ClinGen Low Penetrance/Risk Allele Working Group Recommended Terminology – Version 1.0
Working Group Page: https://clinicalgenome.org/working-groups/low-penetrance-risk-allele-working-group/
Date Approved: February 18, 2020

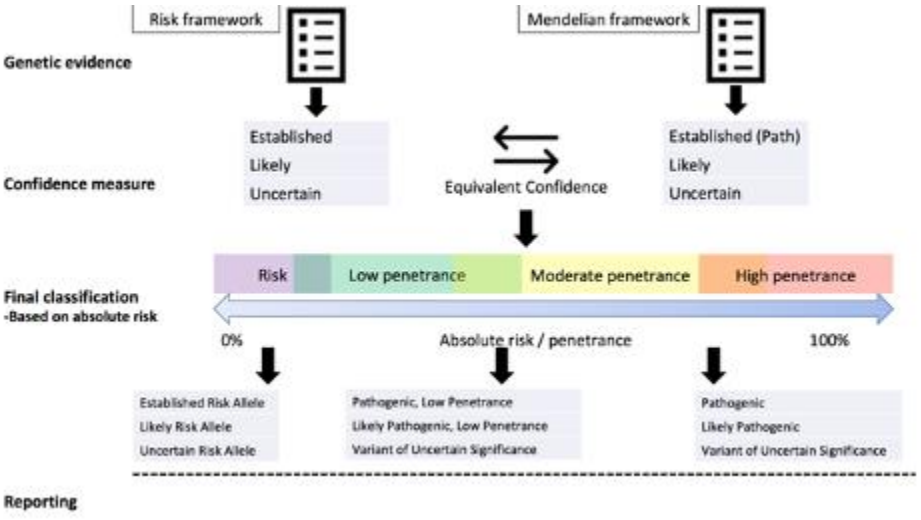
Recommended terminology when describing variants with decreased penetrance for Mendelian conditions

A proposal by the ClinGen Low Penetrance/Risk Allele Working Group

The Low-Penetrance/Risk Allele Working Group aims to develop a consensus on the terminology needed to categorize both risk alleles and low-penetrance Mendelian variants and to develop a standardized classification framework to evaluate these variants. Our work applies to clinically significant genetic variants regardless of population frequency or variant type (SNV/indel, CNV, etc.), but excludes variants that are significant only in the context of a polygenic risk score. Although the concept of "risk alleles" as common, complex entities with "low relative risk and.. meager... predictive power" is referenced in the current ACMG/AMP sequence variant interpretation guidelines (Richards et al. 2015), there is currently no widely-accepted framework for the classification of these types of variants or the terminology with which to describe them.

To address these gaps, we aimed to devise a terminology scheme that would avoid the assignment of different terminology based on the assessment framework used, thus avoiding the problem of multiple classification types for the same variant. As the number of large-scale sequencing efforts accumulates, genetic evidence for disease-associated rare variants will increasingly come from association studies of unrelated individuals rather than segregation analysis. Toward that end, we developed a unifying terminology scheme that is independent of the framework used to determine the clinical significance of a variant (see figure below).

The figure outlines a forward-looking scenario, and some quantitative elements may be challenging to implement in practice based on currently available evidence regarding the penetrance associated with a given variant. Therefore, in this document, we provide recommendations for terminology for variants in the lower penetrance spectrum that combines this model with current practice. These recommendations were arrived at through polling the broader ClinGen community and internal discussions and polling within the working group itself.



Methods

To arrive at this recommended terminology, the ClinGen Low-Penetrance/Risk Allele Working Group (https://clinicalgenome.org/working-groups/low-penetrance-risk-allele-working-group/) conducted multiple internal Likert surveys, an external community-wide Likert survey, and multiple discussions on working group calls. Numerous terms were considered during the surveys and subsequently reduced using a modified Delphi approach. The following are the major conclusions based on the results of these surveys:

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We advocate that information regarding disease penetrance be included on clinical genetic reports when available. If accurate absolute risk information is available, it should be stated.

This may be provided as aggregate gene-level penetrance or penetrance for individual variants if there is specific evidence for the reported variant. When penetrance information is limited or unavailable, or penetrance is being assumed based on gene-level information, this should be explicitly stated. In an ideal scenario, the report would include absolute risk estimates, though this is not generally feasible at this time.

Large, systematic studies in populations unbiased for their ascertainment, are needed to determine the disease penetrance associated with genetic variants to inform clinical care of patients at risk for genetic disorders.

Low/reduced-penetrance variants

We advocate using the quantitative descriptor "low penetrance" (i.e. "Pathogenic, low penetrance", etc.) in the primary variant classification terminology when sufficient quantitative penetrance estimates are available. However, when this information cannot be obtained, the terms "Pathogenic, reduced penetrance" and "Likely pathogenic, reduced penetrance" may be substituted.

We define a "low-penetrance" variant as a variant that may have evidence of segregating in a Mendelian pattern but for which the majority of carrier individuals do not develop features of the disease. Individuals carrying these variants manifest disease at a higher rate than the background prevalence for the associated condition, such that the presence of a "low-penetrance" variant alone is clinically significant. Common examples of this include the *CHEK2* 1100delC variant associated with breast cancer, *PKP2*-associated arrhythmogenic right ventricular cardiomyopathy, and neurodevelopmental disorders associated with 16p11.2 deletions and duplications, though the definition of risk allele has not been formally established.

We advocate for the use of classification categories with quantitative descriptors of post-test risk (i.e. "Pathogenic, low penetrance", etc.) when evidence estimating disease penetrance is available and reliable. However, today this information is not always available and not possible to determine in some scenarios.

Alternatively, when robust quantitative estimates are not available, the term "Pathogenic, reduced penetrance" can be used to describe variants in this category. The term "reduced penetrance" is a context-dependent term applied to a variant relative to the highly penetrant variants most often seen in a specific disease; thus, it cannot be appropriately used for all scenarios. For example, if all variants are of equally low penetrance for a disease, then there is no opportunity to describe the general lack of penetrance in the primary classification using "reduced penetrance". Additionally, the term "reduced penetrance" is not consistently associated with any specific level of disease risk, and the level of risk associated with the use of the term "reduced penetrance" frequently varies between different genes and variants.

Risk alleles

We advocate using the term "risk allele" for sites associated with a very small increased risk of disease. Further, we advocate for using the qualifying terms – "Established risk allele", "Likely risk allele", and "Uncertain risk allele" – corresponding to three classification tiers initially suggested by the ACMG/AMP Mendelian sequence variant classification guidelines.

The term "risk allele" refers to variant(s) with very low penetrance such that their effects are incomplete and do not manifest in a Mendelian pattern of inheritance. A "risk allele" that is associated with disease is not necessarily comprised of the causative genetic variant(s) as it may be genetically linked to another variant that directly contributes to disease, or may exist be part of a set of variants where the major contributing variant to disease risk cannot be separated from the other variants. Additionally, the risk allele may be environmentally-dependent. Examples of risk alleles that have been traditionally considered in this category include the *FV* Leiden and *APOE* e4 alleles, though the definition of risk allele has not been formally established.

The term "risk allele" is currently used and has an established role in clinical genetics and laboratory genetics practice. Risk alleles have additional complexities not commonly seen in traditional Mendelian genetics. For instance, the risk allele may be comprised of multiple variants in *cis*; the risk may be modified due to zygosity; the risk may be modified due to variants in *trans*; and the variant may not confer actual functional risk, but is genetically linked to the causative variant. Although these variants may have a complex nature, especially when the risk being conferred is due to variants in *trans* or homozygous variants, the term risk allele can capture these complexities better than other terms considered.

We suggest using a parallel approach with classification terminology for a "protective allele" that is associated with a reduction rather than an increase in disease risk.