A179 · Calibrated Computational and Functional Evidence for At-Scale Clinical Classification of In-Frame Indels

Presenter: Haneen Abderrazzaq — Northeastern University

Authors: Haneen Abderrazzaq, Mugdha Singh, Ross Stewart, Larry Babb, Malvika Tejura, Abbye E. McEwen, Timothy Bergquist, Silvia Casadei, Matthew W. Snyder, Nahum Smith, Alan F. Rubin, Steven E. Brenner, Douglas M. Fowler, Lea M. Starita, Vikas Pejaver, Anne O'Donnell-Luria, Predrag Radivojac

Session: Day 2 · Fri Oct 2, 2026 · 2:15–4:15 PM

Insertions and deletions (indels) represent a substantial source of human genetic variation, yet remain less well characterized than missense variants, posing a persistent challenge for variant classification. Relatedly, computational predictors for in-frame indels have yet to be rigorously evaluated and calibrated for clinical use, limiting their adoption in clinical variant interpretation workflows. Here, we present a calibration framework, extending a previous approach for missense predictors, for eight in-frame indel prediction tools, including MutPred-Indel, VEST-indel, and CADD, enabling their integration into ACMG/AMP-based clinical classification. We first estimated the prior probability of pathogenicity for rare in-frame indels in disease-associated genes, finding distinct priors for insertions and deletions. Applying a likelihood ratio framework based on local posterior probabilities, we established score thresholds for each tool corresponding to distinct pathogenic and benign evidence strengths. All tools achieved multiple calibrated evidence strengths, demonstrating that existing indel predictors carry measurable clinical utility. Combining these calibrated computational thresholds with functional data we have separately generated and calibrated, we assigned quantitative evidence to ClinVar variants of uncertain significance (VUS), enabling reclassification of indels to a likely pathogenic/pathogenic or likely benign/benign status. Across ten genes, we resolved up to 55% of the existing ClinVar VUS and further preclassified up to 5,500 in-frame indels not yet reported in ClinVar, providing a precomputed resource for future variant classification. Our results demonstrate that the combination of calibrated computational and functional evidence can substantially reduce the VUS burden of in-frame indels and ultimately improve clinical variant classification and decision-making.

Calibrated Computational and Functional Evidence for At-Scale Clinical Classification of In-Frame Indels

Haneen Abderrazzaq[1]*, Mugdha Singh[2,3], Ross Stewart[1], Larry Babb[2], Malvika Tejura[4], Abbye E. McEwen[4,5,6], Timothy Bergquist[7], Silvia Casadei[5], Matthew W. Snyder[5], Nahum Smith[5], Alan F. Rubin[8], Steven E. Brenner[9], Douglas M. Fowler[4,5], Lea M. Starita[4,5], Vikas Pejaver[7,10], Anne O'Donnell-Luria[2,3], Predrag Radivojac[1]

[1]Khoury College of Computer Sciences, Northeastern University, Boston, MA, USA; [2]Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA; [3]Division of Genetics and Genomics, Boston Children's Hospital, Harvard Medical School, Boston, MA, USA; [4]Department of Genome Sciences, School of Medicine, University of Washington, Seattle, WA, USA; [5]Brotman Baty Institute for Precision Medicine, University of Washington, Seattle, WA, USA; [6]Department of Laboratory Medicine and Pathology, School of Medicine, University of Washington, Seattle, WA, USA; [7]Institute for Genomic Health, Icahn School of Medicine at Mount Sinai, New York, NY, USA; [8]Collaborative Centre for Genomic Cancer Medicine, University of Melbourne, Melbourne, VIC, Australia; [9]University of California, Berkeley, CA, USA; [10]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY, USA

In-frame (non-frameshifting) insertions and deletions (indels) constitute a substantial source of human genetic variation. Nevertheless, they remain less well characterized than missense variants and continue to pose a challenge for clinical variant classification. To address this challenge at scale, it is essential to develop accurate computational predictors and generate high-throughput functional data for evaluating the effects of these variants, and to subsequently calibrate both sources of evidence for clinical use. In this work, we present the results of two separate but related studies of in-frame indels related to their clinical use for rare disease diagnosis. First, we recognized that computational predictors for in-frame indels have yet to be rigorously calibrated for clinical use, which limits their adoption in clinical variant interpretation workflows. We addressed this problem by extending a previously proposed framework for the calibration of missense variant effect predictors,[1] and calibrating eight in-frame indel prediction tools (CADD, ESM1b, FATHMM-indel, INDELpred, MutPred-Indel, ProGen2, PROVEAN, VEST-indel), enabling their integration into ACMG/AMP-based clinical classification compatible with forthcoming SVCv4. We estimated the prior probability of pathogenicity for rare in-frame indels in disease-associated genes, and found distinct priors for insertions and deletions. Applying a likelihood ratio framework, we then established score thresholds for each tool corresponding to distinct pathogenic and benign evidence strengths. All evaluated tools achieved multiple calibrated evidence strengths, demonstrating that existing indel predictors carry measurable clinical utility. Second, we generated high-throughput functional data for ten disease-associated genes using Saturation Genome Editing and calibrated these data using ExCALIBR[2]. We then combined these two sources of evidence to assign quantitative scores to ClinVar variants of uncertain significance (VUS), enabling reclassification of in-frame indels to a likely pathogenic/pathogenic or likely benign/benign status.[3] Across the ten genes, we resolved up to 55% of the existing ClinVar VUS and further preclassified up to 5,500 in-frame indels not yet reported in ClinVar, providing a precomputed resource for future variant classification. Our results demonstrate that the combination of calibrated computational and functional evidence can substantially reduce the VUS burden of in-frame indels and ultimately improve clinical variant classification and decision-making.

References

1. V. Pejaver et al., Calibration of computational tools for missense variant pathogenicity classification and ClinGen recommendations for PP3/BP4 criteria, Am J Hum Genet 109, 2163 (2022).
2. D. Zeiberg et al., Gene-based calibration of high-throughput functional assays for clinical variant classification, bioRxiv 2025.04.29.651326 (2025).
3. M. Tejura et al., A scalable approach to resolving variants of uncertain significance, bioRxiv 2026.02.14.705848 (2026).