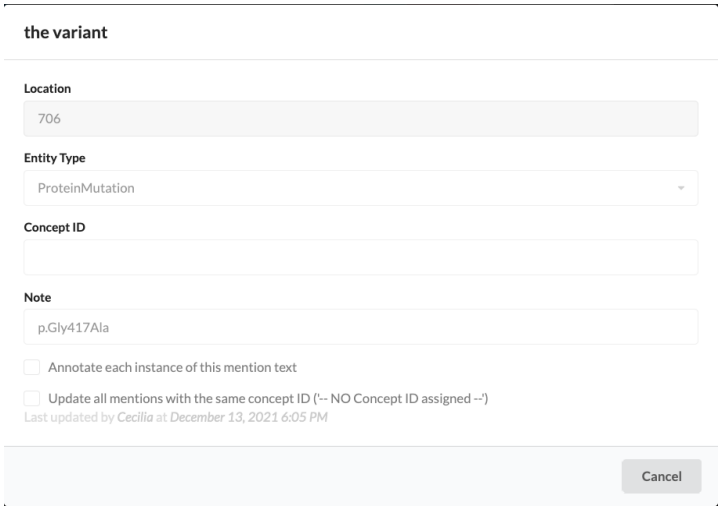
Annotation guidelines

Assign abstract as curatable if it has some relation and it is in the context of AD/ADRDs, otherwise select uncuratable.

1-Only annotate abstracts

Entity annotations:
Abstracts are pre-tagged by Pubtator. You don't need to correct all these. Only need to correct the ones that are relevant to the annotation task. For example, if gene or disease are not captured correctly for the relation to be annotated, then this needs to be corrected (for example, if A beta 1 has been assigned to a gene that is not APP, and the right selection should have been A beta 1-42(43) instead)

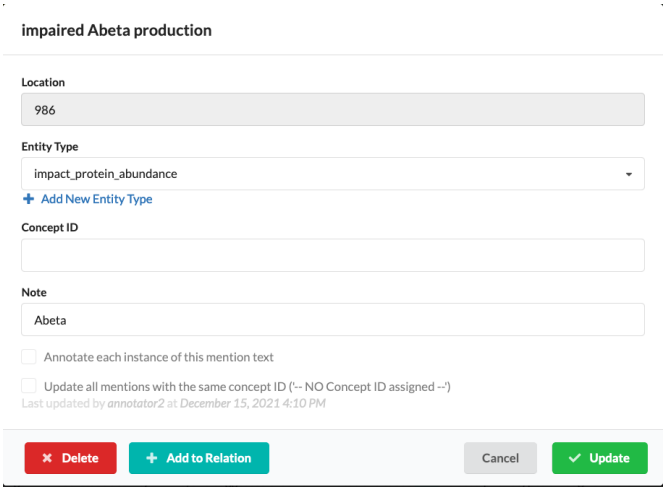
2-Highlight the mutation mention phrase (e.g., like "this mutation", "the variant") and add in the Note section the specific mutation following the HVGS nomenclature.



3-If the impact is on a different protein (so-called "target_protein"), then add also info in the Note section of the impact type with name of the target_protein

> *"These results support our previous conclusions that the L435F and C410Y mutations cause loss of Presenilin function and gamma-secretase activity, including impaired Abeta production in the brain"*

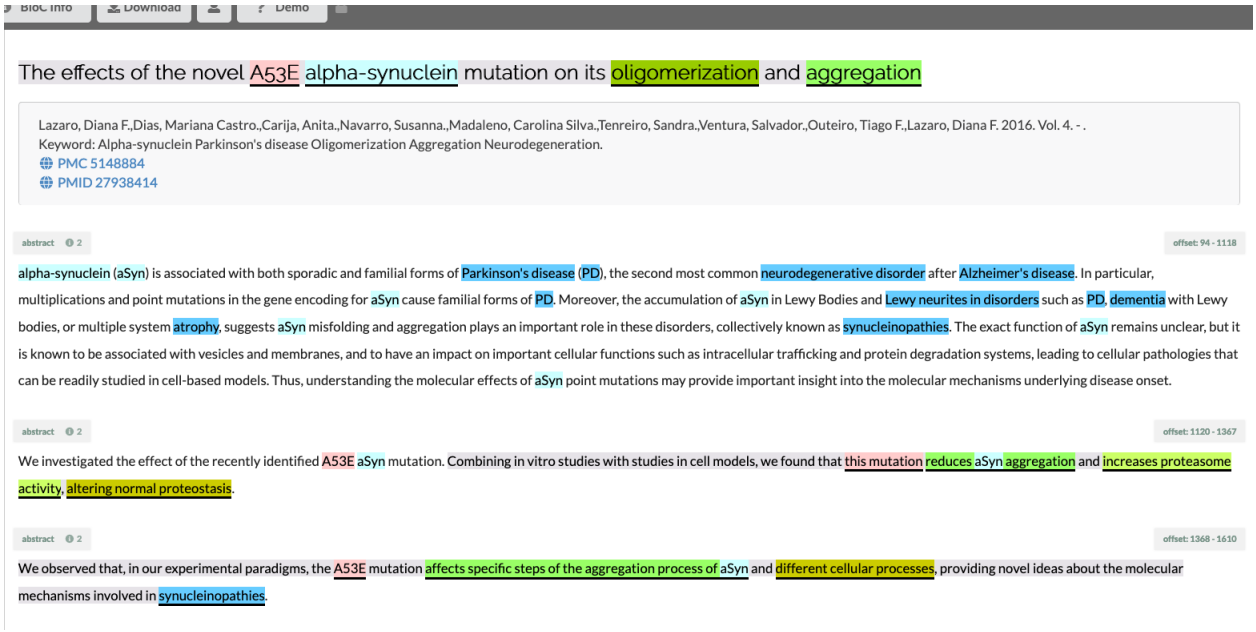
These are mutations in Presenilin 1, then the impact "impaired Abeta production" should have Note Abeta (or APP).

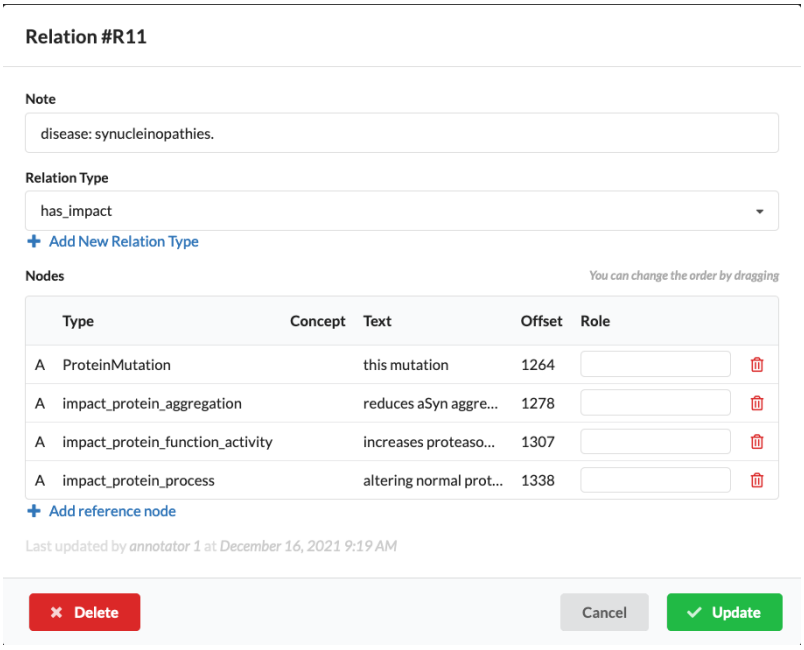


4-For disease, these must be within the scope of AD/ADRDs. If only one disease is mentioned in abstract and it is tagged by Pubtator, then no need to do anything. If one disease is mentioned but not tagged (or the tag is incorrect), then annotate it as disease. If more than one disease, and only one involves the variant, then add a note on variant of impact sentence:

> E.g., Variant X of gene Y affects structure and is associated with AD, while variant Z of gene Y affects function in Lewis body dementia.
> Annotate variant X with Note disease: AD and select impact on structure
> Annotate variant Z with Note disease: Lewis body dementia and select impact on function/activity

For example, there are 3 different diseases/disorders mentioned in the abstract below. In these cases all of them are under umbrella synucleinopathies. Since the abstract is pointing to the general disorder, when annotating the relation indicate in Note: disease:synucleinopathies





5-Select all relevant impact sentences at the end, and tag it as entity: sentence**.** Make sure you indicate as new annotation and do not erase any existing annotation (unless is intentional)

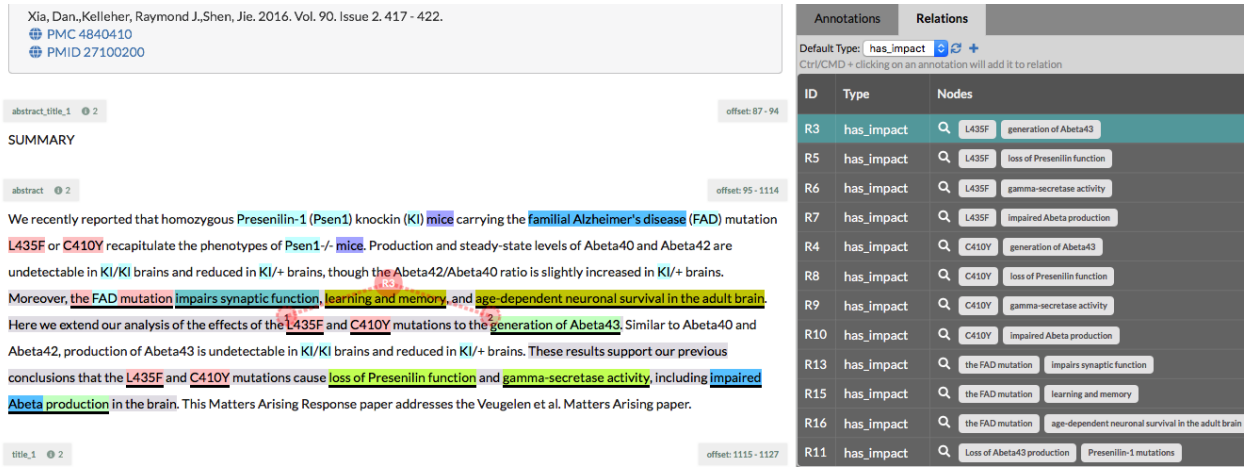
We investigated the effect of the recently identified A53E aSyn mutation. Combining in vitro studies with studies in cell models, we found that this mutation reduces aSyn aggregation and increases proteasome activity, altering normal proteostasis.

In gray is the sentence, where other annotated entities are highlighted in their respective colors.

6-Relation annotation

1). We are annotating has_impact relation between a mutation and an impact type

When more than one impact in the same sentence for a mutation, create separate relations for each of them.



2) Investigational sentences (those stating what authors intend to do, not the result of it): only need to annotate such sentences with entity type “sentence”, no need to annotate the relation(s) in them; Add note “investigation”

3) Negation sentences: We will still add the relation between the mutation and impact but need to add NOTE “negation”;

4) Unique relation: if multiple sentences provide the same relation annotations (in terms of uniqueness in the relation), then highlight all the impact sentences, annotate the unique relation out of only one sentence of them.