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Transposable Elements in Maize—the Activator-Dissociation (Ac-Ds) System

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Introduction

Although unstable mutants in maize (*Zea mays*) were described as early as 1914 (Emerson 1914, 1917, 1929; Rhoades 1936, 1938), the first explanation of such mutants in terms of transposable DNA was provided by Barbara McClintock's elegant series of experiments on the activator-dissociation (*Ac-Ds*) controlling-element system of maize (McClintock 1947, 1948, 1951). McClintock demonstrated genetically that *Ac* and *Ds* were short regions of DNA which could move (transpose) from one chromosomal location to another. McClintock also established that *Ds* could transpose only in response to the action of *Ac* (i.e. both elements were required in the same nucleus for *Ds* transposition), and that *Ac* could transpose autonomously (i.e. in the absence of *Ds*). A total of eight transposable element systems have been recognized in maize, the best characterized of which are *Ac(Mp)-Ds*, *Spm* and Robertson's mutator (reviewed in Fedoroff 1983; Nevers *et al.* 1984). All but Robertson's mutator occur as two-element systems, similar to *Ac-Ds*. Transposable elements have now been shown to be widespread in living organisms—occurring in prokaryotes and lower eukaryotes as well as other higher eukaryotes, including animals.

Transposable elements can be inserted into DNA at different positions in the genome and many alter the expression of neighbouring genes. In general, integration of the element is detected by an altered phenotype (e.g. integration of the element into a snapdragon gene involved in the synthesis of red or purple anthocyanin pigment may render the flowers yellow or colourless). Mutations caused by transposable elements are often unstable and, as noticed by McClintock, removal of the element from the gene usually results in the restoration of gene activity (e.g. flower colour) so that unstable mutants often look variegated. Instability of a mutant can also be noticed cytologically as breaks, deletions, duplications, inversions or translocations (McClintock 1946, 1947, 1951, 1956, 1965). Studies of maize transposable elements and their effects on the genome were, until very recently, restricted to those transposon-induced mutations which were amenable to classical genetic analysis. Molecular analysis of the *Ac-Ds* transposable elements was initiated in the late 1970s with the restriction mapping of *Ds* mutants at the Shrunken locus (*Sh*) (Burr and Burr 1980; Doring *et al.* 1981). Fine-structure analysis of *Ds* elements commenced in Canberra with the cloning and sequencing of *Ds* from the alcohol dehydrogenase 1 locus (*Adh1*) on the long arm of chromosome 1 (Peacock *et al.* 1983; Sachs *et al.* 1983; Sutton *et al.* 1984). Other *Ds* and *Ac* elements have since been isolated from various genetic loci and their sequence data are now available (see Table 1).

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Table 1. Some *Ds* and *Ac* elements and their genetic loci and sequence data

Ds/Ac Element	Locus	Flanking duplicated sequence[A]	Inverted terminal sequence	Family of internal homology[B]	Reference
Ds1	*Adh1*	GGGACTGA	TAGGGATGAAA	1	Peacock *et al.* (1983)
	Wx-m1			1	S. Wessler (personal communication)
Ds101	?	CGTCTC	AGGGATGAAA	1	W. L. Gerlach, E. S. Dennis and W. J. Peacock (unpublished data)
Ds6	*Wx-m6*			2	Fedoroff *et al.* (1983)
Ds9	*Wx-m9*	CATGGAGA	T/C AGGGATGAAA	2	Pohlman *et al.* (1984)
Ac9	*Wx-m9*			2	
Ds5933	*Sh*	CGAAGTGG	TAGGGATGAAA	2	Doring *et al.* (1984*b*)
Ds6233	*Sh*	GGGACAAG	TAGGGATGAAA	2	Weck *et al.* (1984)
	Adh1-2F11	CCCACTGA	TAGGGATGAAA	2	H.-P. Doring (personal communication)
	Bz-wm	Not done	Not done	3	J. Schiefelbein (personal communication)

[A] Direct repeat.
[B] 1, elements with homology to *Ds1* (*Adh*); 2, elements with homology to *Ac9* (*Wx*); 3, elements with homology to *Bz-wm Ds*.

Structural Features of *Ac-Ds* Controlling Elements

Sequence comparisons between the *Adh1* mutant, *Adh1-Fm335* [which has a *Ds* insertion (*Ds1*) in the 5′ non-translated region of the *Adh1* gene] and its progenitor *Adh1* locus (*Adh1-PrF*) allowed the identification of *Ds* and progenitor sequences at the site of insertion. The *Ds1* element is flanked by an 8 bp repeat (GGGACTGA), generated from a single copy of the sequence in the progenitor, directly at the point of *Ds1* insertion (Peacock *et al.* 1983; Sachs *et al.* 1983; Sutton *et al.* 1984). *Ds1* itself terminates in an 11 bp inverted sequence and has the structure [5′-TAGGGATGAAA-AC-GGT . . . (separated by 373 bp) . . . ACC-AC-TTTCATCCCTA-3′]. The same 11 bp inverted repeat has been found at the termini of *Ds6233* (*Sh*) (Weck *et al.* 1984), *Ds5933* (*Sh*) (Doring *et al.* 1984*b*) and 2F-11 (*Adh1*) (Doring *et al.* 1984*a*). In each case, the insertion of *Ds* was accompanied by a duplication of 8 bp of the target DNA. A variation of this arrangement is found at the termini of *Ac9* (*Wx*) and the *Ds9* element derived from *Ac9* (Fedoroff *et al.* 1983; Pohlman *et al.* 1984). These elements terminate in an imperfect 11 bp inverted repeat (the outermost base differs in the two repeats, see Table 1). Several other copies of the *Ds1* element have been cloned, and one example terminates in a 10 bp inverted repeat which causes a 6 bp target-site duplication (Table 1). The 10 bp inverted repeats are completely homologous to the inner 10 bp of the 11 bp inverted repeats. Sequence comparisons between the internal regions of *Ds1* and *Ac9* have revealed no sequence homology (other than for 26 bp that includes a terminus) except for the terminal repeats. This observation indicates that only the inner 10 bp of the 11 bp of the inverted repeats are required for transposition.

The *Ac9* element has been found to have two open-reading frames (ORFs)—a large ORF1 of 2·5 kb and a small ORF2 of 630 bp (Pohlman *et al.* 1984). ORF1 and ORF2 are in opposite orientation to each other and are separated by a short intragenic region (Pohlman *et al.* 1984). This arrangement is reminiscent of the bacterial transposable element *Tn3*, which has a large transposase gene and a small resolvase gene (Heffron 1983). Evidence supporting the hypothesis that ORF1 encodes a transposase is the observation that a small deletion in ORF1 of 200 bp was coincident with the conversion of the autonomous *Ac9* element at *Wx-m9* to a non-autonomous *Ds* element (*Ds9*) in the same location.

The significance of the termini of a transposable element for transposition and excision is well known in bacterial systems, and so it is not surprising that the different families of *Ds* elements and the *Ac* element have the same termini. A new finding is that several elements from different plant species all share a common sequence at their termini; the *Tgm1* element from soybean, the *Tam1* and *Tam2* elements from snapdragon, and the *Spm-I8* receptor element from maize all end in the sequence CACTA and all four elements generate a 3 bp duplication at the target site (reviewed in Nevers *et al.* 1984). Whether these similarities are due to convergent evolution, conservation of function, or chance has not been established.

In the presence of *Ac*, all *Ds* mutants are unstable. The *Ds1* element at the *Adh1* locus (*Adh1-Fm335*) reverts to full activity with high frequency (*c.*3% of gametes assayed show wild-type activity) in the presence of *Ac*. The *Adh1* locus from a number of these revertants

Table 2. Sequences of revertants and null derivative

	Site of *Ds* insertion	
Ds1 duplication (from Peacock *et al.* 1984)	G G G A C T G A [ ]	G G G A C T G A
Revertants		
RV1	G G G A C T G T	C G G A C T G A
RV53	G G G A C T G T	C G G A C T G A
RV10	G G G A C T G T	C C G A C T G A
RV26	G G G A C T G T	. . C A C T G A
RV31	G G G A C T G .	. G G A C T G A
RV46	G G G A C T . .	. G G A C T G A
	Site of *Ac* insertion	
Ac-9 duplication (from Pohlman *et al.* 1984)	C A T G G A G A [ ]	C A T G G A G A
Wx revertant	C A T G G A G .	. A T G G A G A
	Site of *Ds* insertion	
Ds6233 duplication	C T T G T C C C [ ]	C T T G T C C C
Sh revertant	C T T G T C C .	. T T G T C C C

Null derivative of *Adh1-1Fm335*

TATATAAATCAGGGCTCATTTTCTCGCTCCTCACAGGCTCATCTCGCTTT

GGATCGATTGGTTTCGTAACTGGTGAGGGACTGAGGGTCTCGGAGTGGAT

CGATTTGGGATTCTGTTCGAAGATTTGCGGAGGGGGGCAATGGCGACCGC

GGGGAAGGTGATCAAGT .....

The above is the sequence of a portion of the 5′ region of the *Adh1-1F* allele. The TATA box, transcription start and translation start points are single underlined. The target sequence of the *Ds1* insertion is double-underlined. The *Ac*-induced deletion is indicated by a score line above the deleted sequence region. In addition to the sequence shown, the whole *Ds1* element and the 3′ 8 bp direct repeat is deleted:

G G A C [T G A . . . . G G G A A G G] T G A

Target sequence 3′ end of deletion

Sequence deleted is boxed

was cloned and sequenced. In each case, though the 8 bp duplication remained in an altered form, the *Ds1* element was no longer present. There are sequence variations at the junction between the site of insertion of the *Ds* element and the genomic DNA. These alterations are either base deletions or complementary transversions, or both, on both sides of the insertion point (Table 2). Examination of revertants of *Ac* also fit this pattern (Pohlman *et al.* 1984) and *Ds6233* (*Sh*) (Weck *et al.* 1984; H.-P. Doring, N. Fedoroff and P. Starlinger, unpublished data).

A model for insertion of *Ds* is that 8 bp staggered cuts are made in the target DNA, followed by single-strand joining of the *Ds* ends to the target DNA. The gaps are then filled to produce the duplication. Excision must also involve 8 bp staggered cuts and trimming of the *Ds* element back to flush-ended 11 bp inverted repeats. The gaps in the genomic DNA are filled in and at some stage the opposite strand is used as a template to obtain the complementary transversions. In all cases of excision of *Ds* (families 1 and 2) or *Ac* elements, a portion or all of the 8 bp duplication remains (6, 7 or 8 bp). In one case at least, excision of the *Ds* element has resulted in a 70 bp deletion adjacent to the *Ds* element, which removes a portion of the 5′ untranslated region, together with the translation initiation signal, and the first six amino acids of the coding region. Naturally occurring null mutations of genes may be due to similar deletions, as the result of controlling-element insertion and grossly imprecise excision. Yet, though excision may be imprecise, transposition of *Ds* is exact and no sequences outside the 11 bp inverted repeats are transferred to the new site of insertion. In the *Adh1* mutant the *Ds* element is inserted in the 5′ untranslated region. Transcription is initiated in the normal position and though, as in the wild type, it is induced by anaerobic conditions, the steady-state level of *Adh1* mRNA is greatly reduced in the mutant. In the revertants, *Adh1* mRNA levels and enzyme activity are fully restored. The additional 5–8 bp in the 5′ untranslated region do not affect the position or level of transcription initiation, but remain as a footprint of the *Ds* mutation within the gene.

Families of *Ds* Elements

The *Ds1* and *Ds9* elements share no internal sequence homology; yet each element has the ability to respond to *Ac*, indicating that both are *bona fide Ds* elements. Each of these is a member of a distinct family of *Ds* elements. When the maize genome is digested with a restriction enzyme which does not cut within *Ds1*, approximately 50 bands with homology to *Ds1* are detectable by hybridization analysis (the number and position of hybridizing bands varies with the maize line). Five *Ds1* homologous genomic clones, *Ds101, Ds103, Ds105, Ds121* and *Ds123*, have been isolated and sequenced (Peacock *et al.* 1984; W. L. Gerlach, E. S. Dennis and W. J. Peacock, unpublished data). Four of the five clones terminate in the same inverted repeat as *Ds1 (Adh1)* and are flanked by 8 bp direct repeats. The fifth clone, *Ds101*, has only 10 bp inverted terminal repeats, flanked by 6 bp direct repeats (see previous section). All five elements are about 400 bp in length and have 90–95% overall homology to *Ds1*. Therefore, *Ds1* has homology to sequences elsewhere in the genome which have terminal structures characteristic of *Ds* elements. *Ds* elements with internal homology to *Ds1* have been designated as family 1. A similar number of hybridizing bands are detectable when *Ds9* is used as the probe against restricted maize DNA. *Ds* elements known to share internal sequence homology with *Ds9* include *Ds6*, *Ds5933*, *Ds6233*, *Adh1-2F11* and the *Activator* element *Ac*. These elements have deen designated as belonging to *Ds* family 2. A *Ds* element which has no internal sequence homology to members of either *Ds* family 1 or 2 has recently been closed at the *bz-wm* locus (Bronze weak mutable) by J. Schiefelbein and O. Nelson (J. Schiefelbein, personal communication). This element is tentatively assigned to *Ds* family 3.

Evolution of *Ds* Elements

The existence of three distinct *Ds* families may simply reflect the fact that only the terminal inverted repeat structure is required for *Ds* function. The low degree of sequence divergence between members of *Ds* family 1, according to this theory, would be due to a relatively recent origin. Evidence from analysis of *Ds1*-related sequences in the immediate ancestor of *Zea mays*, *Teosinte*, and the more distant relative, *Tripsacum*, does not, however, support this contention. About 50 *Ds1* related sequences are detectable by Southern analysis in *Teosinte* and *Tripsacum*, even under very stringent conditions, indicating a high degree of sequence homology. Two clones containing *Ds1*-related sequences have been isolated from *Tripsacum*. These related sequences terminate in the same inverted repeats as found in *Zea mays* and are 90–95% homologous with *Ds1*. The structure of the related sequences indicates that they are true *Ds* elements. The high level of sequence conservation over the evolutionary time separating *Zea mays* and *Tripsacum* (1–10 million years) supports the suggestion that the internal sequence of the *Ds1* family of elements is under selective pressure. If this is so, the *Ac-Ds* system may have a functional role in maize development. This idea was first proposed by McClintock, after she noticed that controlling elements transpose and may instigate other types of genetic change at predetermined times during development (McClintock 1965, 1971).

That *Ac* and *Ds* elements can affect the expression of many different games in maize has been firmly established (McClintock 1954, 1957, 1961, 1965; Fedoroff 1983). Mutation can be due to the insertion or the excision of a transposable element (see earlier). For example, unless exactly 6 bp remain after excision of an element inserted into the coding region of a gene, the reading frame will not be maintained and reversion is unlikely. As each transposition event is a source of mutation, the rate of transposition at given loci effectively changes the mutability of those loci. Different *Ds* elements can have quite different transposition frequencies (Peacock *et al.* 1984). For example, *Ds1* in the *Adh1* locus (*Fm335*) transposes at a high frequency in an *Ac1* background. However, the other *Ds1*-related sequences present in the same genome, as judged by changes in the restriction pattern over a comparable period, do not change detectably. This observation may mean that the chromosomal location of a particular element is important to its rate of transposition. *Adh1-Fm335*, for example, shows a high degree of homology between the 11 bp inverted repeat of the element and the genomic sequence at the site of integration. In all cases of *Ds* insertion, short repeats are present in the target region, so the rate of excision may be influenced by interactions between the inverted repeats of the transposable element and their flanking genomic sequences.

The efficiency of *Ac* in mediating transposition varies with the number of *Ac* elements (or *Ac* dosage) in the genome. At increasing dosage of *Ac1*, *Ds* transposition decreases. Also, the developmental stage at which transposition occurs is later at the higher doses of *Ac1*. Rhoades and Dempsey (1982, 1983) have described a second *Ac* element, *Ac2*, which differs from *Ac1*, both in dosage effect and time of action. *Ac2* will only effect *Ds* transposition at high dosage. The required dosage differs for different *Ds* mutable alleles. For example, two doses of *Ac2* are required to effect *Ds* transposition from *bz2-m*, but four doses of *Ac2* are required to act on the *Ds* at the *C1* locus. Furthermore, *Ac2* does not appear to be simply a weaker form of *Ac1*, as *Ac1* cannot effectively increase *Ac2* dose (M. Rhoades, personal communication). This raises the intriguing possibility that the maize genome may have multiple families of *Ac* elements, each with slightly different functions for maize development.

Mechanism of *Ac-Ds* Transposition

Experiments by Brink and Greenblatt on the modulator (*Mp*) transposable element of maize (now recognized as an *Ac* element) have shown genetically that transposition occurs during chromosome replication (Brink and Nilan 1952; Greenblatt and Brink 1962, 1963;

Greenblatt 1968, 1974*a*, 1974*b*, 1974*c*). *Mp* was shown by these workers to transpose from a newly replicated sister chromatid (donor site) to a site about to be replicated within the same replicon (receptor site). As a result, transposition of the element is polar relative to the replicon arrangement (i.e. the receptor site is distal to the replicating fork). No copy of the *Mp* element remains at the donor site. The *Mp* element is found to transpose less frequently to an unreplicated region of a second replicon, to a different chromosome, or even to receptor sites which have already replicated. In no case, however, is transposition detected from unreplicated donor sites.

One model for *Ac-Ds* transposition, given the confinement of the event to the period of DNA replication, is that transposition is normally prevented by a repressor encoded by *Ac*. According to this model, the repressor binds to the terminal repeats of the transposable element. At replication, the number of sites for repressor binding doubles, and therefore the efficiency of repressor binding decreases. Transposition at this stage becomes a race between the transposase which excises the element and the repressor which binds to the newly replicated site to prevent excision. This model would predict that *Ds* elements which are flanked by those sequences in the target DNA (i.e. outside the element itself) having high sequence homology to the terminal repeats of the element (i.e. the putative repressor binding site) should be more frequently successful in excising than those *Ds* elements which do not show target sequence homology to the terminal repeats. This has been found to be the case with *Ds1* (*Adh1*).

Frequency of Occurrence of Transposable Elements

So far mutants due to transposable elements have been documented in 36 species of plants (Nevers *et al.* 1984). It is likely that they are an important component of all plant genomes. In *Drosophila* it has been suggested that most of the middle repetitive DNA (*c.* 20% of the genome) may be transposable elements (Young 1979). In maize we know there are at least three families of *Ds* sequences in the genome. Each of these families has at least 50–100 copies of the element per genome. Assuming an average length of 1 kb per element, this makes a total of 300×1 kb = 300 kb of DNA involved in the *Ds* families. Assuming 10 different systems, transposable elements occupy 3000 kb of DNA of the maize genome. However, there is every reason to believe that there are many other systems which have not yet been detected, since transposable element-like structures have been found by chance, in such random genomic clones as in *Adh1F* (M. M. Sachs, E. S. Dennis, W. L. Gerlach and W. J. Peacock, unpublished data) and *Cin-1* (Shepard *et al.* 1984). Altogether, these elements may constitute a considerable percentage of the maize genome.

Origin of Controlling Elements

The autonomous controlling elements (e.g. *Ac* and *Spm* of maize) were originally discovered in material that experienced repeated chromosomal breakage and rearrangement (breakage–fusion–bridge cycles or exposure to atomic radiation), and Rhoades and Dempsey (1982, 1983) have isolated three new mutable systems from material undergoing chromosome breakage. Other mutable alleles have been induced by similar treatments involving 'genomic stress'. McClintock proposed that transposable elements constitute a system for generating genomic diversity and hence provide adaptability when the need arises (McClintock 1978). 'Genomic stress', as she named it, operates as a last resort under catastrophic conditions by increasing variability through increasing mutational frequency by the mobilization of transposable elements.

Practical Uses for *Ac-Ds* System

Ac elements can be used to give molecular tags to genes. As it is difficult to isolate genes which do not produce much protein or for which the product has not been identified,

this technique provides a way of isolating any gene purely on the basis of altered phenotype. A gene of interest is rendered mutant by *Ac* element insertion. A molecular probe for *Ac* exists (Fedoroff *et al.* 1983); therefore it should be possible to isolate the sequence flanking the *Ac* element (i.e. the mutant gene), and this sequence then be used to isolate the wild-type gene. Such an approach has been exploited in *Drosophila*, using *P* element (Bingham *et al.* 1981) and has recently been used by Fedoroff *et al.* (1984) to clone the *Bz* locus of maize. This technique is limited to genes into which *Ac* will transpose.

The two-element nature of the *Ac-Ds* system also makes it amenable for use as a vector similar to the *P* element system of *Drosophila* (which has been used to transform micro-injected embryos (Rubin and Spradling 1982; De Ciccio *et al.* 1983). The gene to be transferred would be flanked by the inverted terminal repeats of the *Ds* element on a plasmid vector. Theoretically, when the recombinant plasmid is introduced into a cell containing *Ac*, the region between, and including, the *Ac-Ds* terminal repeats transposes into the chromosomal DNA. In the *Ac-Ds* system, the gene could be maintained in a stable form by crossing the transformed plant into a background which lacks *Ac*.

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