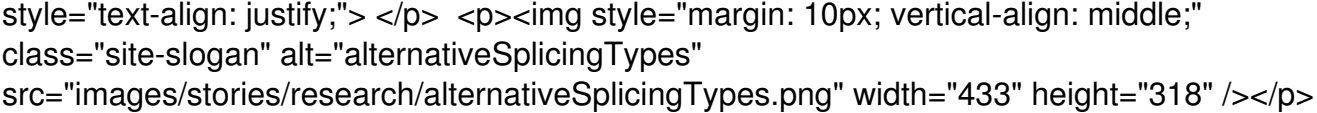


Types of Alternative Splicing

Written by Administrator

Saturday, 07 July 2007 09:54 - Last Updated Tuesday, 06 March 2012 10:30

Alternative splicing events are classified into four main subgroups: (i) exon skipping (cassette exons), where the exon can be spliced out of the transcript together with its flanking introns; (ii) alternative 5' splice sites and (iii) 3' splice sites selection, which are the results of the recognition of two or more splice sites at one end of an exon; and (iv) intron retention, in which an intron can remain in the mature mRNA molecule (Figure 2). Finally, there are other, less frequent, complex events that give rise to alternative transcript variants, including mutually exclusive events, alternative transcription start sites, and multiple polyadenylation sites.





Bioinformatic analyses indicate that higher eukaryotes exhibit a higher proportion of alternatively spliced genes (genes that generate more than one type of mRNA molecule), and alternatively spliced exons than do lower metazoans. In particular, more than 70% of human genes undergo alternative splicing. Alternative splicing does exist in lower metazoans, as well as in fungi and in the protozoan *Dictyostelium discoideum*. However, these studies indicate that alternative splicing events in these species are extremely rare. In these organisms, the most prevalent type of alternative splicing was found to be intron retention, which was found to be the rarest alternative splicing event in vertebrates and invertebrates (<5%) and may indicate that these are cases of mis-splicing. On the other hand, exon skipping, which is the most prevalent type of alternative splicing in vertebrates and invertebrates (~30-40%), is the rarest (if not absent) form in these organisms. Thus, alternative splicing is believed to be a major source for the phenotypic complexity in higher eukaryotes. Indeed, exon skipping exhibits a gradual increase in its relative prevalence along the eukaryotic tree, suggesting it is the more important event in shaping phenotypic complexity.

Following this line, alternative splicing might conceivably explain part of the discrepancy between the number of human protein-coding genes (~25,000), which is only slightly higher than the numbers in nematode (~19,000 genes) and lower than in rice (~40,000 genes), and the phenotypic complexity. Plants exhibit low levels of alternatively spliced genes in general, but exhibit high relative levels of intron retention (~30%) and a very low level of exon skipping (<5%) 19,20,35. From an evolutionary perspective, this suggests that alternative splicing played a less prominent role in plant evolution than in vertebrate and invertebrate evolution where alternative splicing greatly enhances transcriptomic and proteomic diversity. This could be explained by the fact that plants exhibit extensive whole/partial genome duplication events. Gene duplication gives rise to a state of genetic redundancy, in which one of the newly formed gene copies enters a period of reduced evolutionary pressure. Selective constraints ensure that one of the duplicates retains its original function, while the second copy is free from these constraints and, thus, accumulates mutations, which in turn may lead to a different expression pattern or to neofunctionalization that advances organism speciation. Indeed, it was shown that whole genome duplication in plants is associated with speciation 37,39. This presumably led to a reduced need for alternative splicing, and in particular for exon skipping, as an essential mechanism for genomic innovations leading to speciation. Indeed, Yanai and colleagues found an inverse correlation between the size of a gene's family and its use of alternatively spliced isoforms 40. Moreover, Gu and co-workers revealed loss of alternative splicing after gene duplication. This suggests that exon duplication and alternative splicing are interchangeable evolutionary mechanisms and that the requirement for diversification may be satisfied by either of the two mechanisms. Although the importance of

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alternative splicing in higher eukaryotes is well established, the prevalence and presence of alternative splicing (and regulated splicing in general) in lower eukaryotes is unclear. Recent findings in yeast (*C. neoformans*) revealed evidence for a variety of alternative splicing events in 4.2% of the genes, including exon skipping and selection of alternative 5' and 3' splice sites. This finding supports reports regarding the presence of alternative splicing in several yeasts and protozoa. Such studies shed light on the origin of alternative splicing, with recent estimates suggesting that the origin of multi-intron genes dates back to ancient eukaryotes.

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