4243 Novel alternative splicing events within the human kallikrein locus.

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Alternative splicing is one mechanism that regulates gene expression. Here, we examine a novel but common type of splicing within the kallikrein gene family, at chromosomal locus 19q13.4. According to this type of splicing: (a) for the kallikreins that the intron between coding exons 3 and 4 is around 100 bp, the intron is not spliced out during the maturation of the pro-mRNA ("intron retention") and (b) for the kallikreins that the intron between coding exons 3 and 4 is larger than 100 bp, during maturation of the pro-mRNA, exon 3 is extended by approximately 100 bp ("exon extension"). From this type of splicing, the ORF is altered with creation of a premature termination codon (PTC) within the added area of the 100 bp. This PTC is more than 50 bp upstream of the last exon-exon splice junction and qualifies these alternative spliced forms of the kallikreins genes as candidates for degradation by the mechanism of "nonsense-mediated mRNA decay" (NMD). We have identified and characterized this type of splicing for eight of the fifteen kallikrein genes. More specifically, we found "intron retention" for the genes KLK1, KLK2, KLK3, KLK4, KLK5 and KLK15, and "exon extension" for the genes KLK9 and KLK13. By using bioinformatics we found that this type of splicing can also be seen for the rest of the kallikrein genes. Furthermore, we were able to find ESTs (Expressed Sequence Tags) that encode for these variants. Expression profiling of these splices variants in 36 normal human tissues, by RT-PCR, revealed that they have similar expression profile with the classical form of the gene. Furthermore, we showed that these variants are regulated by steroids but the patterns of regulation of the splice variant are different from those of the classical forms.

These results indicate that a universal type of splicing may participate in the expression of the kallikrein gene family, by producing splice variants that are targets for degradation by the mechanism of "nonsense-mediated mRNA decay".

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