A survey of alternative transcripts of human tissue kallikrein genes

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Abstract

Alternative splicing is prevalent within the human tissue kallikrein gene locus. Aside from being the most important source of protein diversity in eukaryotes, this process plays a significant role in development, physiology and disease. A better understanding of alternative splicing could lead to the use of gene variants as drug targets, therapeutic agents or diagnostic markers. With the rapidly rising number of alternative kallikrein transcripts, classifying new transcripts and piecing together the significance of existing data are becoming increasingly challenging. In this review, we present a systematic analysis of all currently known kallikrein alternative transcripts. By defining a reference form for each of the 15 kallikrein genes (KLK1 to KLK15), we were able to classify alternative splicing patterns. We identified 82 different kallikrein gene transcript forms, including reference forms. Alternative splicing may lead to the synthesis of 56 different protein forms for KLK1-15. In the kallikrein locus, the majority of alternative splicing events occur within the protein-coding region, and to a lesser extent in the 5' untranslated regions (UTRs). The most common alternative splicing event is exon skipping (35%) and the least common events are cryptic exons (3%) and internal exon deletion (3%). Seventy-six percent of kallikrein splice variants that are predicted to encode truncated proteins are the result of frameshifts. Eighty-nine percent of putative proteins encoded by splice variants are predicted to be secreted. Although several reports describe the identification of kallikrein splice variants and their potential clinical utility, this is the first extensive review on this subject. Accumulating evidence suggests that alternative kallikrein forms could be involved in many pathologic conditions or could have practical applications as biomarkers. The organization and analysis of the kallikrein transcripts will facilitate future work in this area and may lead to novel clinical and diagnostic applications.

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Keywords: Kallikrein; Alternative splicing; Differential expression; Serine protease; Splice variant; Cancer biomarker

Contents

1. Introduction ............................................................ 2
2. Methodology ........................................................... 3
   2.1. Alternative splicing in the kallikrein locus .................... 4
   2.2. The coding exons ................................................. 5
   2.3. The non-coding exons ............................................ 5
   2.4. Encoded proteins ................................................. 5

Abbreviations: KLK, hK Kallikrein gene, kallikrein protein; UTR, untranslated region; RACE, rapid amplification of cDNA ends; EST, expressed sequence tag; ORF, open reading frame

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1. Introduction

Human tissue kallikreins (KLK, hKs) are a group of serine proteases encoded by 15 structurally similar, hormonally-regulated genes that tandemly localize on chromosome 19q13.4 [1,2] and found to have clinical utility in various diseases, including cancer [3]. The presence of more than one mRNA form for the same gene is common among kallikreins. In the kallikrein locus, alternative transcripts are the result of splicing in the coding or non-coding regions, use of alternative transcription or translation start and stop sites and combinations thereof. Here, we review the numerous alternative transcripts of the kallikrein genes in order to facilitate the identification of novel kallikrein transcripts and future investigations towards their diagnostic and therapeutic applicability.

Alternative splicing, first proposed by Gilbert in 1978 [4], generates multiple mRNA forms from one gene and may yield several different proteins. Splice variants were found for 35–74% of all human genes [5–12]. Of all mechanisms that increase protein diversity, alternative pre mRNA splicing is considered to be the most significant source in vertebrates, as approximately 70–88% of alternative splicing events result in changes in the encoded protein [5,8,11]. Processes such as alternative use of promoters, splice sites, translational start sites and translational termination codons can serve as mechanisms for regulating alternative splicing. The use of alternative transcriptional start sites and poly A sites can also generate a variety of mRNAs.

Alternative transcripts can be detected using a combination of RT-PCR techniques, cloning and sequencing or by using fiber-optic arrays and exon junction microarrays [10,13–18]. Although they have several limitations [7], expressed sequence tags (ESTs) are also very useful in identifying putative alternative transcripts.

Alternative splicing may generate segments of mRNA variability that can insert or remove amino acids, shift the reading frame, or introduce a termination codon. Alternative splicing can also remove or insert regulatory elements controlling translation, mRNA stability or localization [19]. The use of alternative translation initiation sites is key in generating a versatile repertoire of functionally different proteins within individual cells. Diseases associated with mutations may disturb the initiation step of translation by changing the context around the AUG start codon or by introducing upstream AUG codons [20–25]. See reference [26] for more details.

The mechanism that allows transcription to initiate at an alternative start site or terminate at a different poly A site is associated with the use of alternative promoters, a less well-characterized phenomenon than alternative splicing that still contributes to genome complexity [27]. Although 60–80% of genes with alternative promoters produce transcripts with identical open reading frames (ORFs) [27], this mechanism can also lead to different proteins through the use of alternative ORF or creation of novel ORFs [28,29]. A recent review describes the interrelationships between splicing and promoter regions [27].

Before being transported to the cytoplasm for translation, the mRNA is spliced and polyadenylated [30]. The poly A tail enhances translation and mRNA stability [31,32]. Aberrant polyadenylation may alter cell viability, growth and development and may ultimately lead to disease [33].

Alternative splicing has been implicated in many physiological and pathophysiological processes and 15% of mutations in the mammalian genome that cause disease are associated with an affected RNA splicing signal [34].

<table>
<thead>
<tr>
<th>Nomenclature and schematic representation of splicing events</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Table 1</strong></td>
</tr>
<tr>
<td>Nomenclature and schematic representation of splicing events</td>
</tr>
<tr>
<td>Our definition</td>
</tr>
<tr>
<td>Skipped exon</td>
</tr>
<tr>
<td>5' Truncated exon</td>
</tr>
<tr>
<td>3' Truncated exon</td>
</tr>
<tr>
<td>Internal exon deletion</td>
</tr>
<tr>
<td>Cryptic exon</td>
</tr>
<tr>
<td>5' Exon extension</td>
</tr>
<tr>
<td>3' Exon extension</td>
</tr>
<tr>
<td>Complete intron retention</td>
</tr>
<tr>
<td>Classical splicing</td>
</tr>
</tbody>
</table>

Boxes represent exons and horizontal lines represent intervening introns. Diagonal lines show splicing arrangement. The first 4 diagrams represent splicing events involving only exons, while the last 5 diagrams represent splicing events involving introns and exons.
Many splice variants are also implicated in cancer. Recent reports indicate that 10–30% of alternatively spliced human genes possess tissue-specific splice variant forms [35] and that at least 316 genes possess cancer-specific mRNA variants, 73% of which display cancer- and not just tissue-specific splicing patterns [36]. Furthermore, the usage of consensus GT–AG splice sites is significantly less frequent in cancer-specific mRNA splice forms, while GC–AG usage is specifically increased [37]. The amount of proteins encoded by variant transcripts varies between individuals. This can result in the differential penetrance of a disease-causing gene and may indicate that alternative splicing could be a potential genetic modifier of human disease [38]. In addition to their potential diagnostic and prognostic relevance, recent reports suggest that splice variants may have important therapeutic applications [39,40].

2. Methodology

All publicly available kallikrein mRNA sequences until December 2003 were identified and compared to their reference forms, as described below.

In order to differentiate between “reference” and alternative kallikrein transcripts, we arbitrarily selected one transcript that we considered to be the “reference” form. The reference form satisfied the five characteristics of a kallikrein gene, as defined by Yousef et al. [41]. If more than one candidate “reference form” existed, the form with the longest 5′-UTR in the mRNA was selected.

In order to distinguish between kallikrein mRNA forms with incomplete 5′ ends from mRNA forms with alternative transcription start sites, we verified from the literature whether 5′ rapid amplification of cDNA ends (RACE) or any other method was performed to validate the presence of an alternative transcriptional start site.

Table 2
Reported human kallikrein mRNA transcripts

<table>
<thead>
<tr>
<th>Gene</th>
<th>Number of mRNA forms per gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>KLK1</td>
<td>4</td>
</tr>
<tr>
<td>KLK2</td>
<td>7</td>
</tr>
<tr>
<td>KLK3</td>
<td>11</td>
</tr>
<tr>
<td>KLK4</td>
<td>9</td>
</tr>
<tr>
<td>KLK5</td>
<td>6</td>
</tr>
<tr>
<td>KLK6</td>
<td>8</td>
</tr>
<tr>
<td>KLK7</td>
<td>3</td>
</tr>
<tr>
<td>KLK8</td>
<td>5</td>
</tr>
<tr>
<td>KLK9</td>
<td>3</td>
</tr>
<tr>
<td>KLK10</td>
<td>2</td>
</tr>
<tr>
<td>KLK11</td>
<td>4</td>
</tr>
<tr>
<td>KLK12</td>
<td>4</td>
</tr>
<tr>
<td>KLK13</td>
<td>9</td>
</tr>
<tr>
<td>KLK14</td>
<td>1</td>
</tr>
<tr>
<td>KLK15</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td>82</td>
</tr>
</tbody>
</table>

Our major focus was in the protein-coding region of mRNAs, where splice variants can encode for different proteins compared to the reference protein. Events for splice variants with only partially characterized protein coding regions were not included in the analysis.

Splicing events were noted both in the protein-coding and the untranslated regions as follows:

- **Cassette Exons:**
  - Skipped exon: A constitutive exon (exists in the reference form) which is skipped in the alternative form.
  - Cryptic exon: Present in the alternative form but absent in the reference form.

- **Exon Isoforms:**
  - Exon extension — Lengthening at one or both ends of an exon.
  - Exon truncation — Shortening at one or both ends of an exon.

- **Intron retention:** The presence of an intron within two adjacent transcript-confirmed exons.

- **Internal exon deletion:** A mid exon gap where a cryptic intron is introduced.

The nomenclature for describing these events is similar to that conventionally used [42–44]. We have also compared these definitions to the nomenclature used by Wang et al. [37] to characterize the same splicing events (see Table 1).

Events in the protein-coding regions were quantified per gene and per intron/exon. Using in-silico translational tools (www.expasy.org/tools/), when published reports were not available, encoded proteins were predicted and categorized by event including frameshift, in-frame deletion, or in-frame insertion.

**Fig. 1. Frequency of kallikrein splicing events within the coding regions.** Of all coding region alternative splicing events in the kallikrein locus, the most common event is exon skipping with a frequency of 36%, followed by exon extension (24%), exon truncation (18%), intron retention (16%), cryptic exon (3%) and internal exon deletion (3%). For definitions, see Table 1.
The prediction of signal peptide using the SMART algorithm (smart.embl-heidelberg.de/) indicated if the variant protein is likely to be secreted.

Although splice variants are included under the definition of alternative transcripts, if post-transcriptional modifications occur in the 5′ or 3′-UTRs that are not the result of the splicing definitions listed above, the alternative transcripts generated may not be considered splice variants. All kallikrein mRNA transcripts, stratified per kallikrein gene, are listed in Table 2.

### 2.1. Alternative splicing in the kallikrein locus

As of December 2003, a total of 82 kallikrein mRNA forms, including reference forms, has been reported (Table 2). With the exception of KLK14, all kallikreins have at least one alternative transcript, exclusive of their reference form. KLK3, followed by KLK13, has the highest number of alternative transcripts.

Splicing is seen mostly in the protein coding regions and to a much lesser extent in the 5′-UTR. Although several
kallikrein transcripts have confirmed alternative poly A tails, no splicing events have been detected in this region.

2.2. The coding exons

Exon skipping is the most common event in the kallikrein locus, as 35% of splicing events lead to a skipped exon (Fig. 1). Coding exons 4 and 2 are most commonly skipped among kallikrein genes (Fig. 2A).

3' Exon extension events occur twice as often as 5' extension events and 3' exon truncation occurs close to three times as often as 5' truncation (Fig. 2A).

Intron retention almost always results in the retention of intron 3 between coding exons 3 and 4. The only exception was found in KLK3 variant PSA-LM (Accession # AF335478), in which the intron 1 is retained (Figs. 2B and 6).

The least common kallikrein splice forms include a cryptic exon and internal exon deletion (3% each), each event occurring uniquely in one gene. Cryptic exons are found in two transcripts of KLK13 [45] (Figs. 2 and 16) (AY293174 and AY293175) and internal exon deletion occurs in one transcript of KLK12 (accession # NM_019598) (Figs. 1, 2 and 15).

3' Exon truncation has been detected in exons 3, 4 and 5 on one occasion each, while 3' exon truncation occurs almost exclusively in exon 3 (also present in exon 4 for KLK3 variant PSA-RP5). 5' Exon extension was observed mostly in exon 3 and to a lesser extent in exons 5 and 2. 5' Exon extension was seen once in coding exon 1, twice in exon 2, three times in exon 3 and four times in exon 4. It was not observed in exon 5. Internal exon deletion is present in exons 3 and 5 in one splice variant each (Fig. 2).

Splice sites are usually conserved among the kallikrein variant forms. However, rare CC–AG pairs were found in several KLK3 variants [46]. A GC–AG intron is found in intron 3 of both KLK10 transcripts.

2.3. The non-coding exons

An alternative promoter region was confirmed in splice variants of KLK6 and KLK4. Splicing events that were identified in the 5'-UTR were internal exon deletion and exon truncation events that occurred in different KLK5 transcripts (accession #s AY273981 and AY273980, respectively) (see Fig. 8).

Some non-conserved splice sites were generated in the 5'-UTR. This occurs in KLK10 where a TG is used as the donor site. In KLK5, Dong et al. reported a variant with a non-conserved GG splice donor site but since it is only one nucleotide away from a GC donor site, this variant is likely the same as the KLK5 variant described in accession # AY279380.

Although multiple transcripts of the same gene have variations in their 3' terminal sequences, many are likely incomplete mRNA sequences. The only genes that have alternative transcripts with confirmed alternative polyadenylation sites are KLK2 and KLK3 [43,46] (Figs. 5 and 6).

2.4. Encoded proteins

Five kallikrein genes (KLK4, 6, 7, 11 and 13) have transcripts with one alternative translation initiation site each (see Figs. 7, 9, 14, 16). Although only variants of KLK2 and KLK3 KLK3 have been experimentally shown that they may encode proteins [47]). Although only variants of KLK2 and KLK3 have been experimentally shown that

<table>
<thead>
<tr>
<th>Gene with alternative transcript(s) associated with cancer</th>
<th>Type of cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>KLK2</td>
<td>Prostate cancer</td>
<td>[47,50]</td>
</tr>
<tr>
<td>KLK3</td>
<td>Prostate cancer</td>
<td>[47,51,59]</td>
</tr>
<tr>
<td>KLK5</td>
<td>Ovarian cancer</td>
<td>[52]</td>
</tr>
<tr>
<td></td>
<td>Ovarian and prostate cancer</td>
<td>[53]</td>
</tr>
<tr>
<td>KLK6</td>
<td>Breast cancer</td>
<td>(our unpublished data)</td>
</tr>
<tr>
<td>KLK7</td>
<td>Ovarian cancer</td>
<td>[52]</td>
</tr>
<tr>
<td>KLK8</td>
<td>Ovarian cancer</td>
<td>[55]</td>
</tr>
<tr>
<td>KLK11</td>
<td>Prostate cancer</td>
<td>[57]</td>
</tr>
<tr>
<td>KLK13</td>
<td>Testicular cancer</td>
<td>[45]</td>
</tr>
</tbody>
</table>
they may encode proteins [47], protein sequences for other variants have been predicted using bioinformatic tools. Among these, three KLK4 transcripts have identical AUG start codons different from that of the reference protein (Fig. 7). KLK13 and KLK6 have two (Figs. 9 and 16), while KLK7 and KLK11 each have one (Figs. 10 and 14). Of these splice variants, the only one that may encode a protein that includes a signal peptide and is therefore likely secreted is KLK11 (accession # NM_144947). A total of 56 different protein forms may be generated by alternative transcripts of kallikrein genes (41, if we do not include the reference proteins). Of these, 95% encode for truncated proteins. Seventy-six percent of kallikrein splice variants that are predicted to encode for truncated proteins exhibit a frame shift (Fig. 3). This event occurs in all kallikreins except KLK7, KLK10, KLK11 and KLK14. To a lesser degree, in-frame deletions make up 24% of truncation events. In-frame insertions seen in KLK8 and KLK12 comprise 5% of all events that alter protein products in the kallikrein locus (Fig. 3).

A recent genome wide report of splicing patterns by Modrek et al. indicated that 74% of splicing events occur in the coding region, 22% in the 5’-UTR and only 4% in the 3’-UTR and that exon skipping is the most common splicing event [8]. Our results for kallikreins generally agree with these findings. Clark et al. analyzed 2793 genes and reported that cassette exon events were most prevalent compared to other alternative events [12]. They also stated that over one-third of all exons have alternative ORFs. Interestingly, the presence of a frame shift was found to be highly correlated with the GC content of introns.

The regulation of the individual splicing events is not well understood. The high incidence of exon skipping has stimulated research into the regulation of this splicing event. In silico analysis of mRNAs that undergo exon skipping identified two motifs, conserved in both mouse and human [48]. Both motifs were complementary and found in the flanking introns of the skipped exon, one rich in pyrimidines while the other is rich in purines. Miriami et al. provided preliminary evidence suggesting a base pairing interaction...
between the two motifs to regulate exon skipping by generating a secondary structure [48].

Since the emergence of PSA as the most powerful prostate cancer marker over two decades ago [49], the diagnostic and prognostic potential of other kallikrein genes is being explored. Recently, differential expression of kallikreins in various types of cancer suggests that splice variants are worth investigating for cancer detection (Table 3). Some kallikrein variants seem to be cancer-specific and/or differentially expressed in cancer and may have potential clinical applications as diagnostic/prognostic biomarkers. For instance, Slawin et al. have recently developed a preoperative KLK2 splice variant-specific RT-PCR that is useful for detecting prostate cancer metastasis and helps predict pathological lymph node positivity in men with clinically localized prostate cancer [50].

Tanaka et al. have reported the existence of an alternatively spliced form of the KLK3 gene which is expressed in 13 of 18 (72.2%) non-cancerous and 4 of 5 (80.0%) cancerous prostate tissues, but in only 3 of 12 (25.0%) blood samples from prostate cancer patients [51]. The difference in KLK3 variant expression levels between noncancerous prostate tissues versus blood samples from cancer patients was statistically significant ($P=0.011$).

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**Fig. 6.** Schematic representation of mRNA transcripts for human kallikrein gene 3 (KLK3). For more details, see legend of Fig. 4 [47,51,59].

**Fig. 7.** Schematic representation of mRNA transcripts for human kallikrein gene 4 (KLK4). For more details, see legend of Fig. 4 [68–74]. The last three putative encoded proteins are speculated to be intracellular [74].
David et al. have reported the identification of two splice variants of the \textit{KLK2} and \textit{KLK3} genes that result from the inclusion of intronic sequences adjacent to the first exon, denoted K-LM and PSA-LM, respectively [47]. With the exception of the signal peptide, K-LM and PSA-LM transcripts encode protein isoforms that are entirely different than the reference hK2 and hK3 proteins. As such, polyclonal antibodies were generated against synthetic peptides derived from amino acid sequences unique to each variant protein. The immunohistochemistry of prostate sections using these polyclonal antibodies indicated that the K-LM and PSA-LM proteins are detected only in the secreting cells of the tubule lumen and Western blot analysis indicated that the K-LM protein is present in seminal plasma. Furthermore, a recent study indicated that \textit{KLK3} may actually produce at least 10 transcripts, which can encode 6 putative protein isoforms [46]. RT-PCR analysis indicates that at least 5 splicing isoforms are expressed in normal, benign prostatic hyperplastic and cancerous tissues. Collectively, these \textit{KLK2} and \textit{KLK3} variants may supplement hK3/PSA diagnostics.

Dong et al. have recently cloned two \textit{KLK5} and two \textit{KLK7} splice variants from normal and cancerous ovarian cell lines [52]. The \textit{KLK5} variants are alternatively spliced in the 5' V-UTR and the \textit{KLK7} transcripts differ by one exon and the length of the 3' V-UTR. By RT-PCR analysis, the \textit{KLK5} variant with a short 5' V-UTR, denoted \textit{KLK5}-short, and the \textit{KLK7} transcript with a longer 3' V-UTR, named \textit{KLK7}-long, were found to be overexpressed in the ovarian cancer cell lines OVCAR-3 and PEO1, respectively, compared to normal ovarian epithelial cells. This differential expression of \textit{KLK5} and \textit{KLK7} variant transcripts between

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**Fig. 8.** Schematic representation of mRNA transcripts for human kallikrein gene 5 (KLK5). For more details, see legend of Fig. 4 [52,53,75].

**Fig. 9.** Schematic representation of mRNA transcripts for human kallikrein gene 6 (KLK6). For more details, see legend of Fig. 4 [54,76–79].

**Fig. 10.** Schematic representation of mRNA transcripts for human kallikrein gene 7 (KLK7). For more details, see legend of Fig. 4 [52,80].
normal ovaries and ovarian cancers suggests that they may be used for the early detection of ovarian cancer by RT-PCR analysis of tissue biopsies or as serum biomarkers, if the variant proteins are secreted [52].

Kurlender et al. have recently identified a novel KLK5 variant with alternative splicing in the 5’-UTR, KLK5-SV1, shown in Fig. 8 [53]. By RT-PCR analysis, KLK5-SV1 was found to be overexpressed in ovarian cancer tissues compared to normal. Higher expression of this variant was also evident in normal prostate tissues compared to their matched cancer tissue counterparts.

Pampalakis et al. have recently identified two splice variants of the KLK6 gene, lacking either coding exon 1 or 2 [54]. The quantification of the reference and two variant KLK6 mRNA forms in normal (76N) and cancerous (21PT and MDA-MB-469) breast cell lines by RT-PCR indicated that the splice variants account for 10–20% of all mRNA species. Additional studies are required to determine the clinical value of these splice variants in cancer.

Magklara et al. have also identified two novel mRNA splice variants of the KLK8 gene, missing 2 or 3 coding exons, named type 3 and type 4 KLK8, respectively [55]. RT-PCR analysis indicated that both variants were over-expressed at relatively high levels in cancerous ovarian tissues, compared to normal ovarian tissues, in which they were not detected. Accordingly, these ovarian cancer-
specific KLK8 variant transcripts represent potential cancer biomarkers.

The KLK11 gene has two transcript variants named the brain-type and prostate type [56]. Using quantitative RT-PCR, the expression of these KLK11 transcripts in matched normal and cancerous prostatic tissues were compared [57]. Both variants were overexpressed in cancerous prostate vs. normal tissues and lower expression of prostate-type KLK11 was associated with higher tumor stage, grade and Gleason score. No such association was seen with the brain-type isoform. These data suggest that KLK11 splice variants may have clinical value as biomarkers for prostate cancer diagnosis and prognosis.

The work of Chang et al. has revealed that the KLK13 gene possesses at least five tissue-specific splice variants expressed exclusively in the testis [45]. The reference KLK13 mRNA is predominately expressed in a variety of tissues including the breast, prostate, testis and salivary gland [58]. Using RT-PCR they have shown that KLK13 splice variants are expressed in a fraction of morphologically normal testicular tissues, but absent in the adjacent cancerous tissues [45]. Due to the conservation of their signal peptide sequences, the KLK13 splice variants are predicted to be secreted if they are translated. Taken together, these lines of evidence suggest that transcript variants of the KLK13 gene should be further examined as molecular markers for testicular cancer.

3. Conclusion

We have reviewed all known kallikrein mRNA forms. These are shown schematically in Figs. 4–18. Although the functional and diagnostic relevance of most kallikrein
alternative transcripts is still under investigation, preliminary evidence indicates that some are expressed exclusively in cancer tissues. We hope that this review will help in the further investigation of these numerous transcripts and their encoded proteins as new diagnostic and therapeutic targets.

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