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Polymorphic splice enhacer motifs

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Context

Exonic polymorphisms may have several consequences: they may be biologically silent or lead to missense or nonsense codons. A nonsense mutation consisting of a guanine to thymine transition at position 6 (G6T) of exon 18 of the *BRCA1* gene is associated with skipping of exon 18 *in vivo*. Potential mechanisms explaining the link between nonsense mutations and RNA processing alterations (nonsense mediated mRNA decay) include a nuclear nonsense codon recognition mechanism. Exonic splice enhancers (ESEs) have been identified that are recognised by serine/arginine-rich (SR) proteins, each of which recognises a distinct but degenerate motif. The authors of this paper have developed a mathematical scoring matrix which predicts the likelihood of interaction between SR proteins and ESEs. Using an SR protein binding matrix, it was predicted that the polymorphism would affect binding of the SF2/ASF protein. The aim of this study was to determine if polymorphisms within ESE motifs result in exon skipping.

Significant findings

The presence of the G6T mutation in exon 18 of a *BRCA1* minigene consisting of exons 17, 18 and 19 with short intervening intronic segments led to skipping of exon 18 in the mature transcript. The SR binding motif scores, rather than the type of polymorphism (missense or nonsense), predicted the likelihood of exon skipping. Examination of a database of 50 single-base substitutions which lead to exon skipping in vivo showed that more than half reduced or eliminated at least one high-scoring SR protein binding motif in the mutant allele. This was observed for nonsense, missense and silent mutations.

Comments

This paper demonstrates a further mechanism whereby polymorphisms lead to altered gene function and disease. Silent mutations within exonic sequences may have quite profound effects on gene expression and the use of the predictive matrix developed by Krainer and co-workers should be very useful in determining if an exonic polymorphism affects transcript processing. As the authors point out, the evolution of exonic sequences is constrained not only by the requirements for protein coding but also by the presence of ESE motifs.

Methods

In vitro translation/splicing, HeLa nuclear extract

Additional information

References

1. Liu HX, Cartegni L, Zhang MQ, Krainer AR: A mechanism for exon skipping caused by nonsense or missense mutations in *BRCA1* and other genes. Nat Genet. 2001, 27: 55-58.