A149 · SwissIsoform: A Biological and Functional Annotation Database for Translation Start Site Protein Isoforms

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Ribosome profiling, a technology that sequences ribosome-bound mRNA fragments, has shown that one-third of human genes contain translation start site protein isoforms. Previous research has identified divergent localization patterns between canonical and isoform proteins and rare disease variants in isoform-specific regions previously thought to be untranslated. While follow-up experiments on specific translation isoforms can yield mechanistic insights into gene function and connections to rare genetic disease, without systematic characterization of these thousands of candidate isoforms, prioritizing ones for further study is difficult.

To improve the accessibility of protein isoform research, we present SwissIsoform, an online annotation database of 39,721 protein isoforms discovered in ribosome profiling across six cell lines. We derived orthogonal evidence through precomputed in silico experiments grouped into six categories (Predicted Structure, Mutational Landscape, Evolutionary Conservation, Localization, Structural Characteristics, and Detection), each comparing an alternative isoform to its annotated protein. For ease of interpretation, we implemented a two-pass LLM framework: the initial pass evaluates metrics within each category for evidence of divergences from the canonical protein and a subsequent pass reasons over the canonical protein's known context in tandem with each category's results to synthesize a holistic hypothesis for how the isoform functionally deviates. To assist clinicians in understanding if variants of interest intersect differentially translated regions, we included a variant querying option to identify affected isoforms and the variant's type and effect. SwissIsoform is the inaugural catalogue of translation start site isoforms, which will further enable research on how isoforms influence human health and disease.

SwissIsoform: A Biological and Functional Annotation Database for Translation Start Site Protein Isoforms

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