
SVI Recommendation for Absence/Rarity (PM2) - Version 1.0

The ClinGen Sequence Variant Interpretation (SVI) Working Group proposes decreasing the weight of criterion PM2 ("Absent from controls, or at extremely low frequency if recessive, in Exome Sequencing Project, 1000Genomes Project, or Exome Aggregation Consortium") from a Moderate strength level to a Supporting strength level (PM2_Supporting).

After substantial analysis and modeling, the SVI WG proposes this weight adjustment due to concerns that absence or rarity is given too much weight in the 2015 framework and that this type of evidence does not meet the relative odds of pathogenicity for a Moderate pathogenic evidence, estimated to be 4.33:1 (PMID:29300386). This concern is supported by findings from the Exome Aggregation Consortium (ExAC) database that 99% of identified high-quality variants have a frequency <1%, that 54% of identified high-quality ExAC variants are only seen once in the entire data set, suggesting that rarity is actually common, and that all individuals harbor variants that are absent from the rest of the population (PMID: 27535533).

By decreasing the weight of this criterion, this change will potentially impact variant classifications. Therefore the SVI proposes a novel criteria combination not listed in the combining rules outlined in the 2015 ACMG/AMP guideline. We propose that the combination of one Very Strong criterion and one Supporting criterion reach a classification of Likely pathogenic. This combination rule is supported by the Bayesian framework which shows that one Very Strong Pathogenic criterion and one Supporting Pathogenic criterion results in Post_P of 0.988, which falls within the Likely pathogenic range (0.90-0.99). This combining rule will allow novel LoF variants, that reach PVS1 and PM2 reduced to supporting, to still be classified as Likely pathogenic. We anticipate that other adjustments in the relative weight of evidence will be necessary in the future to accommodate this change in PM2 weight.