Fitting a naturally scaled point system to the ACMG/AMP variant classification guidelines

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Abstract

Recently, we demonstrated that the qualitative American College of Medical Genetics and Genomics/ Association for Medical Pathology (ACMG/AMP) guidelines for evaluation of Mendelian disease gene variants are fundamentally compatible with a quantitative Bayesian formulation. Here, we show that the underlying ACMG/AMP "strength of evidence categories" can be abstracted into a point system. These points are proportional to Log(odds), are additive, and produce a system that recapitulates the Bayesian formulation of the ACMG/AMP guidelines. Strengths of this system are its simplicity and that the connection between point values and odds of pathogenicity allows empirical calibration of strength of evidence for individual data types. Weaknesses include that a narrow range of prior probabilities is locked in, and that the Bayesian nature of the system is inapparent. We conclude that a points-based system has useful attributes of user friendliness and can be useful so long as the underlying Bayesian principles are acknowledged.

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Figure 1