Illumina Clinical Services Laboratory Assertion Criteria for Gene Curation

Summary

Gene curation is defined as the evaluation and classification of the strength of association between a gene and disease based on publicly available evidence. The final classification is based on a set of guidelines outlining the type and strength of the evidence required for each classification. The curation is based on the evidence available at the time and is revisited as more evidence emerges. If applicable, professional judgement and expertise are utilized in determining the evidential strength and the final classification.

Overview of the Curation Protocol

Gene curation is performed for all genes in which candidate variants have been identified in the case management part of the workflow for analysis of whole genome sequencing. Gene curation steps are performed for all diseases / phenotypes associated with a gene that are relevant to the phenotype of the case under investigation. Curation is also performed for genes from a prioritised list of genes of interest.

Information is gathered from each of the following sources listed below: GeneReviews, Genetics Home Reference, OMIM, Orphanet, HGMD, HGNC, ClinVar, UniProt, NCBI Gene, PubMed, PubMed Central, Google Scholar and Google. All information is recorded in a word document template

The information required to evaluate the strength of any potential gene: disease associations includes:

1. The number of studies describing the association.
2. The number of pathogenic variants reported in probands with the disease under curation.
3. Frequency of possible pathogenic variants in the general population – this should be consistent with disease prevalence, penetrance and inheritance.
4. Evidence of segregation of pathogenic variants with disease in multiple multigeneration families.
5. Functional data supporting the role of the gene in the disease - the amount of data required depends on the strength and type of evidence.
6. Evidence from animal models supporting the disease association by recapitulation of the human phenotype in the model organism.
7. Information, where available, on the mechanism of disease.

The strength of the gene: disease association is classified according to the guidelines outlined in Table 1.

Once the information has been gathered and a provisional classification reached for the gene: disease association, the curation is reviewed at a group meeting or by a senior reviewer to reach consensus on the final classification.

Once reviewed, the information gathered in the curation is summarized in an evidence summary that include both clinical and functional evidence including:

1. The number of variants seen in the gene associated with the disease.
2. The consequence of the variants found in the literature / HGMD / ClinVar etc.
3. The pathogenicity of the variants associated with the disease.
4. The number of patients in whom variants were found.
5. The number of studies describing the gene: disease association.
6. The results of functional studies and their relevance to the mechanism of disease.
7. Candidate genes based on data from animal models.
8. Insight into the disease mechanism.
9. Final classification of the gene: disease association.

Table 1

Classification	**Score**	**Evidence**
Definite association	5	• Well-established association
Strong association	4	• Association demonstrated in multiple studies (at least two preferably three or more depending on the strength of the study) with multiple pathogenic variants in unrelated probands • Frequency of possible pathogenic variants in the general population should be consistent with phenotype frequency, inheritance pattern and disease penetrance • Established inheritance pattern and demonstration of segregation of a pathogenic variant in the gene with the specific disease • Strong functional experimental data supporting a role for the gene in the specific disease (number required depends on strength and type of data, could include animal models) • Mechanism of disease established • No valid evidence that the gene is not involved in the specific disease
Likely association	3	• Pathogenic variants reported in the gene in at least three unrelated probands with the disease • Preferably two studies. If only one study, study must be strong • Plausible / theoretical disease mechanism suggested • Some supporting functional experimental data • No valid evidence that the gene is not involved in the specific disease
Weak/possible association	2	• Limited evidence i.e. a single study (possibly a case study) or fewer than three reported pathogenic variants OR multiple potentially pathogenic variants reported in unrelated probands where evidence for pathogenicity of the variants is weak

		• Candidate gene based on evidence from animal model which mimics the human phenotype / pathway analysis with variants reported in human disease
No association	1	• No previously reported association with a phenotype • Candidate gene based on evidence from animal model which mimics the human phenotype / pathway analysis but with no pathogenic variants reported in human disease • Novel gene, variants come through based on inheritance. Gene function suggests a plausible role in the disease.
Disputed association	1	• Equally valid evidence for and against an association • Weak disputed evidence from high profile publications • Non-replicated study
Negative association	1	• Evidence has been reported refuting the involvement of the gene with a specific disease which is stronger than evidence supporting a role
Association with phenotype of biochemical trait	1	

Useful sources

Literature searches:
PubMed: https://www.ncbi.nlm.nih.gov/pubmed
PubMed Central (PMC): https://www.ncbi.nlm.nih.gov/pmc
Google Scholar: https://scholar.google.com/
Google: https://www.google.com/

Gene and disease information:
ClinVar: https://www.ncbi.nlm.nih.gov/clinvar/
Genetics Home Reference: https://ghr.nlm.nih.gov/
GeneReviews: https://www.ncbi.nlm.nih.gov/books/NBK1116/
HGMD: http://www.hgmd.cf.ac.uk/ac/index.php
HGNC: http://www.genenames.org/
NCBI Gene: http://www.ncbi.nlm.nih.gov/gene
Online Mendelian Inheritance in Man (OMIM): https://www.ncbi.nlm.nih.gov/omim
Orphanet: http://www.orpha.net/consor/cgi-bin/index.php?lng=EN
Uniprot: https://uniprot.org