Genomenon Gene Disease Relationship Assessment Standards

Preliminary Considerations

This document outlines the methodology used to assess and classify the strength of the relationship between a gene and causing a disease. This assessment is limited to germline diseases and is primarily limited to monogenic diseases.

Our assessment standards are based on a compilation of published criteria, including those published by ClinGen.

Discrepant classifications

Classifications may differ between experts. Discrepancies in classifications may be related to the information identified, how the information is reviewed or weighted, and/or the scoring of the different lines of information.

The classification is based on the currently available evidence. New evidence or changes to how classification criteria are applied may result in a different classification. **If you have questions about a classification, you are welcome to contact us.**

Approach

Genomenon's approach to identifying diseases/conditions for assessment involves reviewing existing databases for known or suggested gene disease relationships and utilizing our genomic language processing capabilities within Mastermind to identify potentially novel relationships for assessment.

Criteria

Our assessment involves identifying and analyzing different types of data from numerous sources in order to establish an accurate classification of the gene disease relationship.

External review

- External database that list and/or assess gene disease relationships are reviewed (e.g OMIM and ClinGen)
- This review is primarily to ensure that all relevant diseases are identified for assessment

Mouse model evidence

- Information from Mouse Genome Informatics is reviewed to determine if there is a mouse models that recapitulated the human phenotype
- Up to ~15% of the maximum score can be applied based on the mouse model evidence

Case evidence

- Peer reviewed publications are reviewed for affected patients with rare variants
- Additional weight is given when there are multiple unrelated affected patients, segregation with disease, and additional studies with separate case cohorts
- Caution is noted for variants that are present in gnomAD, for patients with multiple potentially causative variants, variants identified for which the zygosity does not match with the suggested inheritance pattern, and for variants found in both affected and healthy control individuals
- Up to ~50% of the maximum score can be applied based on the case level evidence

Functional data

- Peer reviewed publications are reviewed for functional evidence
- In vitro and in vivo studies are considered for variants that show a significantly different functional effect as compared to wild type
- Caution is noted for functional studies that may not be representative of the mechanism of disease
- Up to ~35% of the maximum score can be applied based on the functional level evidence

Scoring

- The score is combined for each of the evidence type
- The total score will be converted to a classification to determine the relationship to disease
    - The primary classifications include: Definitive, Strong, Moderate, Limited, and No known association
    - The additional classifications of Disputed and Refuted are used for situations where there is contradictory evidence in one or more publications
- Other factors may impact the final classification (e.g. diseases that may have significant non-genetic components or diseases for which there is only one publication with affected patients)
- For diseases classified as Definitive, the inheritance pattern is provided

References

DiStefano, MT, *et al.* The Gene Curation Coalition: A global effort to harmonize gene-disease evidence resources. Genet Med. 2022 Aug;24(8):1732–1742. (PMID: 35507016).

Strande, NT, *et al.* Evaluating the Clinical Validity of Gene-Disease Associations: An Evidence-Based Framework Developed by the Clinical Genome Resource. Am J Hum Genet. 2017 Jun 1;100(6):895–906. (PMID: 28552198).