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A new method for prioritizing non-coding genetic variants associated with complex diseases

Because 98% of the genome does not code for a protein, unraveling how non-coding genetic variants contribute to complex diseases remains a great challenge. Stanford researchers have developed a novel method that prioritizes and assesses the functionality of non-coding genetic variants. This technology improves upon currently available methods in several ways.

The current gold standard to prioritize genetic variants such as the CADD score is based on evolutionary conservation and works well for coding variants. However, it is poorly suited for prioritizing non-coding variants. This new method is specifically designed to prioritize non-coding variants by integrating multiple annotations and metrics. It relies on an approach that is based on the biology of the specific cell type of interest rather than evolutionary conservation, and therefore able to prioritize genetic variants that are not evolutionarily conserved and common within the population, both of which have previously been overlooked.

Furthermore, for a given cell type, the algorithm appropriately assigns the non-coding variants to their gene targets by identifying the genes they are in close physical proximity with based on three-dimensional chromatin conformation. It also associates the non-coding variant with a regulatory element known to be present at the site of the target gene in the cell, thereby offering a proposed method of action by which the non-coding variant regulates expression of its target gene.

Overall, this technology provides a novel solution for identifying non-coding variants involved in complex diseases and advances the ability to interpret non-coding variants for personalized health care.

Applications

- **Diagnostics**
  - Identification and prioritization of genetic variants for molecular diagnosis of inherited diseases
  - Recognition of risk factors in healthy individuals
- **Research**
  - Identification of genetic targets for research on pathophysiology of inherited diseases
  - Prediction of the functionality of genetic variants

Advantages

- A platform that integrates multiple sources of prior information in defining genetic variants and phenotype associations
- Higher sensitivity and specificity in prioritizing non-coding risk variants than existing methods
- Annotation can be cell-type specific and predicts mechanism of action of the non-coding variants

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