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Integrative analysis will help

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There is one additional confounding factor to consider while identifying disease-associated variants. Genes associated with a disease are identified by detecting deleterious variants that are affecting genes within diseased individuals more often than in healthy populations. This might be misleading, however, because the variants associated with this gene might be correlated with other unanalyzed variants in the genome. Hence, all variants (including the variants within a gene) statistically associated with a disease might not be causative and additional analysis may be required to identify the real disease-causing mutations. We need to annotate the effect of individual variants, however, before we can predict the outcome of a large number of variants.

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Each protein has several evolutionary constraints imposed upon it based on its biological function. The effect of a deleterious variant can only be understood when all these functional constraints acting on a protein are known and can be considered. The fibroblast growth factor receptor provides a case-in-point (Figure 3). This protein has been shown to host well-documented disease-causing variants that manifest in craniofacial defects in humans. However, several of the disease variants have no clear mechanism of pathogenicity in that they do not fall in any of the protein regions known to be sensitive to amino acid changes. Certainly, a sequence change should not hinder a protein from folding to its native state, bind to a specific ligand, and perform its function [21], but the determining the effects of a given variant is often non-trivial. This determination can sometimes be made when a sufficient number of homologues are available, along with variants known to be harmful in such homologues.

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Mutations may not only affect the native state of the protein but could also affect the stability of intermediates within the folding pathway. Such considerations typically ignored while assessing the effect of mutations on a protein's structure. In addition,

mechanistic insight into the mutation- induced structural changes requires knowledge of the folding kinetics, which still remains elusive in these models. Finally, while mutations that occur on the active site of the protein reduce efficiency or ablate function entirely, mutations that are distant from an active site may also affect protein efficiency [26].

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Effect of Mutations on Disordered Regions:

The discovery and prominent role (>30% of eukaryotic proteome) of intrinsically disordered regions has challenged the paradigm that structure determines the function [48]. The hubs in PPI networks tend to contain higher degrees of disordered regions, and these regions typically become well-ordered upon ligand or protein binding [49,50].