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The increasing amounts of sequenced genomic information have added a new dimension to comparative genomics and structural biology. The advent of next generation sequencing technology has made it possible to not only analyze the variation of genetic information within healthy human populations but also to map out the genetic basis for a number of diseases. However, it remains a nontrivial task to understand the evolutionary constraints preventing a particular amino acid change on a protein. In this review, we emphasize that it is essential to integrate information from sequences, structures, and interaction networks to rationalize the phenotypic effects of these variations.

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