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Cystic Fibrosis Research News

Title:

Exon identity influences splicing induced by exonic variants and in silico prediction efficacy

Lay Title:

Predicting effects of mutations on CFTR's mRNA

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What was your research question?

Around 11% of mutations identified in cystic fibrosis are reported to affect the mRNA, a single-stranded molecule that carries genetic code from DNA in a cell to its protein-making machinery. Defects in mRNA linked to mutations are often overlooked and are difficult to predict. Here we tested how 65 mutations affected mRNA and also tested the performance of 6 computer programmes usually used to predict mRNA defects.

Why is this important?

As Next Generation Sequencing is beginning to be used for genetic diagnosis, the number of recognised variants has steadily increased, highlighting the importance of knowing whether these variants caused disease or not. The effect of these variants on mRNA are often overlooked. These effects can either be evaluated in the laboratory through experiments on gene fragments or patients' samples, which can be tedious. These effects can also be predicted using specialised software, which is easier but less accurate. Our results guided a better choice of software to improve predictions rates.

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What did you do?

In this study, we first compared results from laboratory experiments using samples from patients then we measured the effect of 65 variants known to cause disease or marked as variants with unknown significance. Six different software packages were used to predict the impact of these variants on mRNA. We then compared the results from the laboratory to the software predictions.

What did you find?

Our results showed that laboratory experiments on gene fragments can predict the impact of mutations when patient samples are not available. We identified 26 variants that alter mRNA which would affect the CFTR channel. Software prediction rates had a 50%-60% success rate. These rates could be markedly improved once the position of the mutation to guide the choice of the software was taken into account.

What does this mean and reasons for caution?

Next Generation Sequencing will identify an important number of new variants whose impact on mRNA will be evaluated using computer programmes. We need to understand the limits and strengths of these software packages in order to correctly predict the impact of these variants on mRNA. This study also highlights the need to validate software predictions using laboratory experiments such as gene fragments or mRNA studies in patients.

What's next?

We now need to test these software tools with other variants identified in patients.

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