SHORT COMMUNICATION

Intron/Exon Structure Confirms That Mouse *Zfy1* and *Zfy2* Are Members of the *ZFY* Gene Family

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***Zfy1* and *Zfy2* are homologous zinc finger genes on the mouse Y Chromosome. To ask whether these genes are properly classified as members of the *ZFY* family, we have characterized and compared their genomic organization to that of mouse *Zfx*, human *ZFX*, and human *ZFY*. We show that *Zfy1* has 11 exons distributed across at least 56 kb, and *Zfy2* has a minimum of 9 exons distributed across at least 52 kb. The *Zfy2* locus contains regions similar in size and sequence to all 11 exons of *Zfy1*, plus an additional 5′ UTR exon. All splice sites conform to the GT–AG rule. There are two instances of additional AG dinucleotides immediately 5′ of 3′ splice sites. *Zfy1* and *Zfy2* are homologous to other *ZFY* family members within the coding region, but the untranslated regions show no sequence similarity. Within the coding region, there is conservation of exon length and splice sites, with each splice preceding the second nucleotide of a codon. We conclude that *Zfy1* and *Zfy2* are indeed members of the *ZFY* family, which has evolved from a single common ancestral gene.**

ZFX and *ZFY* are homologous zinc finger genes located on the human X and Y chromosomes, respectively (17). Closely related genes that together constitute the *ZFY* family have been found on the sex chromosomes of most placental mammals. In mice there are four genes: *Zfx*, on the X Chromosome (13); *Zfa*, an expressed retroposon of *Zfx* on Chromosome 10 (1, 13); and *Zfy1* and *Zfy2*, genes resulting from an intrachromosomal duplication during rodent evolution on the Y Chromosome (2, 14, 15, 23).

Despite key similarities between *Zfy1* and *Zfy2* and the other members of the *ZFY* family, there are also major differences that set the two mouse Y genes apart. Similarity between *Zfy1* and *Zfy2* and the rest of the gene family can be demonstrated by a BLASTN (1.4.7MP) search of GenBank (Release 89) and EMBL (Release 41.0), using either *Zfy1* or *Zfy2* cDNA. Such a query identifies members of the *ZFY* family prior to any other sequences. Furthermore, the mouse Zfy proteins exhibit the *ZFY* family two-domain structure of an amino-terminal acidic half and a carboxy-terminal tandem array of 13 zinc fingers separated by a short basic region similar to a nuclear localization signal (1, 13, 17, 18, 20). Finally, the zinc fingers of *Zfy1* and *Zfy2* display the unusual odd–even two-finger periodicity evident in all *ZFY* homologs (10, 13, 15, 17, 21). In contrast to these similarities, however, the mouse *Zfy* genes are grouped separately from the rest of the family by both nucleotide and amino acid sequence analysis (6, 8, 10). In a comparison of amino acid similarity using the Clustal method (DNASTAR, Madison, WI), the mouse Zfx protein is 94.6% similar to human ZFX, 90.7% similar to human ZFY, but only 63.9 and 64.8% similar to mouse Zfy1 and Zfy2, respectively, which are 94.8% similar to each other. Furthermore, *Zfy1* and *Zfy2* have TATA box promoters (24) and lack the highly conserved 5′ CpG islands present in the *Zfx*, *ZFX*, and *ZFY* loci (11). Finally, *Zfy1* and *Zfy2* expression is restricted and found most abundantly in the adult testis (7, 9, 15), but mouse *Zfx* and human *ZFX* and *ZFY* are widely expressed (13, 18, 21).

To resolve the question whether mouse *Zfy1* and *Zfy2* are properly classified as members of the *ZFY* gene family, we have characterized and compared the intron/exon structure of these genes to the similar data available for mouse *Zfx* and human *ZFX* and *ZFY*. Although there are other mammalian genes with the zinc fingers clustered in the 3′ exon, the details of their genomic structure differ from those for the *ZFY* family (3, 5, 19). By sequencing the entire exonic portions of *Zfy1* and *Zfy2* in genomic clones, we have confirmed the published cDNA data (2, 9, 15, 24) and identified all the intron/exon boundaries known for these loci (Fig. 1A). The work employed material from both the *Mus musculus* and the *Mus domesticus* Y Chromosomes (see legends to Figs. 1 and 2). The cDNA sequences used had previously been characterized as full

Sequence data from this article have been deposited with the GenBank Data Library under Accession Nos. L39900 to L39903 and have been used to correct U15737 to U15740.

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A

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                                        Exon 1A
Zfy2      ctggagagctctgctattgc|tccagtggcc.........tacattaaag|gtaagagatcccaagctaag
                              -319                      -98

                              -333       Exon 1B        -189
Zfy1      gggtctgtaggtgggtgggg|cctgtagaga.........gggctgtaag|gtgagttttaagtgttaaca
Zfy2     (gggtctgtaggtgggtgggg|cctgtagaga.........gggctgtaag|gtgagttttaagtgttaaca)

                              -188       Exon 2         -123
Zfy1      ctctttcttccattagccag|agaccggccc.........cactggtctg|gtgagttctgagtgtggtca
Zfy2  gtccctctttcttccattag|ccagagaccggccc.........cactggtctg|gtgagttctgagtgtggtca
                         -97                              -28

                              -122       Exon 3         -77
Zfy1      gtcttttatcttatttttag|attatctgaa.........attctgttct|gtaagtatatctcctggtag
Zfy2     (tatttttatcttatttttag|attatctgaa.........attctgtcct|gtaagtataacttctagtag)

                              -76        Exon 4         -28
Zfy1      ttcttatctttctgtttcag|acatgaattt.........tatggcccag|gtaattaaagcaaaaccaga
Zfy2     (ttcttgtctttctgtttcag|acatgaattt.........tattgtccag|ctaattaaagcaaaaccata)

                              -27        Exon 5          61
Zfy1      tttgttgttccctggtttag|gagctgactt...ATG...GATGGAATAG|gtataatatttcttgattat
Zfy2      tttgttgttccctggtttag|gagctgactt...ATG...GATGGAATAG|gtataatatttcttgattat
                              -27                        61

                              62         Exon 6          613
Zfy1      aattctttttatctttaag|GAGCTGATGC.........ATGATGTCTT|gtaagtcttgagccacatgg
Zfy2      aattctttttatctttaag|GAGCTGATGC.........ATGATGTCTT|gtaagtcatgaaccatatgg
                              62                         613

                              614        Exon 7          763
Zfy1      ataatacatttcctatttag|TGGATGAACC.........GATGATGTAG|gtaaggaaacttttaatttt
Zfy2      ataatacatttcctatttag|TGGATGAGCC.........GATGATGTAG|gtaaggaaacttttaatttt
                              614                        763

                              764        Exon 8          904
Zfy1      tatagtttgttttcttttag|GAGAAACTAT.........GAAGATACTG|gtaactacatggcttacttt
Zfy2      catagtttgttttcttatag|GAGAAACTAT.........GAAGATACTA|gtaagtacatggcttatttt
                              764                        904

                              905        Exon 9         1027
Zfy1      agtaaatgaagttttctatag|AAGTAATTGT.........GCAGCTTATG|gtaagtaacagcgtgaaaat
Zfy2      cataaatgaagttttctatag|AAGTAATTGT.........GCAGCTTATG|gtaagtaacagcgtgaaaat
                              905                       1027

                              1028       Exon 10        1168
Zfy1      tttttgatgtacattgttag|ATAATAATTC.........TACAAGTCAG|gtaaggaagtaataattcta
Zfy2      tttttggtgtacattgttag|ATAATAATTC.........TACCAGTCAG|gtaaggaagaaataattcta
                              1028                       1168

                              1169       Exon 11        2558
Zfy1      ctgttttgttccctttttag|CAATATTTGT...TAA...TTAACAACAC|aatccctgattttatgttga
Zfy2      ctgttttgttccctttcttag|CAATATTTGT...TAA...ATATTGCTTC|gatttgactttatgttttat
                              1169                       2475
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B

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Exon 3
Zfy1      ATTATCTGAATAAT----------------GTTATAATATGTTCCTGACATCATTCTGTCCT
Zfy2     (ATTATCTGAATAATGTTATAATCTGTACTAAGTTATAATATGTCCCTGACATCATTCTGTCCT)

Exon 4
Zfy1      ACATGAATTTATATTTATTATACCTGCTATCAGTTCATTTATGGCCCAG
Zfy2     (ACATGAATTTATATTTATTATACCTGGTATCAGTTCATTTATTGTCCAG)
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FIG. 1. Intron/exon boundaries of *Zfy1* and *Zfy2* and genomic sequence for two new regions of the *Zfy2* locus homologous to *Zfy1* 5′ UTR exons. (**A**) Nucleotide sequence at the splice sites for all known *Zfy1* and *Zfy2* exons. Vertical lines mark the intron/exon boundaries. Noncoding and intervening sequences are in lowercase, and coding sequences are in uppercase. Translation initiation and termination codons are shown within exons 5 and 11, respectively. The first and last nucleotides of the exons are numbered according to their positions relative to the first nucleotide of the initiator codon in published cDNA sequence. *Zfy1* numbering is based on the original cDNA (GenBank Accession No. X14382) (2), plus 83 5′ UTR nucleotides revealed by RACE (24) and two alternative 5′ UTR exons revealed by RT-PCR (9). This encompasses all published cDNA data; the *M. musculus* or *M. domesticus* Y origin of this material was not reported. *Zfy2* numbering is based on cDNA (GenBank Accession No. M24401) from FVB/N (*M. domesticus* Y) (15). The *Zfy2* sequences in parentheses are homologous to the respective *Zfy1* exons, but are absent from any known *Zfy2* cDNA. Underlining denotes interesting features discussed in the text.

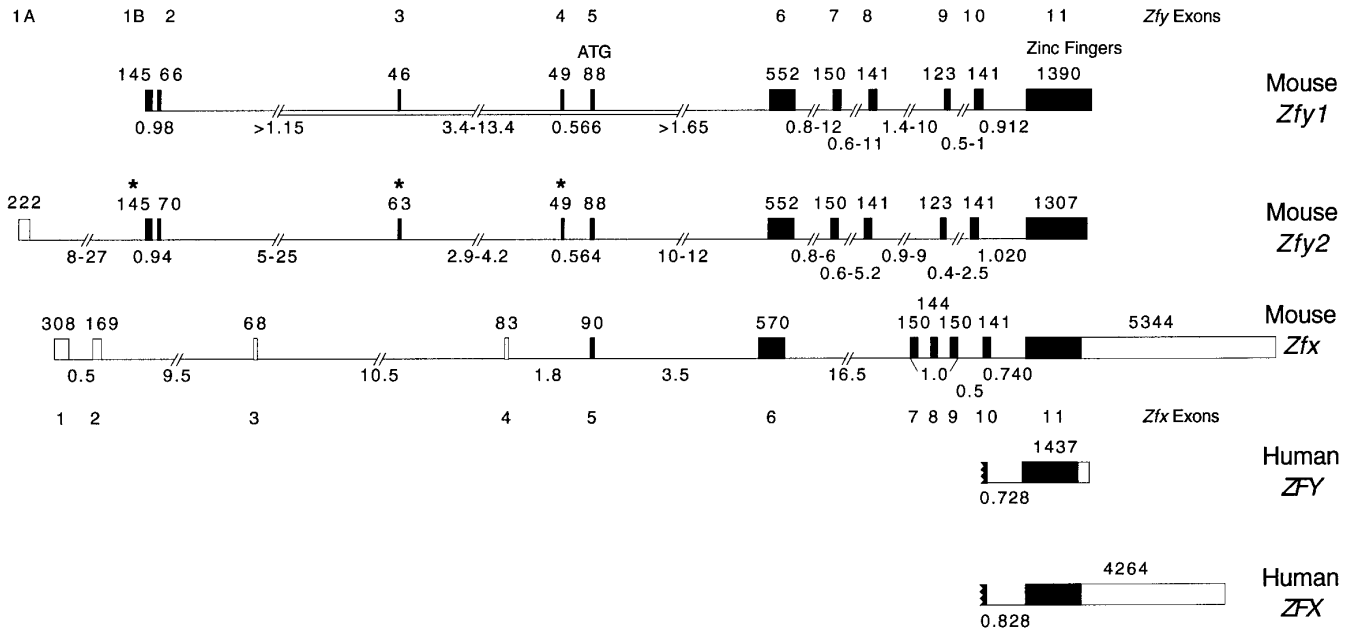

FIG. 2. Genomic organization of the *ZFY* gene family. The structures of the *Zfy1* and *Zfy2* loci are presented and compared to those of mouse *Zfx* and human *ZFX* and *ZFY* (4, 12, 21). Exons are indicated by boxes and are to scale except where jagged edges represent exon boundaries that are not precisely defined. The number above a box indicates the size of the exon in base pairs. An asterisk indicates *Zfy2* regions that are homologous to *Zfy1* exons, but are absent from any known cDNA. The homologous *Zfy1* and *Zfy2* exons, as well as exons (or parts of exons) of the other genes with homology to *Zfy1* and *Zfy2,* are in black. The remaining exons (or parts of exons) are in white. The horizontal lines indicate introns, with the number(s) below the line indicating the intron size in kilobases. The introns are to scale except where hash marks occur. Where a size range and hash marks occur, the introns are to scale within the range except for *Zfy2* introns 1A and 5, which have been shortened to compact the figure. The *Zfy* exons are numbered at the top, and the *Zfx* exons are numbered below that locus. As indicated, the initiator ATG is within exon 5, and the zinc fingers are encoded by exon 11. The double horizontal line indicates the region based on *M. musculus* Y genomic data.

length and includes alternative splices. Sequencing was performed using AmpliTaq Cycle Sequencing kits (Perkin–Elmer–Cetus, Norwalk, CT) manually or employing an ABI 373A DNA sequencer (ABI, Foster City, CA). Genomic templates were plasmids and endonuclease-digested λ DNA (see Fig. 1 legend). Primers were designed from published cDNAs and our genomic sequence. Three regions of 5′ DNA in the *Zfy2* locus were found to be homologous to *Zfy1* 5′ UTR exons, although the regions have never been reported in *Zfy2* cDNA. These portions of the *Zfy2* locus were sequenced using *Zfy1* primers to assess the possibility that they might be legitimate exons (in parentheses in Fig. 1 and marked with an asterisk in Fig. 2). Intron/exon boundaries were determined by aligning genomic sequence with published cDNA sequence using DNASTAR DNA analysis software.

All the *Zfy1* and *Zfy2* splice sites for exons represented in cDNAs conform to the GT–AG rule (16, 22). In contrast, of the three potential *Zfy2* exons (in parentheses in Fig. 1 and marked with an asterisk in Fig. 2), two break this rule, with GG instead of AG 5′ of potential exon 1B and CT instead of GT 3′ of potential exon 4 (underlined in Fig. 1A). [The GG 5′ of *Zfy1* exon 1B is not unexpected since it is the first exon of the gene, and thus the dinucleotide is not a splice acceptor (24).] Since there have been no reports of naturally occurring splice sites using GG or CT dinucleotides (16, 22), we can predict that the 1B and 4 regions of *Zfy2* are not exons, despite homology to *Zfy1* exons. Our

The intron/exon boundaries presented here for exons 1A and 2 correct those previously reported (24). (**B**) Genomic sequences of *Zfy1* exons 3 and 4 and the similar regions of *Zfy2* (GenBank Accession Nos. L39900–L39903). As in (A) the parentheses around the *Zfy2* sequences indicate that these regions have never been found in *Zfy2* cDNA. The dashed line indicates a gap introduced to facilitate sequence alignment. Underlining denotes sequence differences. *Zfy1* and *Zfy2* sequences were obtained either directly from FVB/N (*M. domesticus* Y) strain-derived cosmids or from *Eco*RI subclones of these cosmids (23), except for *Zfy1* exons 3, 4, and 5, obtained from a 129/SvJae (*M. musculus* Y) J1 ES cell-line-derived bacteriophage (R. Jaenisch, Whitehead Institute, Cambridge, MA, pers. comm.). *Zfy1* exons 1B and 2 were sequenced from plasmid pEMS325A, a subclone of cosmid cEMS132. *Zfy1* exon 3 was sequenced from pEMS696, a subclone of bacteriophage PEMS83, and *Zfy1* exons 4 and 5 were sequenced directly from PEMS83. *Zfy1* exons 6, 7, and 8 were sequenced from pEMS383A, a subclone of cEMS143. *Zfy1* exons 9, 10, and 11 were sequenced from pDP1050. *Zfy2* exon 1A was sequenced from pEMS282 and *Zfy2* exons 1B and 2 were sequenced from pEMS283, both subclones of cEMS142. *Zfy2* exons 3 to 11 were sequenced from pEMS485A (exon 3), pEMS300 (exons 4 and 5), pEMS473A (exons 6, 7, and 8), pEMS480A (exons 9 and 10), and pEMS476B (exon 11), all subclones of cEMS206.

sequence surrounding the potential *Zfy2* exon 3 does not explain why this exon is absent from *Zfy2* cDNA, and it may yet be found in mature transcripts. In Fig. 1B we present the sequence of the regions in *Zfy2* homologous to *Zfy1* exons 3 and 4. The genomic sequence of the *Zfy2* 1B region has been reported previously (24).

There is only one nonhomologous splice site between *Zfy1* and *Zfy2* (Fig. 1A, 5′ of exon 2). This deviation in the *Zfy1* and *Zfy2* loci occurs at the site of an anomaly to a general splicing rule. In more than 98% of intron sequences, additional AG dinucleotides are not present immediately upstream of 3′ splice acceptors, and their absence is believed to be instrumental in the formation of 3′ splice sites (16, 22). *Zfy1* has AG dinucleotides within 10 bp 5′ of the splice acceptor at exons 2 and 9, and *Zfy2* has the same arrangement 5′ of exon 9 (underlined in Fig. 1A). For the 5′ UTR exon 2, *Zfy2* splices at the AG 4 bp 5′ of the AG used by *Zfy1*. This may actually be a site of alternative splicing in both genes, with a different alternative having been captured in the cDNA for each (2, 15, 24). If this is the case, then all splice sites would be homologous between *Zfy1* and *Zfy2*. Although splicing occurs at homologous sites for exon 9 in *Zfy1* and *Zfy2*, this is the only splice difference among the homologous exons of these genes and mouse *Zfx* (12). This difference causes the "in-frame" addition of 11 amino acids to Zfx that are not in the Zfy proteins, nor are these amino acids recognizably encoded in the adjacent *Zfy* intron sequence (2, 12, 13).

Not depicted in Fig. 1 are several dinucleotide repeats found in the introns of *Zfy1* and *Zfy2*. There is a $(GT)_{13}$ in *Zfy1* and a $(GT)_{16}$ in *Zfy2* 90 bp 5′ of exon 6. Parsimony suggests that these repeats predated the duplication of the *Zfy* genes. Differences between the two genes presumably occurring after their split include one repeat specific to *Zfy2*, $(CA)_{13}$ 195 bp 3′ of exon 8. Three repeats are specific to *Zfy1*, $(GT)_{\geqslant 29}$ 140 bp 3′ of exon 7, $(GT)_{\geqslant 13}$ 190 bp 3′ of exon 8, and $(AT)_{11}$ 120 bp 5′ of exon 11. Interestingly, this latter repeat is absent in both *Zfy1* and *Zfy2* of BALB/cAncr (4). Since our data are from the FVB *M. domesticus* Y Chromosome and BALB/c has a *M. musculus* Y, we assume that the repeat appeared after the evolution of these two Y Chromosomes.

Figure 2 shows the genomic organization of *Zfy1* and *Zfy2* in comparison with other mouse and human members of the *ZFY* family. As anticipated by earlier work, the genomic organization of the two mouse Y genes is highly homologous (14, 23). We have now demonstrated that *Zfy1* has 11 exons distributed across at least 56 kb, and *Zfy2* has a minimum of 9 exons distributed across at least 52 kb. The *Zfy2* locus contains exons, or exon-homologous regions (marked with an asterisk in Fig. 2), similar in size and sequence to all 11 exons of *Zfy1* (black boxes), plus an additional 5′ UTR exon 1A (white box). Despite searching, no homology to this *Zfy2* exon was found upstream of *Zfy1* (24). Intronic fragments and the sequences of introns 1B and 10 had previously been shown to be homologous between the two loci (4, 23, 24). We have extended this observation to include the sequence immediately surrounding each exon (or exon-homologous region) (Fig. 1) and the entirety of intron 4 (sequence not shown).

It is now possible to compare in detail the intron/exon structures of the mouse *Zfy1* and *Zfy2* genes with what is known for other members of the *ZFY* gene family (Fig. 2). The most extensive data available are for mouse *Zfx*, with less complete data for human *ZFX* and *ZFY* (4, 12, 20, 21). Our results show that the organization within the coding region is conserved (black boxes), but there is little similarity of the mouse *Zfy* genes to the 5′ UTR exons of mouse *Zfx* (white boxes). The homology of *Zfy* to *Zfx* begins within exon 5, a few bases 5′ of the initiation ATG in all three genes, and concludes at the protein termination codon. Of the seven coding exons, two have exactly the same lengths in *Zfy1*, *Zfy2*, and *Zfx*, while the remaining four have similar lengths, excluding the long *Zfx* 3′ UTR. All five genes share several features. The acidic protein domain is encoded by several exons, the putative nuclear localization signal is in the penultimate exon, and all 13 zinc fingers are encoded within the final exon, which also includes the entire 3′ UTR. Within the coding region, all splice sites for the three mouse genes and those known for human *ZFY* and *ZFX* are conserved, with the single exception of the exon 9 acceptor as discussed above. Strikingly, in the coding regions of the five genes, all known splice sites fall between the first and the second nucleotides of a codon triplet. This means that any coding exon(s) could be spliced out without disrupting the reading frame. Comparison of the sequence immediately surrounding each exon did not reveal any intron homology between the *Zfy* genes and *Zfx*, though the last introns of all five family members were previously shown to exhibit similarity (4).

The intron/exon structure described here strongly supports the conclusion that mouse *Zfy1* and *Zfy2* are members of the *ZFY* family, which has evolved from a single common ancestral gene. All these genes have preserved the ancestral genomic structure within the coding region, but the untranslated regions have diverged beyond recognition, at least in the case of mouse *Zfx* versus mouse *Zfy* genes. New evidence includes the conservation of splice sites within the coding region, the splicing pattern at the second nucleotide of a codon, and exon lengths.

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