Effects of disease-related mutations on transcription factor binding

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1 250 sanainen abstrakti (230 sanaa tässä)

Many diseases are caused by hereditary mutations. So far, most of the identified mutations affect the coded protein sequence. However, an increasing number of the identified disease-related mutations occur in gene regulatory sequences. These mutations pose a threat to influence the mechanism by which a cell regulates the transcription of its genes.

Here we have studied the effect of disease-related mutations on transcription factor binding affinity computationally by using position specific scoring matrixes. We have compared our results with experimentally verified cases where a mutation in the gene regulatory region either creates a new transcription factor binding site or deletes a previously existing one. We have also investigated the statistical properties of the changes on transcription factor binding affinity according to different mutation types in dinucleotides. This is because the DNA bending ability is known to be different for separate dinucleotide steps. Further, it has been found that contacts between TFs and purines are especially important and because the bending of DNA has an effect on TF binding .

Although accurate binding site prediction is difficult in general, our results demonstrate that computational analysis can provide valuable information about the effect of mutations on transcription factor binding sites. The analysis provides a list of testable hypothesis, ordered according to the significance of mutation effect, that can be readily tested in laboratory to verify the real mutation effect in vitro. Results should also be taken into account when studying the disease mechanisms on molecular level.

2 50 sanainen abstrakti (50 sanaa tässä)

We have studied computationally the effect of disease-related mutations on transcription factor binding affinity. The results have been compared with experimentally verified results. We have also investigated the statistical properties of the changes on transcription factor binding affinity according to mutation types. Valuable results have been obtained for laboratory tests.