DeepADAR: A deep learning approach to model regulatory elements of ADAR-based RNA editing and its application to gRNA design

Andrew J. Jung[1,2,3*], **Alice J. Gao**[1,2,3], **Rachana Jayaraman**[3], **Lucy Chen**[3]
Martino M. Gabra[3], **Antonia C. Du Bois**[3], **Erle Holgersen**[3], **Kahlin Cheung-Ong**[3]
Eli Bogart[3], **Leo J. Lee**[1,2*], **Brendan J. Frey**[1,2,3*]

[1]University of Toronto, [2]Vector Institute, [3]Deep Genomics

Abstract

RNA editing is an important post-transcriptional modification which increases transcriptomic diversity and regulates other cellular processes. In humans, the predominant form of RNA editing is adenosine-to-inosine (A-to-I) conversion, mediated by adenosine deaminases acting on RNA (ADAR) enzymes. Recently, RNA therapeutics leveraging endogenous ADAR to induce site-specific editing have emerged as promising approaches for correcting disease causing mutations and modulating gene expression. However, the precise mechanisms by which cis-regulatory elements control ADAR editing are highly complex and remain largely unknown. With improvements in methods for ADAR editing detection and quantification, a data-driven approach utilizing large-scale RNA-seq data from the existing literature has emerged as a promising strategy for modeling and understanding the general regulatory elements of ADAR editing. Here, we present DeepADAR, a deep learning model that learns regulatory elements of ADAR editing by training on a large number of high-confidence ADAR editing sites supported by RNA-seq data. DeepADAR not only achieves strong performance on predicting editing sites in held-out test data, but also successfully distinguishes sites with varying editing efficiencies in CRISPR mutagenesis experiments and RNA-editing quantitative trait loci (QTLs). Furthermore, we demonstrate how the endogenous regulatory elements of ADAR editing learned by DeepADAR can be utilized to predict ADAR editing induced by guide RNAs (gRNAs) in a zero-shot setting. Notably, DeepADAR can predict both on-target and off-target editing induced by gRNAs, demonstrating its potential utility in RNA therapeutics design.

*Correspondence: {andrewjung, frey, ljlee}@psi.toronto.edu

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