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Commentary

From Genetic Noise to Meaningful Signals: The Art of Genomic Variant Prioritization

Marissa Trossini*

Department of Genomic Medicine, University of Sao Paulo, Sao Paulo, Brazil

DESCRIPTION

The human genome contains millions of genetic differences, yet only a small proportion are expected to influence biological functions or contribute to disease. Genomic variant prioritization is a computational process designed to identify the variants most likely to have meaningful biological consequences from a large collection of detected genomic changes. By combining genetic evidence, functional information, population data, clinical observations and computational predictions, prioritization methods can transform an extensive list of variants into a focused set of candidates that deserve closer attention. Modern sequencing technologies can identify numerous single-nucleotide changes, insertions, deletions, copy-number alterations and other forms of genomic variation. A typical sequencing analysis may produce thousands of variants in an individual, making manual evaluation impractical. Many of these changes are harmless because they occur commonly in healthy populations or have little influence on gene activity. Others may affect important biological processes but remain difficult to interpret because their functional consequences are uncertain. Prioritization helps distinguish potentially significant variants from those that are less likely to explain a particular phenotype.

One of the earliest considerations in prioritization is population frequency. A variant that occurs frequently among healthy individuals is generally less likely to cause a rare, highly penetrant condition, although frequency alone cannot establish whether a variant is harmless. Population databases provide allele-frequency information across different ancestral groups and can help remove common background variation. Care is necessary because some populations remain underrepresented in genomic resources and a variant may appear rare simply because adequate reference data are unavailable for that population. The predicted effect of a variant on a gene or its encoded product provides another important layer of evidence. Variants that introduce premature termination signals, disrupt essential splice regions or alter conserved coding sequences may receive greater priority than changes located in regions with limited functional evidence. However, genomic interpretation extends beyond protein-coding regions. Variants positioned within promoters, enhancers, untranslated regions, regulatory elements and noncoding transcripts can also influence gene activity. Consequently, modern prioritization frameworks increasingly consider regulatory architecture rather than focusing exclusively on protein sequences.

Phenotypic information is particularly valuable when evaluating variants associated with rare or complex conditions. Clinical features can be represented using standardized terminology and compared with known gene-disease relationships. A variant located in a gene associated with a person's characteristic phenotype may receive a higher priority than an equally rare variant in an unrelated gene. This phenotype-driven approach can reduce the number of candidates requiring detailed evaluation and can highlight connections that might otherwise remain hidden. Computational prediction tools add another dimension by estimating whether particular genomic changes are likely to affect molecular function. These systems may incorporate evolutionary conservation, protein structure, sequence context, regulatory annotations or patterns learned from previously characterized variants. Their predictions can be useful for ranking candidates, but they should not be treated as definitive evidence. Different algorithms may produce conflicting results, particularly for variants with unusual sequence contexts or limited supporting information. Gene expression and tissue-specific information can further improve prioritization.

CONCLUSION

Functional relationships between genes can also provide useful context. Genes participating in the same pathway or biological process may help explain a phenotype even when direct evidence

Correspondence to: Marissa Trossini, Department of Genomic Medicine, University of Sao Paulo, Sao Paulo, Brazil, Email: marissa.trossini@usp.br

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connecting a particular variant to disease is limited. The quality of prioritization depends heavily on the integration of multiple evidence sources. A rare variant with a predicted damaging effect may initially appear important, but its priority can change when inheritance patterns, gene function, clinical observations and population information are considered together. Conversely, a variant with modest computational predictions may become highly relevant when supported by consistent phenotype and inheritance evidence. Combining independent signals therefore provides a more balanced framework than relying on a single scoring system. If a candidate gene is strongly expressed in a tissue relevant to the observed phenotype, variants affecting that gene may become more compelling.